The National Collaborating Centre

for Chronic Conditions

Funded to produce guidelines for the NHS by NICE

PARKINSON'S DISEASE

National clinical guideline for diagnosis and management in primary and secondary care

Published by

Royal College of Physicians

Setting higher medical standards

Acknowledgements

The National Collaborating Centre for Chronic Conditions would like to thank Rob Grant, Susan Varney, Ian Lockhart, Lina Bakhshi, Alison Richards, Jane Ingham, Ester Klaeijsen, Nick Latimer and Bernard Higgins for their work and advice on this project.

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The National Collaborating Centre for Chronic Conditions

The National Collaborating Centre for Chronic Conditions (NCC-CC) is a collaborative, multi-professional centre undertaking commissions to develop clinical guidelines for the NHS in England and Wales. The NCC-CC was established in 2001. It is an independent body, housed within the Clinical Standards Department at the Royal College of Physicians of London. The NCC-CC is funded by the National Institute for Health and Clinical Excellence (NICE) to undertake commissions for national clinical guidelines on an annual rolling programme.

Citation for this document

National Collaborating Centre for Chronic Conditions. *Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care*. London: Royal College of Physicians, 2006.

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ISBN 1 86016 283 5

ROYAL COLLEGE OF PHYSICIANS
11 St Andrews Place, London NW1 4LE
www.rcplondon.ac.uk

Registered Charity No 210508

Typeset by Dan-Set Graphics, Telford, Shropshire

Printed in Great Britain by the Lavenham Press Ltd, Sudbury, Suffolk

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Preface

It is almost 200 years since James Parkinson described the major symptoms of the disease that came to bear his name. Slowly but surely our understanding of the disease has improved and effective treatment has been developed, but Parkinson's disease remains a huge challenge to those who suffer from it and to those involved in its management. In addition to the difficulties common to other disabling neurological conditions, the management of Parkinson's disease must take into account the fact that the mainstay of pharmacological treatment, levodopa, can eventually produce dyskinesia and motor fluctuation. Furthermore, there are a number of agents besides levodopa that can help parkinsonian symptoms, and there is the enticing but unconfirmed prospect that other treatments might protect against worsening neurological disability. Thus, a considerable degree of judgement is required in tailoring individual therapy and in timing treatment initiation.

It is hoped that this guideline on Parkinson's disease will be of considerable help to those involved at all levels in these difficult management decisions. The guideline has been produced using standard NICE methodology and is therefore based on a thorough search for best evidence. Because of the unique problems of Parkinson's disease, converting this evidence into recommendations for treatment might have been problematic, but we have been fortunate in having a very experienced and able Guideline Development Group who have interpreted the scientific papers in the light of their considerable clinical experience. I am grateful to them for their hard work and for their expertise.

The guideline includes many recommendations on the use of different classes of pharmaceutical agent, but the recommendations singled out as being of key importance also stress other aspects of management. This is not a negative emphasis based on the problems associated with anti-parkinsonian drugs, but reflects the major role of non-pharmacological aspects of care in this disabling chronic condition. Diagnosis is particularly highlighted. This can be difficult, and while swift assessment by someone with appropriate expertise is important when suspicion of Parkinson's disease first arises, so too is it vital to reconsider the diagnosis if atypical features develop later. The speed with which we have recommended that patients should be seen may seem aspirational, but reflects the importance the Development Group feel should be attached to this. Other key recommendations urge healthcare professionals to be aware throughout the course of the disease of the potential benefits of referral for specialist treatment such as physiotherapy, occupational or speech and language therapy. I would also commend to the reader the excellent section on communication, another area of particular difficulty in this disease.

One of the incidental benefits of producing an evidence-based guideline is that the process highlights those areas in which the evidence is particularly lacking. There are always more of these than we would wish. Towards the end of this document the Development Group has indicated those areas which they believe are particularly deserving of, and amenable to, further research efforts.

Two centuries since its first description, Parkinson's disease remains a huge challenge. We hope that this guideline will not only aid current treatment of the disease, but will also stimulate efforts to improve future management more quickly than has been possible to date.

Dr B Higgins MD FRCP
Director, National Collaborating Centre for Chronic Conditions

DEVELOPMENT OF THE GUIDELINE

1 Introduction

1.1 Background

Parkinson's disease (PD) is named after the London general practitioner (GP), James Parkinson, who vividly described many of the clinical features of the condition in his *Essay on the shaking palsy* (1817).[5]

In this work, Parkinson refers to the condition by its earlier name of *paralysis agitans*, a term that captures a peculiar characteristic of the disease, namely the combination of *movement loss* (ie hypokinesia) with *movement gain* (ie tremor at rest) which characterises the condition.[6]

Shaking palsy was named 'maladie de Parkinson' in 1888 by the French neurologist Jean-Martin Charcot. Charcot admired Parkinson's clinical acumen and powers of description, but criticised him for omitting mention of rigidity, which Charcot believed to be a typical feature of the condition.[7]

1.2 Modern definition

PD is a progressive neurodegenerative condition resulting from the death of the dopamine containing cells of the substantia nigra. There is no consistently reliable test that can distinguish PD from other conditions that have similar clinical presentations. The diagnosis is primarily a clinical one based on the history and examination.

People with PD classically present with the symptoms and signs associated with parkinsonism, namely hypokinesia (ie poverty of movement), bradykinesia (ie slowness of movement), rigidity and rest tremor.

Parkinsonism can also be caused by drugs and less common conditions such as: multiple cerebral infarction, and degenerative conditions such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA).

Although PD is predominantly a movement disorder, other impairments frequently develop, including psychiatric problems such as depression and dementia. Autonomic disturbances and pain may later ensue, and the condition progresses to cause significant disability and handicap with impaired quality of life for the affected person. Family and carers may also be affected indirectly.

1.3 Health and resource implications

PD is a common, progressive neurological condition, estimated to affect 100–180 per 100,000 of the population (6–11 people per 6,000 of the general population in the UK)* and has an annual incidence of 4–20 per 100,000.[8] There is a rising prevalence with age and a higher prevalence and incidence of PD in males.[9]

*The size of the average general practice list in the UK.

PD can lead to extensive disability, which affects both the individual with the disease as well as indirectly family and carers. The economic impact of the disease includes:

- direct cost to the National Health Service (NHS)
- indirect cost to society
- personal impact of PD on individuals with the condition and their family and carers.

The direct costs of treatment to the NHS have been estimated at approximately £2,298 (£ 1998) per patient per year.[10] Significant cost drivers include the onset of motor fluctuations and dyskinesias.[11] The condition is a frequent cause of falls and thus fractures and even death.[12]

The total annual cost of care including NHS, social services and private expenditure per patient in the UK has been estimated at approximately £5,993 (£ 1998).[10] This results in direct costs of approximately £599,300,000 per year in the UK for 100,000 individuals with PD.[10]

Total costs of care increase with age and disease severity.[10] Costs to the NHS were approximately 38% of the total costs.[10]

1.4 How to use this guideline

The purpose of this guideline is to support clinical judgement, not to replace it. This means the treating clinician should:

- take into consideration any contraindications in deciding whether or not to administer any treatment recommended by this guideline
- consider the appropriateness of any recommended treatment for a particular patient in terms of the patient's relevant clinical and non-clinical characteristics.

Wherever possible, before administering any treatment the treating clinician should follow good practice in terms of:

- discussing with the patient why the treatment is being offered and what health outcomes are anticipated
- highlighting any possible adverse events or side-effects that have been associated with the treatment
- obtaining explicit consent to administer the treatment.

For those recommendations involving pharmacological treatment, the most recent edition of the British National Formulary (BNF) should be followed for the determination of:

- indications
- drug dosage
- method and route of administration
- contraindications
- supervision and monitoring
- product characteristics

except in those cases where guidance is provided within the recommendation itself.

2 Methodology

2.1 Aim

The aim of the National Collaborating Centre for Chronic Conditions (NCC-CC) is to provide a user-friendly, clinical evidence-based guideline for the NHS in England and Wales that:

- offers best clinical advice for PD
- is based on best published evidence and expert consensus
- takes into account patient choice and informed decision making
- defines the major components of NHS care provision for PD
- indicates areas suitable for clinical audit
- details areas of uncertainty or controversy requiring further research
- provides a choice of guideline versions for different audiences.

2.2 Scope

The guideline was developed in accordance with a scope, which detailed the remit of the guideline originating from the Department of Health and specified those aspects of PD to be included and excluded.

Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by NICE.[1,13] The full scope is shown in Appendix A.

The guideline covers:

- diagnoses of PD and parkinsonism
- treatment of idiopathic PD.

The scope excludes:

- juvenile onset PD (in people younger than 20 years of age)
- treatment of parkinsonism (a neurological disorder that manifests with hypokinesia, tremor or muscular rigidity) and other tremulous disorders (for example, essential tremor).

The guideline is relevant to primary, secondary and tertiary NHS care settings.

2.3 Audience

The guideline is primarily intended to provide guidance for NHS staff, but will also have relevance to the following people or organisations:

- all healthcare professionals
- people with the disease and carers of these people
- patient support groups
- commissioning organisations
- service providers.

2.4 Involvement of people with Parkinson's disease

The NCC-CC was keen to ensure that the views and preferences of people with PD and their carers informed all stages of the guideline. This was achieved:

- by consulting the Patient Information Unit housed within NICE during the pre-development (scoping) and final validation stages of the guideline
- by having a person with PD and a user organisation representative on the Guideline Development Group (GDG).

The patient and/or a representative of the user organisation were present at every meeting of the GDG. They were involved at all stages of the guideline development process and were able to consult with their wider constituencies.

2.5 Guideline limitations

The limitations of the guideline are as follows:

- Clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health).
- NICE is primarily concerned with health services and so recommendations are not provided for social services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these other sectors.
- Generally the guideline does not cover rare, complex, complicated or unusual conditions.

2.6 Other work relevant to the guideline

This guideline has been developed with the knowledge that other national work on PD and chronic neurological conditions has been completed or is in progress. This includes:

- the National Service Framework (NSF) for Long-term (Neurological) Conditions[14]
- the NSF for Older People[15]
- NICE Guideline on Falls[16]
- NICE Guideline on Dementia[17]
- NICE Guideline on Depression[18]
- NICE Guideline on Epilepsy[19]
- NICE Guidance on Alzheimer's Disease[20]
- NICE Guideline on Anxiety[21]
- NICE Guideline on Nutrition[22]
- NICE Guidance on Deep Brain Stimulation[23]

2.7 The process of guideline development

The development of this evidence-based clinical guideline draws upon the methods described by the NICE Guideline Development Methods manual[1,13] and the methodology pack specifically developed by the NCC-CC for each chronic condition guideline.[24] The developers' role and remit is summarised in Table 2.1.

Table 2.1 Role and remit of the developers

National Collaborating Centre for Chronic Conditions (NCC-CC)	The NCC-CC was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from the National Instiutute for Health and Clinical Excellence (NICE). A multi-professional partners' board inclusive of patient groups and NHS management governs the NCC-CC.
NCC-CC Technical Team	The Technical Team met and comprised the following members: GDG group leader GDG clinical advisor Information scientist Research fellow Project manager Health economist Administrative personnel.
Guideline Development Group (GDG)	The GDG met monthly for 13 months (2004 to 2006) and comprised a multidisciplinary team of professionals, service users (a person with PD), carers, and user organisation representatives who were supported by the Technical Team. The GDG membership details including patient representation and professional groups are detailed in the GDG Membership table at the front of this guideline.
Guideline Project Executive (PE)	The PE was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the Department of Health remit and NICE scope. The PE comprised: NCC-CC Director NCC-CC Manager NCC-CC Senior Research Fellow NICE Commissioning Manager Technical Team.
Sign-off workshop	At the end of the guideline development process the GDG met to review and agree all the guideline recommendations.

Members of the GDG declared any interests in accordance with the NICE technical manual.[1] A register is available from the NCC-CC: **ncc-cc@rcplondon.ac.uk**

The basic steps in the process of producing a guideline are:

- developing clinical evidence-based questions
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economics advice
- distilling and synthesising the evidence and writing recommendations
- grading the evidence statements and recommendations
- agreeing the recommendations
- structuring and writing the guideline
- updating the guideline.

▷ Developing evidence-based questions

The Technical Team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions, which are shown in Appendix B.

▷ Searching for the evidence

The information scientist developed a search strategy for each clinical question. In addition, the health economist searched for supplemental papers to inform models. Key words for the search were identified by the GDG. Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from all searches.

Each clinical question dictated the appropriate study design that was prioritised in the search strategy, but the strategy was not limited solely to these study types. The research fellow or health economist identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. Literature search details are shown in Appendix B.

▷ Appraising the evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the:

- NICE methodology as detailed in *Guideline development methods – information for National Collaborating Centres and guideline developers*' manual[1]
- NCC-CC quality assurance document and systematic review chart, available at **www.rcplondon.ac.uk/college/ceeu/ncccc_index.htm**.

▷ Incorporating health economics advice

Due to the appointment of the health economist midway through the guideline development, the areas for health economic evidence were considered after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economic evidence. Five key areas were separately identified by the clinical lead.

After agreement and selection of specific areas, the information scientist performed a literature search using economic filters on the related clinical questions. No study design criteria were imposed *a priori*. The searches were not limited to randomised controlled trials (RCTs) or formal economic evaluations. See the earlier section on 'Searching for the evidence' for details of the systematic search by the information scientist. The health economist reviewed titles and abstracts identified in the economic searches, and full papers were obtained as appropriate. The

health economist critically appraised the full papers and the relevant data were presented to the GDG at subsequent GDG meetings. See the previous section for information on critically appraising the evidence.

The health economist performed supplemental literature searches using key search terms in the York Centre for Review and Dissemination database, the NHS Economic Evaluation database, PubMed and the Google search engine to obtain additional information for modelling. Areas were modelled due to the limited amount of evidence in or relevance to the UK setting. Assumptions and designs of the models were explained and agreed by the GDG members during meetings and validated by an additional health economist.

▷ Distilling and synthesising the evidence and writing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations.

Evidence tables are available at:
www.rcplondon.ac.uk/pubs/online_home.htm

▷ Agreeing the recommendations

The sign-off workshop employed formal consensus techniques to:

- ensure that the recommendations reflected the evidence base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations.

The sign-off workshop also reached agreement on the following:

- five to ten key priorities for implementation
- five key research recommendations
- algorithms.

In prioritising key recommendations for implementation, the sign-off workshop also took into account the following criteria:

- high clinical impact
- high impact on reducing variation
- more efficient use of NHS resources
- allowing the patient to reach critical points in the care pathway more quickly.

The audit criteria provide suggestions of areas for audit in line with the key recommendations for implementation.[2]

▷ Structuring and writing the guideline

The guideline is divided into sections for ease of reading. For each section the layout is similar and is described below.

Table 2.2 Grading the evidence statements and recommendations

Levels of evidence		Classification of recommendations	
Level	**Type of evidence**	**Class**	**Evidence**
1++	High-quality meta-analysis (MA), systematic reviews (SR) of randomised controlled trials (RCTs), or RCTs with a very low risk of bias	A	Level 1++ and directly applicable to the target population *or* Level 1+ and directly applicable to the target population **AND** consistency of results Evidence from NICE technology appraisal
1+	Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias		
1–	MA, SR of RCTs, or RCTs with a high risk of bias	Not used as a basis for making a recommendation	
2++	High-quality SR of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal	B	Level 2++, directly applicable to the target population and demonstrating overall consistency of results *or* Extrapolated evidence from 1++ or 1+
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal		
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	Not used as a basis for making a recommendation	
3	Non-analytic studies (for example case reports, case series)	C	Level 2+, directly applicable to the target population and demonstrating overall consistency of results *or* Extrapolated evidence from 2++
4	Expert opinion, formal consensus	D	Level 3 or 4 *or* Extrapolated from 2+ *or* Formal consensus
		D (GPP)	A good practice point (GPP) is a recommendation based on the experience of the GDG

Diagnostic study level of evidence and classification of recommendation was also included.[1]

- *Clinical introduction:* sets a succinct background and describes the clinical context.
- *Methodological introduction:* describes any issues or limitations that were apparent when reading the evidence base.
- *Evidence statements:* provide a synthesis of the evidence base and usually describe what the evidence showed in relation to the outcomes of interest.
- *Health economics:* presents, where appropriate, an overview of the cost-effectiveness evidence-base.
- *From evidence to recommendation:* sets out the GDG decision-making rationale and provides a clear and explicit audit trail from the evidence to the evolution of the recommendations.
- *Recommendations:* provides stand-alone, action-oriented recommendations.

▷ Evidence tables

The evidence tables are not published as part of the full guideline but are available on-line at **www.rcplondon.ac.uk/pubs/books/pd**. These describe comprehensive details of the primary evidence that was considered during the writing of each section.

▷ Writing the guideline

The first draft version of the guideline was drawn up by the Technical Team in accord with the decision of the GDG. The guideline was then submitted for two formal rounds of public and stakeholder consultation prior to publication.[1,13] The registered stakeholders for this guideline are detailed in Appendix I. Editorial responsibility for the full guideline rests with the GDG.

Table 2.3 Versions of this guideline

Full version	Details the recommendations. The supporting evidence base and the expert considerations of the GDG. Available at **www.rcplondon.ac.uk/pubs/books/PD**
NICE version	Documents the recommendations without any supporting evidence. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**
Quick reference guide	An abridged version. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**
Information for the public	A lay version of the guideline recommendations. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**

▷ Updating the guideline

Literature searches were repeated for all of the evidence-based questions at the end of the GDG development process, allowing any relevant papers published up until February 2005 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Two years after publication of the guideline, NICE will commission a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be updated approximately 4 years after publication.[1,13]

2.8 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCC-CC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

2.9 Funding

The National Collaborating Centre for Chronic Conditions was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

THE GUIDELINE

3 Key messages

In this chapter three essential components of the guideline will be discussed:

- key recommendations for implementation
- audit criteria
- algorithm.

Recommendations for implementation consist of recommendations selected by the GDG that highlight the main areas likely to have the most significant impact on patient care and patient outcomes in the NHS as a whole.[1,13]

Audit criteria are explicit statements developed from the recommendations for implementation, used to define the structure of care, process or outcome that is to be measured.[1,13]

The algorithm is a flowchart of the clinical decision pathway described in the clinical chapters.[1,13]

Another important section of the guideline is Chapter 12, 'Research recommendations'. This chapter discusses the GDG selected, priority areas for future PD research. Specific research questions are stated, the proposed trial structure is described and an explanatory paragraph is provided. General research recommendations are also included in this chapter.

3.1 Key priorities for implementation

▷ Referral to expert for accurate diagnosis

People with suspected PD should be referred quickly* and untreated to a specialist with expertise in the differential diagnosis of this condition.

▷ Diagnosis and expert review

The diagnosis of PD should be reviewed regularly** and reconsidered if atypical clinical features develop.

Acute levodopa and apomorphine challenge tests should not be used in the differential diagnosis of parkinsonian syndromes.

▷ Regular access to specialist nursing care

People with PD should have regular access to the following:

- clinical monitoring and medication adjustment
- a continuing point of contact for support, including home visits, when appropriate

*The GDG considered that people with suspected mild PD should be seen within 6 weeks but new referrals in later disease with more complex problems require an appointment within 2 weeks.
**The GDG considered that people diagnosed with PD should be seen at regular intervals of 6 to 12 months to review their diagnosis.

- a reliable source of information about clinical and social matters of concern to people with PD and their carers,

which may be provided by a Parkinson's disease nurse specialist (PDNS).

▷ Access to physiotherapy

Physiotherapy should be available for people with PD. Particular consideration should be given to:

- gait re-education, improvement of balance and flexibility
- enhancement of aerobic capacity
- improvement of movement initiation
- improvement of functional independence, including mobility and activities of daily living
- provision of advice regarding safety in the home environment.

▷ Access to occupational therapy

Occupational therapy should be available for people with PD. Particular consideration should be given to:

- maintenance of work and family roles, employment, home care and leisure activities
- improvement and maintenance of transfers and mobility
- improvement of personal self-care activities such as eating, drinking, washing and dressing
- environmental issues to improve safety and motor function
- cognitive assessment and appropriate intervention.

▷ Access to speech and language therapy

Speech and language therapy should be available for people with PD. Particular consideration should be given to:

- improvement of vocal loudness and pitch range, including speech therapy programmes such as Lee Silverman Voice Treatment (LSVT)
- teaching strategies to optimise speech intelligibility
- ensuring an effective means of communication is maintained throughout the course of the disease, including use of assistive technologies
- review and management to support the safety and efficiency of swallowing and to minimise the risk of aspiration.

▷ Palliative care

Palliative care requirements of people with PD should be considered throughout all phases of the disease.

People with PD and their carers should be given the opportunity to discuss end-of-life issues with appropriate healthcare professionals.

3.2 Audit criteria

The audit criteria shown in Table 3.1 are linked to the key priorities for implementation (see previous section). These are intended to be suggestions to aid and monitor the implementation of this guideline at the level of an NHS trust or similar scale healthcare provider.

Table 3.1 Audit criteria

Recommendation	Audit criterion	Exceptions
Referral to expert for accurate diagnosis		
People with suspected PD should be referred quickly* and untreated to a specialist with expertise in the differential diagnosis of this condition. *In suspected mild PD people should be seen within 6 weeks, but new referrals in later disease with more complex problems require an appointment within 2 weeks.	100% of people with suspected PD are seen within 6 weeks of GP referral.	None
Diagnosis and expert review		
The diagnosis of PD should be reviewed regularly** and reconsidered if atypical features develop. **At 6–12-month intervals.	100% of people with PD are reviewed at 6–12 month intervals.	None
Acute levodopa and apomorphine challenge tests should not be used in the differential diagnosis of parkinsonian syndromes.	0% of people with suspected PD are offered acute levodopa and/or apomorphine challenge tests for the differential diagnosis of parkinsonian syndromes.	None
Regular access to specialist nursing care		
People with PD should have regular access to the following: • clinical monitoring and medication adjustment • a continuing point of contact for support, including home visits, when appropriate • a reliable source of information about clinical and social matters of concern to people with PD and their carers, which may be provided by a PDNS.	100% of people with PD have access to a PDNS or other professional capable of providing: • clinical monitoring and medication adjustment • a continuing point of contact for support, including home visits, when appropriate • a reliable source of information about clinical and social matters of concern to people with PD and their carers.	None
Access to physiotherapy		
Physiotherapy should be available for people with PD. Particular consideration should be given to: • gait re-education, improvement of balance and flexibility • enhancement of aerobic capacity • improvement of movement initiation • improvement of functional independence, including mobility and activities of daily living • provision of advice regarding safety in the home environment.	For 100% of people with PD, at diagnosis and each regular review, physiotherapy is available and appropriate referral is activated. This is recorded in the patient's notes.	None

continued

Table 3.1 Audit criteria – *continued*

Recommendation	Audit criterion	Exceptions
Access to occupational therapy		
Occupational therapy should be available for people with PD. Particular consideration should be given to: • maintenance of work and family roles, employment, home care and leisure activities • improvement and maintenance of transfers and mobility • improvement of personal self-care activities such as eating, drinking, washing and dressing • environmental issues to improve safety and motor function • cognitive assessment and appropriate intervention.	For 100% of people with PD, at diagnosis and each regular review, OT is available and appropriate referral is activated. This is recorded in the patient's notes.	None
Access to speech and language therapy		
Speech and language therapy should be available for people with PD. Particular consideration should be given to: • improvement of vocal loudness and pitch range, including speech therapy programmes such as Lee Silverman Voice Treatment (LSVT) • teaching strategies to optimise speech intelligibility • ensuring an effective means of communication is maintained throughout the course of the disease, including use of assistive technologies • review and management to support the safety and efficiency of swallowing and to minimise the risk of aspiration.	For 100% of people with PD, at diagnosis and each regular review, speech and language therapy is available and appropriate referral is activated. This is recorded in the patient's notes.	None
Palliative care		
Palliative care requirements of people with PD should be considered throughout all phases of the disease.	100% of people with PD should be given opportunities to discuss and ask questions about their palliative care requirements with appropriate healthcare professionals.	None

3.3 Parkinson's disease algorithm

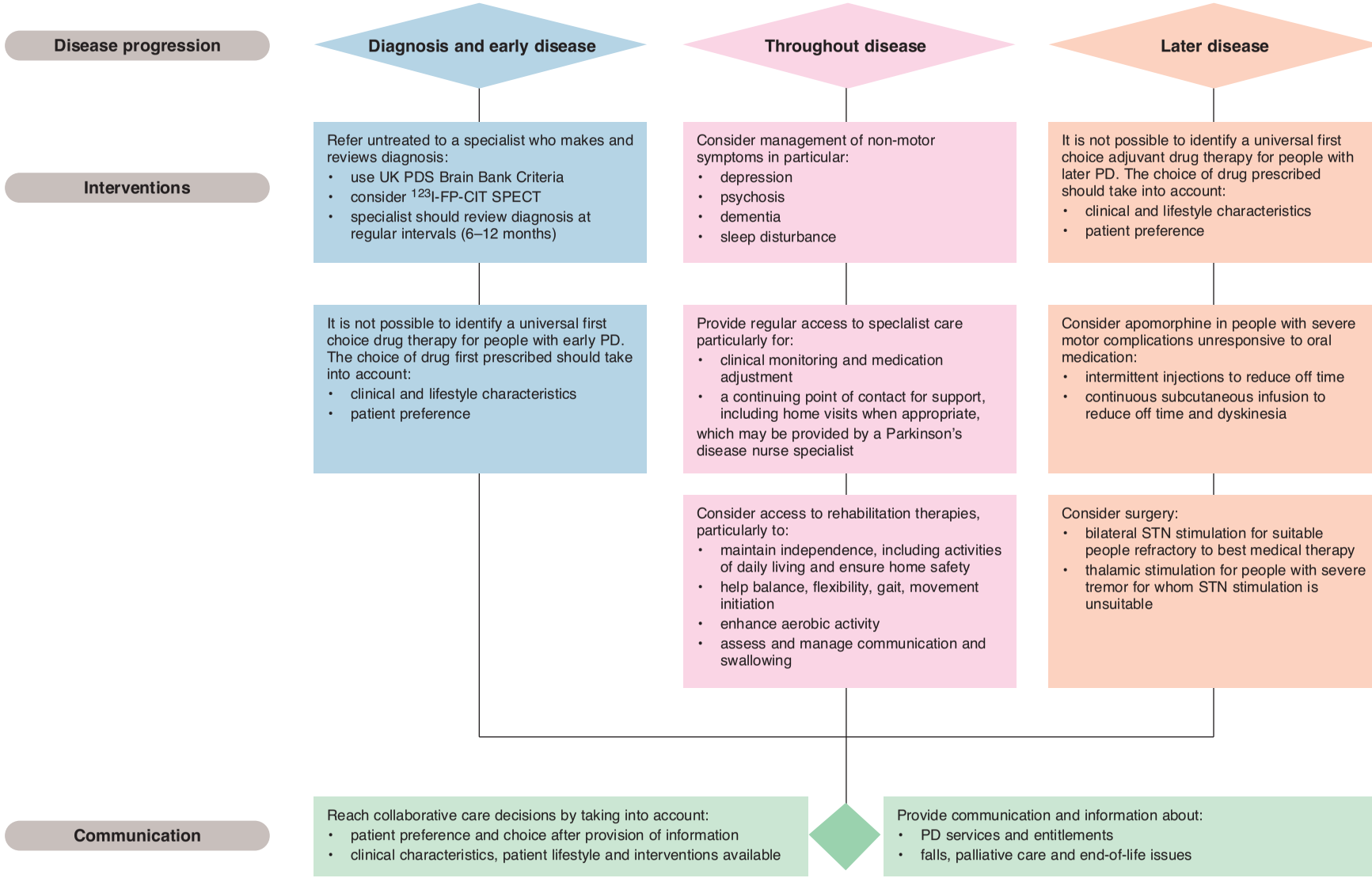

Figure 3.1 Parkinson's disease algorithm: interventions for people with PD.

4 Communication with people with Parkinson's disease and their carers

'I'd like them to remember to ask the patient how he feels and to listen to the patient. I'd like them to be more aware that each patient is an individual.' (patient)[2]

'I think what would have really helped was if someone had encouraged me to keep asking questions. The more you find out the easier it is to understand.' (patient)[4]

4.1 Introduction

Good communication is at the heart of every interaction between people with PD, their carers and health professionals. Issues that need to be considered include:

- style, manner and frequency of communication
- content and means of transmission
- ease of access for those receiving information, and consistency of content
- recognition that people with PD have particular clinical problems requiring carefully and sensitively tailored communication
- communication goals including self-management by people with PD
- involvement of carers.

Communication for people with chronic diseases can be focused on two goals:

- collaborative care in which clinicians are seen as experts in medical conditions, while people with a condition are seen as experts in living with their own condition and are encouraged to identify their problems and define goals.
- self-management education that provides people with problem-solving and management skills for the self-care of a condition.

For people with PD the main objective should be collaborative care, although interventions such as the Expert Patient Programme,[25] which concentrates on self-management, will have a part to play for some individuals. In addition, the NSF for Long-term (Neurological) Conditions (2005),[14] especially Quality requirement 1, which relates to a person-centred service, should underpin the principles of communication with people with PD and their carers.

4.2 Methodology

Six studies[26–31] have addressed communication about the diagnosis of PD. Since there were few RCTs in this area, qualitative studies and cross-sectional studies using questionnaire data collection tools were included. The literature search included the area of self-help in relation to communication and education of people with PD. However, no studies were found which specifically addressed this topic.

Qualitative studies were assigned evidence level 3 in accordance with NICE guidance.[1]

A qualitative study[29,30] using an interpretive phenomenological method identified a number of themes, but did not include a clear audit trail demonstrating how these were derived from the original patient data collected.

A cross-sectional self-report questionnaire study[29,30] collected response data from physiotherapists and occupational therapists who observed video records of patients.

It should be noted that:

- the PROPATH program[26,27] was a pharmaceutically sponsored educational service only available in the USA
- the survey from the Parkinson's Disease Society (PDS)[31] was based on a questionnaire of members in the UK.

The PROPATH program consisted of a disease assessment questionnaire, which was completed by people with PD or their carer. The questionnaire was analysed and computer-generated reports were returned to physicians and individualised recommendation letters returned to people with PD. The questionnaires were analysed by an advisory board of neurologists with broad experience in movement disorders. The reports and recommendation letters were primarily aimed at reducing medication side effects.

4.3 Evidence statements

Two RCTs[26,27] were found, which assessed the effectiveness of the PROPATH education program, as a novel approach to communication with people with PD.

A 6-month follow-up PROPATH study[26] (N=155) showed multiple benefits of the PROPATH intervention which are listed in Table 4.1. (**1+**)

Table 4.1 Effectiveness of PROPATH program versus standard care

Outcome measures (N=322)	**p value**
Rate of disease progression during the program*	0.03
Number of people with PD exercising	0.006
Medical utilisation (in terms of doctor visits)	0.06
Time 'off'	>0.01
Quality-of-life assessment: self-efficacy measure**	
6 months score	<0.05
Total score	<0.01

*Rate of disease progression was calculated by changes in summary score at particular times divided by elapsed time in years. The summary score was an average of on-score and off-score (from Unified Parkinson's Disease Rating Scale (UPDRS)), side-effects index, and patient global assessment.
**Self-efficacy was estimated by a battery of 15 questions, which were assessed on a 0 to 100 horizontal analogue scale.

A separate 12-month follow-up PROPATH study (N=73)[27] observed only one improved clinical outcome in the intervention group: 'patient perception of general health and psychological well-being', which declined in the standard care group (p=0.04). (**1+**)

A multinational Global Parkinson's Disease Survey[28] of people with PD (N=201) and their carers (N=176) assessed what factors affect health-related quality-of-life (HRQL). This study found three factors which had an impact on quality of life and explained 60% of the variability in HRQL between people with PD:

- depression as measured by the Beck Depression Inventory (BDI) ($p<0.001$)
- 'satisfaction with explanation of condition at diagnosis' ($p<0.05$)
- 'feelings of optimism' which may be related to the style and manner of communication, especially at initial diagnosis ($p<0.05$). (**3**)

An interpretative phenomenological study[29] in 16 people with PD identified the theme of 'gaining formal knowledge' and provided the following information on their perspectives:

- Once diagnosed, people with PD identified a need to know more about the condition.
- Information provided at diagnosis was difficult to process by most participants.
- By their own descriptions, they were in 'shock' and did not recall the dialogue between themselves and the diagnosing physicians.
- There were a few exceptions to this and some clearly recalled being given a diagnosis but very little additional information.
- The human significance was passed over and objectified by what is known about the disease and treatment. Self-care and day-to-day coping with the illness were ignored. (**3**)

In a questionnaire study,[30] physiotherapists and occupational therapists (N=91) were asked to compare the video-recorded conversations of people with PD (N=4) and people with cardiac conditions (N=4) without the soundtrack. The aim was for the therapists to gauge their initial impressions of the people seen. The therapists were told the people being interviewed suffered from a neurological disorder, but the clinical diagnosis was not revealed. The video-recorded conversations were of interviews conducted by two doctors each of whom conversed with two individuals from each group using a semi-structured script covering non-medical aspects of the their personal histories. The study found there were significant differences in the ratings for all 15 variables. The therapists observed the people with PD to be:

- more anxious/worried/apprehensive; angry/irritable/hostile; suspicious/unforthcoming; morose/sad/down; bored/detached; tense/ill at ease ($p<0.001$)
- more introverted/shy; anxious/dissatisfied; sensitive/emotional; passive/dependent; less intelligent ($p<0.001$)
- enjoying the conversation less well ($p<0.001$)
- relating less well to the interviewer ($p<0.001$)
- holding up their own end of the conversation less well ($p<0.001$). (**3**)

In addition to their observations, the therapists were asked how likeable the person with PD appeared to them. People with PD appeared less likeable ($p<0.001$). (**3**)

It is worth noting that the people with PD in the above study had mild to moderate symptoms and were leading active lives. The impressions made by the therapists were formed from a short exposure to them on a video recording and therefore have the potential of being modified by further contact and greater knowledge of the individual. These results indicate that negative

impressions may be induced in clinicians by a lack of verbal expressiveness from the person with PD, and this could influence the development of their relationship with their clinician.

Another study[32] (N=1200) assessed patient satisfaction with the educational information they had received (it did not assess the amount of information provided or who provided it). The findings are summmarized as follows.

- The average patient education score indicated that participants were neither particularly satisfied nor dissatisfied with the information they received.
- There was no relation between this score and sex, age or Hoehn and Yahr stage.
- When the analysis included all patients, a higher patient education score was associated with higher HRQL scores in all subscales of the Short Form 36 (SF-36), except for physical function and bodily pain.
- Patients were most satisfied with regard to 'role emotional' and least satisfied with regard to 'general health.'
- After excluding patients with advanced disease (Hoehn and Yahr 4–5), the regression coefficient increased in several subscales (ie patients with less severe disease had better quality-of-life scores), see Table 4.2 for details.
- Scores in all subscales of SF-36 were generally lower in patients with more advanced disease, demonstrating that the disease stage is associated with a decline in HRQL involving all aspects of daily living.
- Motor complications associated with therapy had a substantial affect on each subscale of SF-36. (3)

Table 4.2 Relationship of patient education with SF-36 (regression coefficients of patient education score)

	All patients	Excluding Hoehn and Yahr (stage 4 and 5)
Physical functioning	–0.76	–0.47
Role – physical	3.74*	5.23*
Bodily pain	2.01	0.06
General health	2.10*	1.99
Vitality	3.32*	3.66*
Social functioning	3.04*	4.40*
Role – emotional	4.18*	4.91*
Mental health	2.83*	4.10*

Adjusted for age, sex, number of comorbidities, activities of daily living score, and complications of therapy. The patient education score was 1 for 'not at all satisfied' and 5 for 'very satisfied' with information given. Therefore the difference in subscale score of SF-36 between two extremes was fourfold the number in the table.
*$p<0.05$.

The UK PDS[31] questioned 2,500 of their members from November 1997 to January 1998, regarding communication. Of these members, 1,693 (68%) replied and details of selected responses are given in Table 4.3. (3)

Table 4.3 PDS survey (1999)[31]

Whether the person had PD explained to them on diagnosis (N=1,127)	**(%)**
Very clearly explained	20
Fairly clearly explained	24
Neither clearly nor unclearly explained	9
Not very clearly explained	17
Not at all clearly explained	9
No explanation given	15
Whether people were given an opportunity to ask questions on diagnosis	
Adequate opportunity	28
Fairly adequate opportunity	22
No opportunity at all	15
Did not want/feel able to ask questions at the time	22

How useful people find PD information resources (N=1,693)

	Very useful	**Not very useful**	**Not used/ not available**	**Did not answer**
Hospital doctor/consultant	56	19	14	12
PDS – local branch	40	7	36	17
GP	39	37	13	11
PDS – national office	36	9	36	19
People who have PD or care for someone with PD	36	7	36	21
Newspapers or magazines	32	24	26	19
Pharmacist	25	11	45	19
PDNS	24	3	56	17
Physiotherapist	23	9	50	18
Occupational therapist	19	7	56	19
Television/radio	19	29	32	20
Social services department	18	12	51	18
Speech therapist	16	7	58	19
PDS – field staff (eg area officer)	15	6	57	21

continued

Table 4.3 PDS survey (1999)[31] – *continued*

Subjects on which people need information (N=945)	(%)
New treatments that may be available in future	90
What drugs are available and/or their side effects	84
Specific health problems related to PD	81
How the disease is likely to affect me or the person I care for in the future	75
Aids and equipment and how to get them	49
How PD can affect personal relationships	44
How to get health or social services assistance	41
How to get welfare benefits and financial help	39
How to deal with difficulties in getting services for people with PD from insurance companies, banks, etc.	30
How to find a suitable holiday	29
How to find suitable respite care	26

4.4 From evidence to recommendation

People with PD have to live with the consequences of any clinical decision. Given the nature of the therapies currently available for the condition, there are difficult trade-offs to be made over time between the beneficial therapeutic effects and the short- and long-term adverse consequences of a particular treatment. The choice of initial therapy should aim to optimise the quality of life over the whole expected lifespan of an individual. It is essential that these decisions are specific to an individual and agreed between the person with PD and the appropriate clinicians after a period of reflection including involvement of the family.

The evidence shows that the way in which the diagnosis of PD is communicated is important and often not well done. People with PD may need the information originally given at diagnosis to be repeated and will want more information as the condition progresses. This is one important role that could be carried out by a health professional such as the PDNS (see Chapter 10). No evidence is available on what format this information should best be given in, but a range of products are already available from the UK PDS.

Particular features that need to be taken into account when communicating with people with PD are:

- occurrence of cognitive impairment and depression
- occurrence of a communication impairment (which increases in severity with increasing severity of the disease process)
- negative impression that may be given by a person with PD
- need for emotional support
- involvement of carers.

Effective communication requires well-trained staff and an environment that enables sensitive discussions, as these discussions might lead to emotional distress. The UK PDS recently published guidance about communication with people with PD and their carers.[33] The recommendations arose from a group of 17 people with PD, with ages ranging from 47 to 67, and their carers. The document is shown in Appendix C.

It is important to communicate with carers, particularly when people with PD have cognitive impairment or depression. Carers need:

- general factual information about the condition
- specific information, if permission is given, about the person with PD
- information about services and entitlements to care assessment and support procedures
- advice and support both to optimise the quality of the communication interaction and also to continue effective communication with the person with PD as the condition progresses
- advice and support to maintain their health and well-being.

RECOMMENDATIONS

R1 Communication with people with PD should be aimed towards empowering them to participate in the judgements and choices about their own care. **D**

R2 Discussions should be aimed at achieving a balance between the provision of honest, realistic information about the condition and the promotion of a feeling of optimism. **D**

R3 Because people with PD may develop impaired cognitive ability, a communication deficit and/or depression, they should be provided with:

- both oral and written communication throughout the course of the disease, which should be individually tailored and reinforced as necessary
- consistent communication from the professionals involved. **D (GPP)**

R4 Families and carers should be given information about the condition, their entitlements to care assessment and the support services available. **D (GPP)**

R5 People with PD should have a comprehensive care plan agreed between the individual, their family and/or carers and specialist and secondary healthcare providers. **D (GPP)**

R6 People with PD should be offered an accessible point of contact with specialist services. This could be provided by a Parkinson's disease nurse specialist. **D (GPP)**

R7 All people with PD who drive should be advised to inform the Driver and Vehicle Licensing Agency (DVLA) and their car insurer of their condition at the time of diagnosis. **D (GPP)**

5 Diagnosing Parkinson's disease

'It knocked me for six . . . I became very low . . . I thought it can't be me . . . it's just elderly people who got it.' (patient)[2]

'I found it hard to cope with life . . . I didn't tell anyone . . . I couldn't face the reality of it.' (patient)[2]

5.1 Definition and differential diagnosis

There are many manifestations of PD but the classical diagnostic symptoms are:

- slowness and poverty of movement
- stiffness
- shaking.

The physical signs of PD include:

- slowness of movement (bradykinesia)
- poverty of movement (hypokinesia), eg loss of facial expression and arm swing, difficulty with fine movements
- rigidity
- rest tremor.

At diagnosis, these signs are usually unilateral, but they become bilateral as the disease progresses. Later in the disease additional signs may be present including postural instability (eg tendency to fall backwards after a sharp pull from the examiner: the 'pull test'), cognitive impairment and orthostatic hypotension (OH).

There is no single way to define Parkinson's disease or what is often called idiopathic Parkinson's disease in order to differentiate it from other causes of parkinsonism, such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP).

PD is traditionally defined, pathologically, by the finding of Lewy bodies and degeneration of catecholaminergic neurones at post-mortem. Using a pathological definition of PD is problematic for a number of reasons:

- A pathological diagnosis is not practical in life.
- Lewy body inclusions in catecholaminergic neurones are seen in individuals without clinical evidence of PD; it is presumed that these are pre-clinical cases.
- Lewy bodies have not been found in otherwise typical individuals with PD with Parkin mutations, although such rare young-onset genetic cases of PD might be said not to have idiopathic PD.

In recent years, attempts to define PD genetically have become possible with the discovery of monogenic forms of the disease. However, such families account for a very small proportion of cases.

Another potential way to diagnose PD is using the response to dopaminergic medication. However, this dopaminergic responsiveness can be seen in conditions other than PD such as MSA.

The decline in dopaminergic neurones identified by radionuclide positron emission tomography (PET) or single photon emission computed tomography (SPECT) has also been proposed as a method of defining PD. Unfortunately, this decline is seen in conditions other than PD such as MSA and PSP.

Given these difficulties, it is generally accepted that the diagnosis of PD should be based on clinical findings. The most widely accepted clinical criteria for the diagnosis of PD are those introduced by the UK PDS Brain Bank Criteria (Table 5.1).[35]

It is important to make an accurate diagnosis in a person with suspected PD as this has an important bearing on prognosis. People with PD will have a longer life expectancy than those with MSA or PSP and will respond better to dopaminergic medication.

PD must also be differentiated from other conditions presenting with tremor (Table 5.2). This can be particularly difficult as PD can present with a postural and action tremor similar to that seen in essential tremor.

In addition, PD must be differentiated from other causes of a parkinsonian syndrome or parkinsonism (Table 5.3). The most common problems arise with multiple cerebral infarction and degenerative parkinsonian syndromes such as MSA and PSP. Differential diagnosis can also be difficult in elderly people since extrapyramidal symptoms and signs are common.[34]

Table 5.1 UK PDS Brain Bank Criteria for the diagnosis of PD[35]

Step 1. Diagnosis of a parkinsonian syndrome

Bradykinesia and at least one of the following:
- muscular rigidity
- rest tremor (4–6 Hz)
- postural instability unrelated to primary visual, cerebellar, vestibular or proprioceptive dysfunction.

Step 2. Exclusion criteria for PD

History of:
- repeated strokes with stepwise progression
- repeated head injury
- antipsychotic or dopamine-depleting drugs
- definite encephalitis and/or oculogyric crises on no drug treatment
- more than one affected relative
- sustained remission
- negative response to large doses of levodopa (if malabsorption excluded)
- strictly unilateral features after 3 years
- other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with disturbances of language, memory or praxis
- exposure to known neurotoxin
- presence of cerebral tumour or communicating hydrocephalus on neuroimaging.

Step 3. Supportive criteria for PD

Three or more required for diagnosis of definite PD:
- unilateral onset
- rest tremor present
- progressive disorder
- persistent asymmetry affecting the side of onset most
- excellent response to levodopa
- severe levodopa-induced chorea
- levodopa response for over 5 years
- clinical course of over 10 years.

Table 5.2 Common causes of tremor
Rest tremor
Parkinson's disease
Postural and action tremor
Essential tremor
Exaggerated physiological tremor
Hyperthyroidism
Drug-induced (eg β-agonists)
Dystonic tremor
Intention tremor
Cerebellar disorders

Table 5.3 Causes of a parkinsonian syndrome
Parkinson's disease
Alzheimer's disease
Multiple cerebral infarction
Drug-induced parkinsonism (eg phenothiazines)
Other degenerative parkinsonian syndromes:
• progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome)
• multiple system atrophy (previously Shy–Drager syndrome, olivopontocerebellar atrophy and striatonigral degeneration)

RECOMMENDATION

R8 PD should be suspected in people presenting with tremor, stiffness, slowness, balance problems and/or gait disorders. **D (GPP)**

5.1.1 Methodological limitations of the diagnostic studies

When interpreting the literature about PD diagnosis, the following methodological issues should be considered:

- lack of long-term prospective clinical and pathological follow-up as a reference standard
- lack of operational definitions such as defining specialists or clinical diagnostic criteria
- unclear whether investigators were blinded to initial diagnosis
- sample sizes necessarily limited by the number of cases available with neuropathological outcomes
- PD trial age groups are often young as studies were performed by neurologists who see a younger population of people with PD
- most studies included people with established disease lasting some years
- varying geographical locations

- some studies are in specialised units and may not reflect the diagnostic accuracy of other units in the UK
- exclusion of some studies using magnetic resonance volumetry and magnetic resonance spectroscopy (MRS) as they lacked appropriate population, intervention and outcome criteria
- lack of statistical details of diagnostic accuracy such as sensitivity, specificity and positive predictive values
- lack of economic evaluations of SPECT.

5.2 Clinical versus post-mortem diagnosis

Most experienced specialists have adopted the UK PDS Brain Bank Clinical Criteria (Table 5.1) for the diagnosis of PD.

How do these compare with the accuracy of pathological diagnosis?

5.2.1 Methodology

Three diagnostic studies were found that assessed the accuracy of clinical diagnosis in parkinsonism compared with autopsy.[36–38] These studies compared clinical diagnosis, at various stages of disease progression, to a final diagnosis including details of autopsy findings. The clinical diagnosis was determined using the UK PDS Brain Bank Criteria (Table 5.1) in two of three studies.[37,38] A third study determined a diagnosis of PD when at least two of the three cardinal signs (bradykinesia, rigidity and resting tremor) were present.[36]

5.2.2 Evidence statements

Two studies (N=59[36] and N=100[37]) examined people with a terminal diagnosis of PD and found the frequency of people misdiagnosed with PD (ie they did not meet the pathological criteria at post-mortem) was 35% and 24% respectively.[36,37] When recommended diagnostic criteria (UK PDS Brain Bank) were retrospectively applied, diagnostic accuracy increased from 70% to 82%.[37] (**DS II**)

A more recent UK PDS Brain Bank study[38] examined the brains of 143 people with parkinsonism. These people had previously been seen by a neurologist, with five dedicated movement disorder specialists seeing 92% of the cases, and been given a clinical diagnosis of PD or alternative parkinsonian condition. The clinical diagnosis was later revised in 44 of 122 cases where full follow-up information was available after a mean of 3.4 (range 0.5–12) years. The sensitivity of the final PD clinical diagnosis was 91%, a specificity of 98% and a positive predictive value of 99% (72 out of 73 correctly diagnosed). (**DS II**)

5.2.3 From evidence to recommendation

The pathological studies emphasise the need for particular care in making a clinical diagnosis of PD. There is limited evidence to suggest that the UK PDS Brain Bank Criteria have adequate sensitivity and specificity in comparison with post-mortem findings. The accuracy of diagnosis using the Brain Bank criteria increases as the condition progresses.

The availability of PD brain tissue has fostered much valuable research in recent years and should be encouraged in the future. Diagnostic information derived from post-mortem examination can also be of value to the families of individual patients.

RECOMMENDATIONS

R9 PD should be diagnosed clinically and based on the UK Parkinson's Disease Society Brain Bank Criteria. **B (DS)**

R10 Clinicians should be encouraged to discuss with patients the possibility of tissue donation to a brain bank for purposes of diagnostic confirmation and research. **D (GPP)**

5.3 Expert versus non-expert diagnosis

The diagnosis of PD could be made in primary care by the person's GP or in secondary care by a neurologist, geriatrician or general physician. More recently, PDNSs and other health professionals are developing diagnostic skills. Each may have different levels of expertise in evaluating people with possible PD.

What is the evidence that someone with special expertise is more accurate in diagnosing PD than someone with little experience?

5.3.1 Methodology

Four diagnostic studies[39–42] were found looking at the accuracy of PD diagnosis in a community-based population. The specialist diagnosis was based on the UK PDS Brain Bank criteria in four of the studies.[39,40,42] In one study[41] the expert diagnosis was based on the investigator's confidence in the diagnosis of PD, presence of atypical features, findings of imaging studies, response to levodopa and results of autopsy examinations. The criteria for the initial diagnoses were not specified in any of the trials. These studies were also performed on prevalent rather than incident PD populations.

5.3.2 Evidence statements

One study[39] (N=126) assessed the diagnostic accuracy of neurologist and geriatrician clinical expert diagnosis versus existing clinical diagnosis of parkinsonism from medical records by a non-expert clinician. The standard for comparison was diagnosis according to strict clinical diagnostic criteria (the UK PDS Brain Bank Criteria) after a detailed neurological interview and examination. The study found that neurologists and geriatricians had a sensitivity of 93.5% (95% CI 86.3 to 97.6) and specificity of 64.5% (95% CI 45.4 to 80.8) compared with 'non-specialist'

sensitivity of 73.5% (95% CI 55.6 to 87.1) and specificity of 79.1% (95% CI 64.0 to 90.0) for diagnostic accuracy. While the positive predictive value of specialists was greater than for other doctors, negative predictive values were equivalent. (**DS II**)

Another study[40] applied the UK PDS Brain Bank criteria to 402 cases derived from a computerised list of people with PD receiving anti-parkinsonian medication from 74 general practices in North Wales. In 59% of cases, the GP made the initial diagnosis of PD. The people with PD were seen either at home or in a specialist movement disorder clinic where a neurological examination was performed. A definite PD diagnosis was made in 53% of all cases, thus the error rate in the community-ascertained cases was 47%. (**DS II**)

DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) was a large, multi-site clinical trial[41] in the USA and Canada involving 800 people with early-stage PD who were cared for by 34 investigators with a major interest in movement disorders. A secondary analysis examined the number of people with PD with a change in diagnosis after a mean follow-up of 6 years. The study showed that only 8% had a revised diagnosis. The revised diagnosis was clinical and not based on strict criteria or pathology. (**DS II**)

The UK-PDRG study,[42] which investigated the long-term effectiveness of bromocriptine, selegiline and levodopa therapy, found a total of 49/782 people with PD (6%) had their diagnosis changed during the course of the trial. Individuals were eligible for inclusion in the study if they fulfilled criteria for a clinical diagnosis of PD. The authors do not state whether the revised diagnosis was made by one of the specialists performing the study, although this is likely. The authors also do not state whether a specialist or non-specialist conducted the initial diagnostic examination. (**DS II**)

5.3.3 From evidence to recommendation

These studies provide only circumstantial evidence on the diagnostic ability of experts versus non-experts. However, they show that the diagnosis of PD is wrong in around 47% of community-ascertained cases, 25% of non-expert secondary care diagnosed cases, and 6–8% of cases diagnosed by an expert in movement disorders.

Since medication can mask the symptoms and signs of PD, the GDG felt that people with suspected PD should be referred before treatment is commenced. This can be achieved only if people are seen quickly by experts, for an accurate diagnosis and commencement of treatment, if necessary.

The GDG also had experience that delay in making an accurate diagnosis can lead to psychological stress for the patient and their carer. Similarly, the need to revise an incorrect diagnosis that has, initially, been made by a non-expert can be stressful for patients.

The GDG acknowledges the timeline that the Department of Health and NHS are currently working towards for completion of diagnosis and treatment (18-week target). However, the GDG felt that in the case of PD it should not necessarily mean that patients would have to 'start' treatment within 18 weeks from GP referral but rather that this was when a 'treatment decision' was made for initial consultation and diagnosis.

RECOMMENDATION

R11 People with suspected PD should be referred quickly* and untreated to a specialist with expertise in the differential diagnosis of this condition. **B (DS)**

5.4 Review of diagnosis

Given the error rate in making a diagnosis of PD, even in expert hands, it is apparent that the diagnosis should be kept under regular review.

What is the most appropriate frequency of follow-up after an initial diagnosis of PD?

5.4.1 Methodology

No trials were found which addressed the most appropriate frequency of follow-up of people with PD.

5.4.2 Evidence statements

No evidence was found on the most appropriate frequency of follow-up after the initial diagnosis of the disease.

5.4.3 From evidence to recommendation

In the absence of any evidence on the issue of frequency of follow-up, the GDG concluded that this should be based on clinical priority. In people with early mild symptoms of PD who may not even be on treatment yet, follow-up to check on the diagnosis and the need for treatment may be infrequent (every 6–12 months). Once treatment is commenced, follow-up may need to be more frequent (every 2–3 months) to assess the response to medication, titrate dosage and re-visit the diagnosis. In later disease, people with PD have more complex problems which require changes in medication. This may require review at frequent intervals (every 2–3 months).

RECOMMENDATION

R12 The diagnosis of PD should be reviewed regularly** and reconsidered if atypical clinical features develop. **D (DS)**

*The GDG considered that people with suspected mild PD should be seen within 6 weeks, but new referrals in later disease with more complex problems require an appointment within 2 weeks.

**The GDG considered that people diagnosed with PD should be seen at regular intervals of 6–12 months to review their diagnosis.

5.5 Single photon emission computed tomography

In single photon emission computed tomography (SPECT), a gamma ray-emitting radioactive isotope is tagged to a molecule of interest (a tracer), which is given to the person with PD by intravenous injection. The labelled cocaine derivatives ^{123}I-β-CIT and ^{123}I-FP-CIT (N-ω-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)tropane) have most commonly been used, although only the latter is licensed in the UK. These label the presynaptic dopamine re-uptake site and thus the presynaptic neurone, which can be visualised in two-dimensional images. These demonstrate normal uptake in the caudate and putamen in controls and in people with essential tremor, neuroleptic-induced parkinsonism or psychogenic parkinsonism, but reduced uptake in those with PD, PD with dementia, MSA or PSP.

How useful is SPECT in discriminating PD from alternative conditions?

5.5.1 Methodology

Fifteen studies addressed the diagnostic accuracy of SPECT scanning.[43–58] The reference standard was clinical diagnosis: eight out of the 16 studies[43,45–51] used the UK PDS Brain Bank Criteria, five studies[44,52–55] used 'established' clinical criteria and three studies[56–58] did not state the clinical criteria used to determine the diagnosis. Although many tracers are listed in the evidence statements, only ^{123}I-FP-CIT is licensed for use in the UK. The ^{123}I-β-CIT studies were included as it has a similar structure and labels the same receptors as the ^{123}I-FP-CIT tracer. The GDG agreed that this evidence is supportive of ^{123}I-FP-CIT studies and provides a consistency of effect.

5.5.2 Health economic methodology

Only one study met quality criteria that addressed the economic evaluation of SPECT.[59] This study was based on ^{123}I-FP-CIT SPECT effectiveness data, specificity and sensitivity of clinical examination and prevalence of PD were based predominantly on UK data. However, costs were based on German 2002 data.[59]

5.5.3 Evidence statements

For the differentiation of people with parkinsonism (ie PD, MSA or PSP) from people with essential tremor or controls using SPECT, all studies produced a high sensitivity (range 87% to 98.3%) and specificity (range 80% to 100%).[43,45,49,52,53] A summary of the evidence produced in these five studies is provided in Table 5.4 and Table 5.5. (**DS Ib**)

Three studies (N=80,[47,48,54] N=17,[47,48,54] N=183[47,48,54]) attempting to differentiate PD from other parkinsonian conditions (eg MSA, PSP) had insufficiently high levels of sensitivity (range 77% to 97%) and specificity (range 75% to 83%).[47,48,54] (**DS Ib**)

One study[58] found, by comparing the ^{123}I-β-CIT SPECT imaging diagnosis for people with parkinsonian syndrome with a clinical diagnosis (based on 6 months' follow-up), that there was disagreement between only three out of 35 cases (8.6%) with visual diagnosis and two out of 35 cases (5.7%) with quantitative imaging diagnosis. (**DS Ib**)

Table 5.4 Diagnostic accuracy of SPECT imaging: differentiation of tremulous disorders

Test	Number of participants		Sensitivity (%)	Specificity (%)	Grade
^{123}I-FP-CIT SPECT (institutional read)[45]	158 PD	27 ET	97	100	Ib
^{123}I-FP-CIT SPECT (consensus read)[45]	Same as above		95	93	Ib
^{123}I-FP-CIT SPECT[43]	38 PD	38 Non-PD	87	–	Ib
^{123}I-β-CIT SPECT [49]	60 PD and PSP	36 ET and controls	98	83	Ib
^{123}I-β-CIT SPECT: Striatum/cerebellum and putamen/ cerebellum binding ratio factors[52]	29 PD	62 controls and ET	98.3	–	Ib
	29 PD	32 ET	96.7		
^{123}I-β-CIT SPECT: Visual imaging analysis[58] Visual imaging analysis[58]	35 suspect PD		96	80	Ib
^{123}I-β-CIT SPECT: Quantitative imaging analysis[58]	Same as above		90	100	Ib

Institutional read = visual assessment of ^{123}I-FP-CIT striatal uptake by investigator blinded to clinical diagnosis. Consensus read = hard-copy images – agreement from three or more of the five panel members.
PD = parkinsonian syndrome; PSP = progressive supranuclear palsy; ET = essential tremor.

Table 5.5 Diagnostic accuracy of SPECT imaging: differentiation of PD and controls

Test	Number of participants		Sensitivity (%)	Specificity (%)	Grade
	PD	Controls			
^{123}I-β-CIT SPECT: Striatum/cerebellum binding ratio alone[52]	29	32	94.9	–	Ib
^{123}I-FP-CIT SPECT: Binding index in putamen contralateral to initially clinically affected side[50]	76	20	95	86	II
TRODAT-1 SPECT: Binding index in putamen contralateral to initially clinically affected side[50]	Same as above		92	70	II
TRODAT-1 SPECT: Logistic discriminant parametric mapping[53]	42	23	100	95	II
TRODAT-1 SPECT: Visual inspection[55]	188	45	98	86	Ib
TRODAT-1 SPECT: Quantitative analysis[55]	Same as above		98	88	Ib
TRODAT-1 SPECT: Contralateral putamen/occipital and contralateral putamen/caudate[57]	78	40	100	100	II
TRODAT-1 SPECT: Quantitative imaging analysis. Mean uptake in ipsilateral and contralateral posterior putamen[51]	29	38	0.79	0.92	II

TRODAT-1 = selective dopamine transporter technetium-99m labelled.
Logistic discriminant parametric mapping = technique to distinguish sets of data with maximum accuracy.

5.5.4 Health economic evidence statements

The economic findings indicated:[59]

- SPECT has greater sensitivity but costs more than clinical examination
- SPECT should not be used in all people with PD in place of initial clinical examination
- SPECT could be used to avoid the costs of treating people who do not suffer from PD.

For approximately an additional €733 in Euro 2002 (approximately £511), for the equivalent of a patient-month with adequate treatment, SPECT could be used to confirm a PD diagnosis in people with a positive clinical examination before the initiation of treatment.[59] Adequate treatment month equivalents (ATME) were used to reflect both duration of adequate treatment and severity of incorrect treatments. The authors indicated that a 0.55 ATME gain per patient is equivalent to approximately 17 additional days of treatment to a PD patient or withholding approximately 2 days of treatment and side effects to a patient who does not have PD.

The specificity of clinical examination and frequency of PD in the clinic population of PD had the greatest relative impact on the incremental cost-effectiveness ratio (ICER) of SPECT following positive clinical examination compared with clinical examination alone. In the sensitivity analysis, when the specificity of clinical examination is reduced to 0.80 (from 0.984) the ICER drops to €63 (approximately £44).[59] This suggests that as more non-PD cases are incorrectly classified as PD cases in clinical examination, the greater the cost-effectiveness of SPECT. When the frequency of PD in the clinic population is increased to 74% (from 53%) the ICER increases to €2,411 (approximately £1,697).[59] This suggests that the cost-effectiveness of SPECT decreases when the frequency of PD in the clinic population increases. In these populations, there may be fewer false-negative results and therefore fewer people incorrectly being treated for PD. This would mean there are fewer cost-savings from withholding incorrect treatment and therefore an increase in the relative cost-effectiveness of SPECT.

5.5.5 From evidence to recommendation

Considerable evidence supports the use of ^{123}I-FP-CIT SPECT in people with postural and/or action tremor of the upper limbs in the differentiation of essential tremor from a dopaminergic deficiency state. ^{123}I-FP-CIT SPECT cannot, with high accuracy, differentiate PD from other dopaminergic deficiency states such as MSA and PSP. Future work may demonstrate the value of this technique in differentiating parkinsonism due to neuroleptic medication and psychogenic parkinsonism from a dopaminergic deficiency state.

Several clinical trials using SPECT or PET to follow the progression of PD found that 4%,[60] 11%[61] and 14%[62] with a clinical diagnosis of PD had normal imaging at the start of the trial. Further long-term clinical follow-up of these people is required.

Due to the subjectivity of the effectiveness measurement, the GDG decided the economic study[59] does not support or refute the clinical recommendations. Further development of comparable effectiveness outcomes in diagnostic economic evaluations is required.

RECOMMENDATIONS

R13 ^{123}I-FP-CIT SPECT should be considered for people with tremor where essential tremor cannot be clinically differentiated from parkinsonism. **A (DS)**

R14 ^{123}I-FP-CIT SPECT should be available to specialists with expertise in its use and interpretation. **D (DS)**

5.6 Positron emission tomography

In positron emission tomography (PET), a positron-emitting radioactive isotope is tagged to a tracer molecule, which is administered by intravenous injection. The most frequently used positron-emitting isotope in this field is ^{18}fluorine, which is attached to dopa or deoxyglucose. ^{18}F-fluorodopa is taken up by the presynaptic dopaminergic neurones of the caudate and putamen (corpus striatum). ^{18}F-fluorodeoxyglucose (FDG) is taken up by all metabolically active cells and phosphorylated to a metabolite, which is trapped in the tissue for the time course of the study.

How valuable is PET in the differential diagnosis of parkinsonism?

5.6.1 Methodology

Six diagnostic studies[63–68] were found which addressed the effectiveness of PET scanning compared with clinical diagnosis in the differential diagnosis of a parkinsonian syndrome. No studies were found which compared the effectiveness of PET in the differentiation of PD from essential tremor.

5.6.2 Evidence statements

In one study[68] the diagnostic accuracy of ^{18}F-desmethoxy-fallypride PET imaging for the differential diagnosis of atypical (N=16) versus idiopathic (N=16) parkinsonian syndromes showed a threshold value of 2.495 (caudate uptake ratio). The sensitivity, specificity and accuracy were 74%, 100% and 86% respectively. Using this threshold, the positive and negative predictive values for the diagnosis of atypical parkinsonian syndromes were 100% and 76%. **(DS Ib)**

In one study[67] the multi-diagnosis group discriminate analysis from ^{18}F-FDG PET scan images found sensitivity of 75% and specificity of 100% in the PD group (N=8), sensitivity of 100% and specificity of 87% in the MSA group (N=9), and sensitivity of 86% and specificity of 94% in the PSP group (N=7). **(DS II)**

One study,[69] using ^{18}F-FDG uptake, reported 74% of all participants (early PD (N=15), atypical PD (N=9) and controls (N=15)) were correctly classified when regional cerebral glucose metabolism (rCMRGIc) was analysed. This diagnostic accuracy increased to 95% using topographical profile rating, which is a method for calculating participant scores for abnormal regional metabolic co-variance patterns in individual people with PD. (**DS II**)

One study (N=90),[63] using ^{18}F-fluorodopa uptake, found people with clinically diagnosed PD were correctly classified by PET in 64% of the cases and those with atypical parkinsonism (MSA or PSP) in 69% of the cases. (**DS II**)

In another study[70] the probability of the correct diagnosis by ^{18}F-fluorodopa PET was ≥99% for the majority of people with PD (40/41) and controls (26/28). (**DS II**)

5.6.3 From evidence to recommendation

PET has better spatial resolution than SPECT, so it might be anticipated that PET should be of value in differential diagnosis. However, the evidence for PET's role in differentiating PD from other parkinsonian conditions using FDG requires further confirmation. No work was found on PET's ability to differentiate PD from essential tremor. This lack of evidence stems from the high cost and poor availability of PET. Further research is required in this area.

RECOMMENDATIONS

R15 PET should not be used in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials. **B (DS)**

5.7 Magnetic resonance imaging

Structural magnetic resonance imaging (MRI) provides two- and three-dimensional images of intracranial structures using high magnetic field strengths to excite the hydrogen atoms in water molecules. In PD this technique has been used to examine various structures known to be involved in the pathology of the condition in the hope that it may prove of value in differential diagnosis.

How useful is structural MRI in the differential diagnosis of parkinsonian conditions and essential tremor?

5.7.1 Methodology

Eight diagnostic studies[64,66,71–76] were found which addressed the effectiveness of MRI compared with long-term clinical follow-up in diagnosing people with a parkinsonian syndrome. Various MRI scanning sequences were used.

5.7.2 Evidence statements

Seven of these studies[64,71–76] provided diagnostic accuracy data for MRI using various techniques. The results are summarised in Table 5.6.

Table 5.6 Diagnostic accuracy of MRI

Technique	Participants (N)	Sensitivity (%)	Specificity (%)	Grade
Abnormal putaminal T2 hypointensity[71,72,74]	MSA-P (24) versus PD (27)	87.5	88.89	DS Ib
Proton density putaminal hyperintensity[71,72,74]	Same as above	83.3	100	
T1 MRI: midbrain superior profile[75,76]	PD (27) versus PSP (25)	68	88.8	
T1 MRI: midbrain atrophy[75,76]	Same as above	68	77.7	DS Ib
T2 MRI: tegmental hyperintensity[75,76]	Same as above	28	100	
Putaminal T2 hypointensity and T2 hyperintensity combined[73,74,76]	MSA (28) versus PD (32)	32	100	
Putaminal T2 hypointensity and T2 hyperintensity combined[73,74,76]	MSA (28) versus PSP (30)	32	93	
Putaminal T2 hypointensity and T2 hyperintensity combined[73,74,76]	MSA (28) versus CBD (26)	32	85	DS II
Overall MRI abnormalities[73,74,76]	PD (32) versus MSA (28)	71	91	
Overall MRI abnormalities[73,74,76]	PD (32) versus PSP (30)	70	91	
Overall MRI abnormalities[73,74,76]	PD (32) versus CBD (26)	92	91	
T1 MRI: voxel-based morphometry of cerebral peduncles and midbrain[74–76]	PSP (12) versus PD (12) and controls (12)	83	79	DS II
Diffusion-weighted MRI Putaminal rADC[64]	MSA-P (10) versus PD (11)	100	100	
Diffusion-weighted MRI Putaminal hyperintense rim[64]	Same as above	80	91	DS II
Diffusion-weighted MRI Putaminal atrophy[64]	Same as above	60	100	
Diffusion-weighted MRI Putaminal rADC[72,73,75]	PSP (10), PD (13) and MSA-P (12) versus clinical diagnosis	96	100	DS II

rADC = regional apparent diffusion coefficient; PSP = progressive supranuclear palsy; MSA-P = multiple system atrophy parkinsonian type; MSA-C = multiple system atrophy cerebellar type; CBD = corticobasalganglionic degeneration.

Another study[66] found non-concordance between neuroradiological diagnosis and clinical diagnosis in 2/21 people with PD, 5/14 people with MSA-P and 1/4 people with MSA-C. (**DS II**)

One study[75] reported only 15% of people with PD and 24% of those with PSP had abnormal T2 hypointensity in the posterolateral putamen and none had abnormal putaminal proton density hyperintensity. (**DS Ib**)

One study[74] found two false negatives in the PSP group (one had a diagnosis of clinically probable PSP and one clinically definite PSP) and five false positives (two were non-diseased controls and three had a diagnosis of PD). (**DS II**)

5.7.3 From evidence to recommendation

In expert hands structural MRI has proved of some value in differentiating PD from other types of parkinsonism, but further research is required before it can be recommended in routine clinical practice.

RECOMMENDATIONS

R16 Structural MRI should not be used in the differential diagnosis of PD. **B (DS)**

R17 Structural MRI may be considered for the differential diagnosis of parkinsonian syndromes. **D (DS)**

5.8 Magnetic resonance volumetry

Magnetic resonance volumetry uses the same principles as structural MRI to measure the size of three-dimensional volumes of tissue. This technique has been used to examine the size of various structures involved in the pathology of PD.

Can magnetic resonance volumetry be used in the differential diagnosis of parkinsonism?

5.8.1 Methodology

Two studies[76,77] addressed the diagnostic effectiveness of magnetic resonance volumetry against retrospective clinical diagnosis in determining an accurate diagnosis in people with parkinsonian syndrome.

5.8.2 Evidence statements

One study[77] (N=61) found no differences between people with PD and controls on any of the magnetic resonance volume measures. However, individuals with PSP were distinguished from people with PD and controls with a sensitivity of 95.2% and a specificity of 90.9% (mainly due to frontal grey matter volume measure). **(DS Ib)**

Another study[76] (N=53) found that mean superior cerebellar peduncle volume atrophy on visual image analysis differentiated PSP from PD, MSA and controls with a sensitivity of 74% and a specificity of 94%, whereas in quantitative analysis the best sensitivity and specificity of the volumetric analysis were 74% and 77%. **(DS II)**

5.8.3 From evidence to recommendation

While two studies suggest that volumetric MRI can help in the differentiation of PD from other types of parkinsonism, further work is required before it can be recommended.

RECOMMENDATION

R18 Magnetic resonance volumetry should not be used in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials. **D (DS)**

5.9 Magnetic resonance spectroscopy

Proton MRS measures the concentrations of intermediary metabolites in small volumes of brain tissue. N-acetylaspartate is found in the highest concentration in neurones and their processes, whereas creatine is a marker of energy status and choline is an indicator of membrane synthesis and degradation.

Can MRS be helpful in the correct diagnosis of parkinsonism?

5.9.1 Methodology

A systematic review[78] of mixed study designs assessed the diagnostic accuracy of MRS against a clinical diagnosis of a range of parkinsonian syndromes.

5.9.2 Evidence statements

The review[78] concluded that due to the heterogeneous nature of the available evidence no comments on the variability in metabolite concentrations and ratios between people with parkinsonian disorders could safely be made. **(DS II)**

5.9.3 From evidence to recommendation

Contradictory results have been found on the value of MRS in differentiating PD from controls and other types of parkinsonism.

RECOMMENDATION

R19 Magnetic resonance spectroscopy should not be used in the differential diagnosis of parkinsonian syndromes. **B (DS)**

5.10 Acute levodopa and apomorphine challenge tests

Many people with PD respond to single doses of oral levodopa and/or subcutaneous apomorphine.

Can such responses be assessed using clinical rating scales to provide a diagnostic test for PD?

5.10.1 Methodology

A systematic review[79] and an additional diagnostic study[80] addressed the effectiveness of acute levodopa and apomorphine testing in determining an accurate diagnosis of people with a parkinsonian syndrome. Another review[81] published prior to the included systematic review[79] was excluded because it summarised the same papers.

5.10.2 Evidence statements

The systematic review[79] included 13 studies, four of which examined people with de novo PD and nine others which examined people with well-established PD and with other parkinsonian syndromes. These two groups are presented separately in Table 5.7 and Table 5.8. The diagnostic study[80] followed people with PD for 3 years to investigate whether an acute challenge of carbidopa/levodopa had better diagnostic accuracy compared with the acute apomorphine challenge test. These results are also included in Table 5.8.

The systematic review used logistic regression analysis to determine whether there was a significant difference between the three tests for the misclassification of participants. Two studies[82,83] demonstrated no significant difference between the acute apomorphine challenge test and chronic levodopa therapy. However, two other studies[82,84] provided evidence that there was a difference between the acute levodopa challenge test and chronic levodopa therapy, in favour of chronic levodopa ($p<0.001$). (**DS II**)

The diagnostic study[80] commented on the adverse reactions to acute apomorphine challenges. Drowsiness, nausea, vomiting, hypotension and sweating were reported to such an extent that these effects prevented an increased dosage in some people with PD. Levodopa was better tolerated than apomorphine, with vomiting and nausea still occurring, but infrequently. No statistics were provided on whether the better tolerance of the levodopa challenge over the apomorphine challenge was significant. (**DS III**)

Table 5.7 Diagnostic accuracy of acute apomorphine and levodopa challenge testing in *de novo* PD cases[79]

Test	(N)	Positive predictive value (95% confidence interval)	Grade
Acute apomorphine (1.5–5 mg)	187	0.63 (95% CI 0.56 to 0.70)	DS II
Acute levodopa (125–275 mg)	67	0.69 (95% CI 0.59 to 0.80)	
Chronic levodopa (<1000 mg)	209	0.76 (95% CI 0.70 to 0.82)	

5.10.3 From evidence to recommendation

The evidence demonstrates that acute challenge tests with levodopa and apomorphine add nothing to standard chronic levodopa therapy in the differentiation of established cases of PD from other causes of parkinsonism. Furthermore, when used in the early stages of the disease, as they would be in clinical practice, acute challenges with levodopa and apomorphine are less discriminatory than the standard practice of treating people with levodopa as outpatients. This does not preclude the use of acute apomorphine challenges to assess whether a person with later PD will still respond to dopaminergic medication.

Table 5.8 Diagnostic accuracy of acute apomorphine and levodopa challenge testing in established PD cases[79,80]

Test	(N)		Sensitivity (%) (95% confidence interval)	Specificity (%) (95% confidence interval)	Grade
	PD	Non-PD			
Acute apomorphine 0.7–10 mg[79]	236	126	86 (95% CI 0.78 to 0.94)	85 (95% CI 0.74 to 0.96)	DS II
Acute levodopa 275 mg[79]	135	39	75 (95% CI 0.64 to 0.85)	87 (95% CI 0.77 to 0.97)	
Chronic levodopa <1000 mg[79]	155	47	91 (95% CI 0.85 to 0.99)	77 (95% CI 0.61 to 0.93)	
Acute carbidopa/ levodopa 250/25 mg[80]	83	51	77.1	71.7	DS III
Acute apomorphine	83	51			
1.5 mg[80]			70.5	65.9	
3 mg[80]			76.5	63.9	
4.5 mg[80]			76.5	66.7	

RECOMMENDATION

R20 Acute levodopa and apomorphine challenge tests should not be used in the differential diagnosis of parkinsonian syndromes. **B (DS)**

5.11 Objective smell testing

Around 80% of people with PD may have an impaired sense of smell (hyposomia).[85]

Since smell can be objectively tested with a battery of different odours, is it possible that objective smell identification may be useful in PD differential diagnosis?

5.11.1 Methodology

We found six diagnostic studies looking at the effectiveness of smell testing in PD differential diagnosis. Two techniques were employed: the 'Sniffin Sticks' test[86] and the University of Pennsylvania Smell Identification Test (UPSIT). The tests were used to differentiate parkinsonian syndromes[86–88] and people with PD from healthy controls.[85,89,90]

5.11.2 Evidence statements

A separate summary of the five diagnostic accuracy studies is listed in Table 5.9 and Table 5.10. One study[90] found the discriminatory test scores decreased as a function of age for each of the participant groups and that, on average, lower UPSIT scores are needed to clinically define PD in males than in females. (**DS II**)

Another study[89] reported that of the 40 odorants in the UPSIT test, the combined smell of pizza and wintergreen was the best discriminator. In addition, pizza (oregano smell) alone specifically indicates anosmia for people with PD with a very high sensitivity and specificity (Table 5.10). (**DS II**)

A third study[85] found abnormal olfactory function in 82% of the PD participants tested compared with 23% of controls. (**DS II**)

Table 5.9 Diagnostic accuracy of smell-testing techniques in differentiating parkinsonian syndromes

Technique	Groups (N)	Mean age (years)	Disease duration (years)	Cut-off score	Sensitivity (%)	Specificity (%)	Grade
'Sniffin Sticks'[86]	PD (7) versus MSA (8)	57.7	5.8	19.5 24.8	78 100	100 63	DS Ib
UPSIT test[87]	PD (118) versus MSA (29), PSP (15) and CBD (7)	59.4 63.7	–	25	77	85	DS III
UPSIT test[91]	PD (18) versus VP (14)	70.6 74.1	9.1 6.6	>22	85.7	88.9	DS II
UPSIT test[91]	PD (NR) versus VP (8)	65–75	–	≤23	100	85.7	DS II
UPSIT test[91]	PD (NR) versus VP (6)	76–88	–	≤22	85.7	80	DS II

VP = vascular parkinsonism; NR = not reported.

Table 5.10 Diagnostic accuracy of smell-testing techniques in differentiating parkinsonian syndromes from non-parkinsonian syndromes

Technique	Groups (N)	Mean age (years)	Disease duration (years)	Cut-off score	Sensitivity (%)	Specificity (%)	Grade
B-SIT test[85]	PD (49) versus control (52)	68 71	5	–	82	82	DS II
UPSIT test[90]	Male: PD (52) versus controls (76)	61 to 70	5 (3 months-48 years)	25	81	82	DS II
UPSIT test[90]	Female: PD (20) versus control (104)	61 to 70	See above	30	80	88	DS II
UPSIT test[90]	Male: PD (32) versus controls (128)	≤60	See above	31	91	88	DS II
UPSIT test[90]	Female: PD (28) versus control (112)	≤60	See above	33	79	85	DS II
UPSIT test[90]	Male: PD (25) versus controls (100)	≥71	See above	22	76	78	DS II
UPSIT test[90]	Female: PD (23) versus control (92)	≥71	See above	25	78	82	DS II
Pizza and wintergreen[89]	IPD (96) versus controls (96)	62	Not stated	NA	90	86	DS II
Pizza (oregano smell) only[89]		45.6			76	90	DS II

5.11.3 From evidence to recommendation

Objective smell testing has a moderate sensitivity and specificity in differentiating people with PD from controls. However, there are few data on its ability to differentiate PD from other parkinsonian syndromes. Smell is also diminished in Alzheimer's disease.[92] At present, smell identification adds little in the differential diagnosis of parkinsonism but this situation may change with further research.

RECOMMENDATION

R21 Objective smell testing should not be used in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials. **B (DS)**

6 Neuroprotection

6.1 Definitions

Neuroprotection is a process in which a treatment beneficially affects the underlying pathophysiology of PD (Figure 6.1). This definition is preferred to 'disease-modifying therapy' since the latter may encompass processes, which lead to modification of clinical outcomes without any effect on the underlying pathophysiology of the condition. Good examples of this are drugs that delay the onset of motor complications in PD, such as dopamine agonists. This outcome is not necessarily due to a neuroprotective effect; it may arise from a variety of pharmacokinetic and pharmacodynamic mechanisms.[93,94]

Neurorescue refers to the salvage of dying neurones; this may mean a stabilising of the condition with prevention of further cell loss rather than any progressive increase in cell number (Figure 6.1).[93,94]

Neurorestoration refers to increasing the numbers of dopaminergic neurones by techniques such as cell implantation and nerve growth factor infusion (Figure 6.1). Such surgical techniques are discussed but not reviewed in the chapter on 'Surgery for Parkinson's disease'.[93,94]

Neuromodulation has been used by some to refer to deep brain stimulation (DBS) procedures in PD such as bilateral subthalamic stimulation.[93,94]

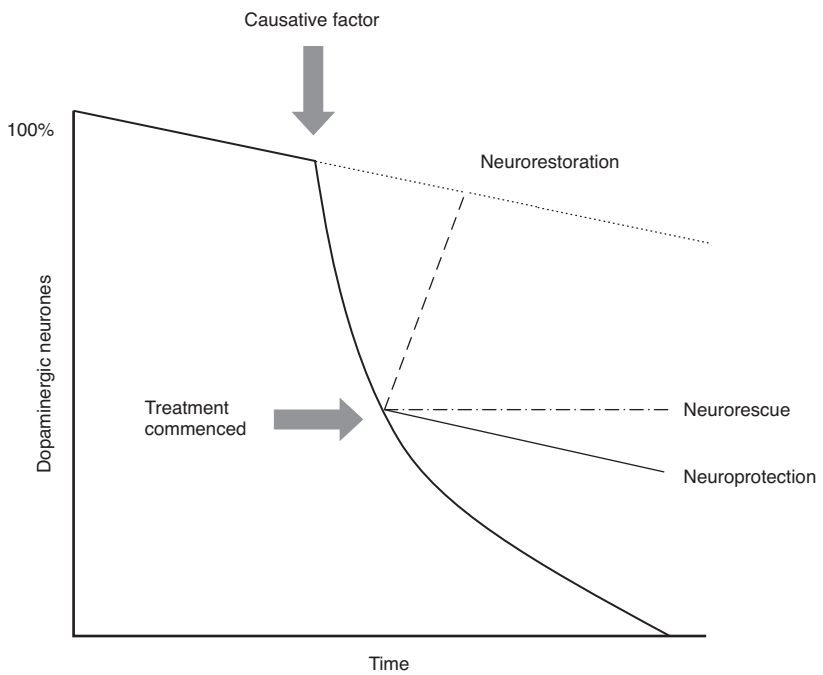

Figure 6.1 Schematic representation of neuroprotective processes[95] (reproduced with permission from the authors)

6.1.1 Pathogenesis of disease modification

Detailed discussion of this topic is beyond the scope of this guideline.[96] However, the main pathophysiological mechanisms upon which agents may be neuroprotective are listed below:

- mitochondrial complex-1 deficiency
- free radical damage and oxidative stress
- proteasomal dysfunction
- apoptosis
- inflammation (microglial activation).

6.1.2 Measuring disease progression

Considerable debate surrounds how to measure the rate of progression of PD in clinical trials of neuroprotective therapies.[93,97] The measures used to date are detailed in Table 6.1 along with a summary of their potential benefits and drawbacks.

Table 6.1 Outcome measures used in neuroprotection trials in PD

Outcome measures	Benefits	Problems
Quality of life	Patient-rated so more meaningful to them.	Open to symptomatic effects of therapy. Likely to have low sensitivity unless agent has large treatment effect.
Clinical rating scales	Standard method used for many years.	Open to symptomatic effects of therapy unless evaluated after drug withdrawal.
Mortality	Has direct relevance to people with PD.	Open to symptomatic effects of therapy. Studies need to be large or long term to have adequate power.
SPECT and PET imaging	Intuitively a good biomarker for the disease. May improve diagnostic accuracy at start of trials. May be more sensitive than clinical outcomes.	People who have PD clinically but have normal baseline scan. People with PD with abnormal baseline radionuclide studies may have PSP or MSA. Lack of clinical correlation of neuroprotection in radionuclide studies to date. Poor sensitivity to change and reproducibility of radionuclide studies. Differential regulation of ligand pharmacokinetics by medication.
Delaying motor complications	Has direct relevance to people with PD.	More likely to be a pharmacokinetic or dynamic effect than neuroprotection.

Adapted from Refs 97,98.

The majority of previous neuroprotection trials have been of parallel group design and placebo controlled. A washout period at the end of the study was often included to remove the symptomatic effects of the active agent. In general, clinical rating scales have been seen as the most acceptable measure of disease modification. One study used a delayed-start design to reduce the numbers of people with PD given placebo.[99] With this technique one group is randomised to active treatment from the outset but one or more other groups are randomised

to start the active drug after a period on placebo (Figure 6.2). If the drug has a symptomatic effect then clinical outcome measures in the groups will merge together, given sufficient follow-up. If the drug delays disease progression then clinical ratings will remain different between the groups.

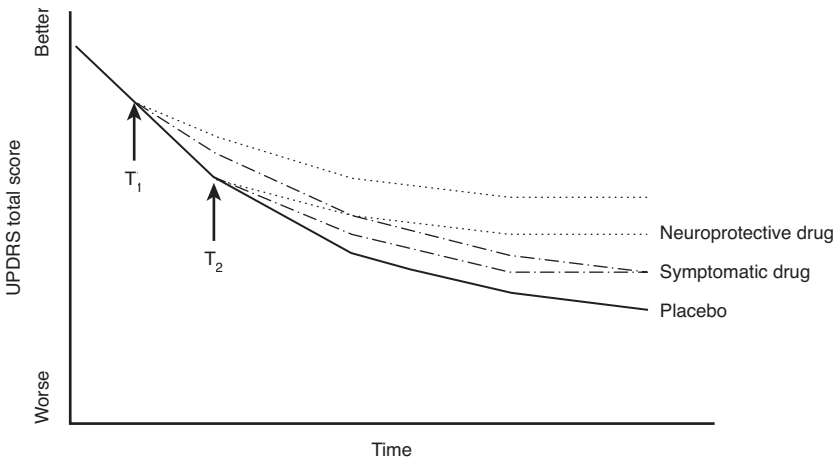

Figure 6.2 Schematic representation of delayed-start design trial.[94]

At time points T_1 and T_2 people with PD are randomised to drug or placebo.

With neuroprotective drugs, outcome scores will be parallel but with drugs that have a symptomatic effect the curves come together.[94]

6.1.3 Methodological limitations of neuroprotective studies

When reviewing the evidence on neuroprotective agents, the following methodological issues should be considered:

- wide range in sample size
- lack of statistical detail on power of small studies
- no documentation of allocation concealment methods
- comparability of results from different centres in multi-site studies
- drug regimen varied between trials (drug, dose, frequency).

6.1.4 Potential neuroprotective agents

Many agents suggested to have neuroprotective properties have undergone systematic review by the National Institute for Neurologic Disorders and Stroke (NINDS).[100] They developed a shortlist of 12 candidate drugs for neuroprotection trials, which are listed in Table 6.2. In addition, vitamin E has been examined for neuroprotective potential.

On the basis of the evidence available, the GDG chose to review the four classes of potential neuroprotective drugs for PD based on the human studies:

- vitamins
- co-enzyme Q_{10}
- dopamine agonists
- monoamine oxidase type B (MAOB) inhibitors.

Table 6.2 Candidate neuroprotective drugs for PD selected by NINDS[100]

Caffeine	Minocycline
Co-enzyme Q_{10}	Nicotine
Creatine	Oestrogen
GM-1 ganglioside	Monoamine oxidase type B inhibitors (rasagiline and selegiline)
GPi-1485	Dopamine agonists (ropinirole and pramipexole)

6.2 Vitamin E

If the generation of free radicals is a significant pathophysiological process in PD, then the anti-oxidant vitamins E and C may be neuroprotective. No trials with vitamin C have been done in PD.

Does vitamin E have neuroprotective properties in PD?

6.2.1 Methodology

Three papers[101–103] were found, which analysed data from the same cohort recruited into the DATATOP study.[104] The DATATOP study (N=800) was a randomised controlled study, which addressed whether vitamin E (tocopherol 2000 IU) was effective in reducing the progression of PD.

6.2.2 Evidence statements

All of the studies[101–103] failed to demonstrate a significant benefit of vitamin E in slowing the progression of PD. (**1++**)

One report[101] examined 24 months' follow-up data and showed the following:

- The probability of reaching the endpoint (onset of disability prompting administration of levodopa) was not reduced in people with PD receiving tocopherol.
- There was no significant change in UPDRS variables for the tocopherol treatment groups.
- There was no evidence of any beneficial effect of α-tocopherol (2000 IU per day) in either slowing functional decline or ameliorating the clinical features of PD. (**1++**)

Another report[103] looked at 24 months' follow-up data and showed:

- no significant benefit of tocopherol in reducing the likelihood of reaching the endpoint (requiring levodopa therapy)
- no significant benefit on any of the secondary outcome measures (UPDRS, Hoehn and Yahr scale, Schwab and England Activities of Daily Living (ADL) scale, neuropsychological testing, Hamilton depression scale). (**1++**)

A third report[102] looked at 14 months' follow-up data and showed no significant effects for tocopherol on the annualised rates of change of any cognitive measure after adjustment for multiple comparisons. (**1+**)

6.2.3 From evidence to recommendation

The DATATOP evidence shows that vitamin E taken as 2000 IU of tocopherol daily is not neuroprotective in PD.

RECOMMENDATION

R22 Vitamin E should not be used as a neuroprotective therapy for people with PD. **A**

6.3 Co-enzyme Q_{10}

Mitochondrial complex I activity is reduced in post-mortem substantia nigra and in the platelets of people with PD.[105,106] Co-enzyme Q_{10} is the electron acceptor for complexes I and II and as a result is a potent anti-oxidant. The level of co-enzyme Q_{10} is reduced in platelet mitochondria in PD.[107] Oral supplementation with co-enzyme Q_{10} reduced dopaminergic neurone loss in MPTP-treated mice.[108]

In view of this positive pre-clinical work, is there any clinical trial evidence that co-enzyme Q_{10} has neuroprotective properties in PD?

6.3.1 Methodology

Two studies[109,110] examined the effectiveness of co-enzyme Q_{10} in reducing the rate of progression of PD. The methodological limitations included a lack of detail concerning randomisation and allocation concealment in one study,[109] and a small sample size without power calculations in both studies.[109,110]

6.3.2 Evidence statements

The two studies[109,110] used validated clinical rating scales as the outcome measures to assess benefit from co-enzyme Q_{10}.

One trial[110] (N=80) compared three different doses (300 mg/d, 600 mg/d and 1,200 mg/d) of co-enzyme Q_{10} with placebo using total UPDRS scale as the primary outcome measure. The primary analysis was a test for trend between placebo and all doses of co-enzyme Q_{10}. This showed a significant difference (5.30; 95% CI 0.21 to 10.39) at the p=0.09 level. In a pre-specified secondary analysis, which compared each of the dosages to placebo, only the 1,200 mg/d group had a significant effect compared with placebo (p=0.04). (**1++**)

This trial[110] also found the following.

- People with PD taking co-enzyme Q_{10} displayed a worsening on the Schwab and England scale as assessed by the examiner (p=0.04) but not by the person with PD (p=0.81).
- Co-enzyme Q_{10} did not have a significant effect on the scores for the Hoehn and Yahr scale or the timed tapping task. (**1++**)

Another trial[109] (N=28) compared a low dose (360 mg/day) of co-enzyme Q_{10} with placebo and showed:

- the UPDRS total score was in favour of co-enzyme Q_{10} treatment (p=0.012)
- a benefit of co-enzyme Q_{10} supplementation on the Visual Function Test (p=0.008) measured with the Farnsworth–Munsell 100 Hue Test. (**1+**)

6.3.3 From evidence to recommendation

The small neuroprotection trials performed with co-enzyme Q_{10} in PD so far have been encouraging, but further evidence is required before it can be recommended routinely.

RECOMMENDATION

R23 Co-enzyme Q_{10} should not be used as a neuroprotective therapy for people with PD, except in the context of clinical trials. **B**

6.4 Dopamine agonists

A considerable body of pre-clinical work has suggested that dopamine agonists are neuroprotective in cell culture and various animal models of PD.[111,112]

What clinical evidence is there that dopamine agonists have neuroprotective properties in PD?

6.4.1 Methodology

Eight studies[42,61,113–118] were found which addressed the neuroprotective effects of dopamine agonists versus levodopa therapy in PD.

One trial[114] was excluded due to the lack of reporting drug dosages used during the trial, which limits the comparability with other trials to show consistency of effect.

GDG members found a related abstract[119] on pergolide therapy, but this abstract was excluded, as the results have not been published in a full paper.

Of the six studies included in the evidence base, half of them were designed as open trials. Usually, this would be a serious methodological issue as open trials are subject to increased performance bias. However, one of the main outcome measures was mortality, which cannot be influenced by the open-trial design. In addition, the long-term follow-up of 4.5 and 10 years is practical justification for an open-trial design.[42,117,115]

There were specific methodological issues associated with the imaging studies. One study reported at baseline that 11% of the people who had been clinically diagnosed with PD had normal scans.[61] Another study did not include a washout period in order to distinguish between the symptomatic and neuroprotective effects of the drugs administered.[113]

6.4.2 Evidence statements

With respect to clinical rating scales, the ropinirole REAL-PET (N=162) study found UPDRS motor score during treatment at 2 years was superior with levodopa compared with ropinirole (a score increase of 0.70 in the ropinirole group and a decrease of 5.64 in the levodopa group, 95% CI 3.54 to 9.14).[61] (**1++**)

Non-significant results reported by the studies included:

- CALM-PD[113] (pramipexole) (N=82) mean total and mean motor UPDRS (**1++**)
- REAL-PET[61] (ropinirole) Clinical Global Impression (CGI) improvement scale (**1++**)
- UK-PDRG study[42] (bromocriptine) (N=782) mean Webster disability scores (**1+**)
- cabergoline study[118] UPDRS part III (motor) (N=412) and part II (ADL). (**1+**)

With respect to mortality, the following results were found.

- The PRADO study[115] (N=587) was terminated when 18 deaths were reported in the levodopa group versus eight deaths in the levodopa/bromocriptine group (p=0.07; adjusted for age and sex p=0.02). The risk ratio of death in the levodopa group compared with the levodopa/bromocriptine group was 2.7, a reduction of 63%. (**1+**)
- All three of the bromocriptine studies[53,116,117] found no significant differences between treatment groups. (**1+**)
- The cabergoline study[118] found no significant difference between treatment groups. (**1+**)

With respect to imaging, several analytical measures found benefit of ropinirole and pramipexole over levodopa; these are summarised in Table 6.3.

Table 6.3 Rate of decline in tracer uptake (1++)

Variable	% Change dopamine agonist	% Change levodopa	Significance
Ropinirole (REAL-PET)[61]	**(SE)**	**(SE)**	
Region-of-interest analysis (reduction in putamen Ki over 2 years)	13.4% (2.14)	20.3% (2.35)	RD 34% (95% CI 0.65 to 13.06, p=0.022)
Statistical parametric mapping (reduction in putamen)	14.1% (1.58)	22.9% (1.70)	RD 38% (95% CI 4.24 to 13.3, p<0.005)
Amplitudes of change (substantia nigra)	4.3 % (3.67)	–7.5 % (3.94)	MD 11.9 (95% CI 1.3 to 22.4, p=0.025)
Pramipexole (CALM-PD)[113]	**(SD)**	**(SD)**	
Striatal ^{123}I-β-CIT (rate of decline) at 22 months	–7.1 (9.0)	–13.5 (9.6)	p=0.004
At 34 months	–10.9 (11.8)	–19.6 (12.4)	p=0.009
At 46 months	–16.0 (13.3)	–25.5 (14.1)	p=0.01

RD = relative difference; Ki = influx constant; SE= standard error; MD= mean difference.

With respect to motor complications:

- the REAL-PET study[61] found:
  - development of dyskinesia favoured ropinirole (odds ratio (OR) 0.09, 95% CI 0.02 to 0.29, p<0.001)
  - time to develop dyskinesias favoured ropinirole (hazard ratio 8.28, 95% CI 2.46 to 27.93, p<0.001) (**1++**)
- the PRADO study[115] found the incidence of dyskinesias favoured bromocriptine (rate ratio: 0.73, 95% CI 0.57 to 0.93). (**1+**)

The cabergoline versus levodopa study[118] found:

- risk of developing motor complications favoured cabergoline treatment (p<0.02)
- the relative risk of developing motor complications was >50% lower with cabergoline compared with levodopa
- cabergoline-treated people requiring levodopa were at the same risk of developing motor complications as those on a stable levodopa dose. (**1+**)

6.4.3 From evidence to recommendation

The apparent reduction in the rate of tracer loss in the ropinirole and pramipexole trials shown by radionuclide imaging raised the prospect that these agonists are neuroprotective. However, there are a number of methodological problems with these studies (as shown in Table 6.1).[97] Clinical motor rating scales were better in levodopa-treated individuals with PD or no different in these trials. The delaying of motor complications by the agonists may be due to a pharmacokinetic or pharmacodynamic effect rather than slowing of disease progression.

RECOMMENDATION

R24 Dopamine agonists should not be used as neuroprotective therapies for people with PD, except in the context of clinical trials. **B**

6.5 Monoamine oxidase type B inhibitors

The propargylamines selegiline and rasagiline are monoamine oxidase type B (MAOB) inhibitors, thereby reducing the turnover of dopamine and hopefully reducing free radical generation.[96] However, they may also have an anti-apoptotic effect.[100]

What *in vivo* evidence is there that MAOB inhibitors are neuroprotective in PD?

6.5.1 Methodology

Two meta-analyses[120,121] and an RCT[99] were found, which addressed the effectiveness of MAOB inhibitors in reducing the rate of progression of PD.

One meta-analysis included 3,525 people with PD in 17 randomised trials; 13 trials were on selegiline, three trials were on lazabemide and one trial was on rasagiline therapy. Only selegiline and rasagiline are licensed for use in the UK. The results of the lazabemide studies were consistent

with the results of the other two therapies, so the full meta-analysis was included in the evidence base. The other meta-analysis[121] was a Cochrane review with a similar authorship. This included 2,422 people with PD from 10 trials where treatment duration or follow-up was 1 year or longer. Nine trials were on selegiline and one was on lazabemide. Several trials were included in both meta-analyses.

The RCT[99] consisted of 404 people with PD randomised to rasagiline or placebo-delayed rasagiline therapy. The delayed-start design (see Figure 6.2) consisted of randomising them to one of three groups:

- rasagiline 1 mg/d for 1 year
- rasagiline 2 mg/d for 1 year
- placebo for 6 months, followed by rasagiline 2 mg/d for 6 months.

6.5.2 Evidence statements

A meta-analysis[120] combined the available data from six trials of selegiline therapy. All trials showed significantly improved scores in favour of selegiline versus controls for UPDRS scores at 3 months as follows:

- total score: 2.7 (95% CI 1.4 to 4.1, p=0.00009)
- motor score: 1.8 (95% CI 0.8 to 2.7, p=0.0004)
- activities of daily living scores: 0.9 points (95% CI 0.5 to 1.4, p=0.00007).

The Cochrane review[121] also found significantly improved scores in favour of MAOB inhibitors from baseline to 1 year on treatment. (**1++**)

Although the large DATATOP study accounted for over 79% of people with PD in a MAOB inhibitors versus placebo comparison, the combined results from the other studies were consistent with those from DATATOP (p=0.004).[120] (**1++**)

The rasagiline trial[99] showed:

- Total UPDRS score for rasagiline 1 mg/d for 1 year versus delayed-start rasagiline 2 mg/d for 6 months was significant –1.82 (95% CI 3.64 to 0.001, p=0.05) in favour of longer treatment.
- Rasagiline 2 mg/d for 1 year versus delayed-start rasagiline 2 mg/d for 6 months was significant –2.29 (95% CI –4.11 to –0.48, p=0.01) in favour of longer treatment.
- ADL score for rasagiline 2 mg/d for 1 year versus delayed-start rasagiline 2 mg/d for 6 months significantly favoured the longer treatment (p=0.005).
- The comparisons of other UPDRS subscales were not significant. (**1++**)

A meta-analysis[120] assessed mortality rates by combining all of the available data from nine trials of selegiline and one trial of lazabemide therapy. The results in eight trials (excluding UK-PDRG), showed:

- no excess in mortality between MAOB inhibitor-treated individuals with PD and controls (p=0.8)
- in the UK-PDRG study there were significantly more deaths in the selegiline arm versus the levodopa arm (OR=1.57, 95% CI 1.09 to 2.30, p=0.015)
- by taking all available data, 20% of deaths occurred in the MAOB inhibitor group compared with 21% in the controls (p=0.2)

- no significant heterogeneity was found between trials (p=0.6), even including the UK-PDRG study
- the Cochrane review[121] found a non-significant increase in deaths among patients treated with MAOB inhibitors compared with controls. (**1++**)

A meta-analysis[120] found five trials, which reported data on motor complications. The combined results showed:

- a 25% reduction in motor fluctuations in MAOB inhibitor group (0.75, 95% CI 0.59 to 0.95, p=0.02).
- no difference in the incidence of dyskinesia between treatment groups (0.97, 95% CI 0.75 to 1.26, p=0.8) compared with non-MAOB inhibitor group.

The Cochrane review[121] found very similar results. However, with regard to motor fluctuations, they found that the result was dependent on the adjusted results of one study (the UK-PDRG study) and if the unadjusted figures were used the overall result became insignificant. Additionally, results were not reported for a number of patients in these studies and a modified worst-case sensitivity analysis also made the results non-significant. (**1++**)

6.5.3 From evidence to recommendation

The benefits of MAOB inhibitors versus control in terms of clinical rating scales were consistent with a known short-term symptomatic effect. There does not seem to be any clear increase or decrease in mortality with MAOB inhibitors. The delayed onset of motor fluctuations with MAOB inhibitors is comparable to the delayed motor complications with dopamine agonists but is likely to represent a levodopa-sparing effect involving pharmacokinetic or pharmacodynamic factors.

The sustained difference in total UPDRS in the rasagiline versus placebo delayed-start design trial suggests this agent may be neuroprotective. However, the relatively short follow-up in this trial may not have been long enough to see the UPDRS scores in the different trial groups merge, as would be seen with a symptomatic effect.

Further large trials with longer-term follow-up are required to assess whether the MAOB inhibitors have neuroprotective properties in PD.

RECOMMENDATION

R25 MAOB inhibitors should not be used as neuroprotective therapies for people with PD, except in the context of clinical trials. **B**

7 Symptomatic pharmacological therapy in Parkinson's disease

7.1 Introduction

Symptomatic therapies for PD treat the symptoms of the disease but do not necessarily slow the rate of progression of the condition. In this guideline the symptomatic pharmacological therapies have been classified on the basis of the clinical manifestations of a person with PD. Thus:

- Early disease has been used to refer to people with PD who have developed functional disability and require symptomatic therapy.
- Later disease has been used to refer to people on levodopa who have developed motor complications.

Clinical trials and regulatory authorities define the term 'later disease' in the same way. However, since motor complications can occur soon after starting levodopa, particularly if large doses are used, 'later disease' is something of a misnomer. The term is generally preferred to the alternative 'advanced disease'.

7.1.1 Methodological limitations of symptomatic therapy studies

When reviewing the symptomatic therapy evidence, the following methodological issues should be considered:

- trial duration is often too short
- drug regimen variations between trials (type of drug, dose, frequency)
- small sample size which limits generalisability and sensitivity of tests to detect outcome differences between groups
- lack of reporting methods of randomisation and allocation concealment
- lack of washout periods between treatment arms in crossover studies
- lack of reporting results of first arm from crossover studies, which leads to risk of carry-over effect
- lack of intention-to-treat analyses
- lack of defining the clinical criteria for diagnosis
- clinical versus statistical significance
- over-representation of younger patients limiting generalisability.

Most of the poorly designed trials were performed in the 1970s and 1980s when trial design was in its infancy. Drugs evaluated in such trials may not have been found to be efficacious in this review. However, this does not mean that they are ineffective. In such cases, clinical experience may be the only appropriate judge of efficacy and safety.

The Cochrane reviews included in this chapter have received a 1++ grading for the methodology of the systematic review as applied by the Cochrane group, but this grading does not apply to the trials contained within these reviews. Although the methodologies of the systematic reviews were of good quality, the trials contained within the reviews sometimes suffered from

methodological limitations. The results of these trials should be treated with caution due to the inherent methodological limitations. In light of this, it was felt to be inappropriate to present evidence statements based on the individual trial data.

Efficacy outcome measures in later disease trials are considerably different from those in early disease. The people with PD in such trials have already developed motor complications and the aim of adjuvant therapy is to reduce the time the person with PD spends 'off' and to reduce the dose of levodopa, which has played some part in the generation of the complications in the first place. 'Off' time is measured from patient-completed 30 minute epoch 'on'/'off' diary cards, which are usually averaged over a 3-day period. Levodopa dose is recorded throughout the trial. Usually the UPDRS scale components are also noted during later disease trials.

7.2 Early pharmacological therapy

7.2.1 Introduction

It was evident from reviewing the evidence-base that there is no single drug of choice in the initial pharmacotherapy of early PD. Table 7.1 may help to guide the reader through the following section.

Table 7.1 Options for initial pharmacotherapy in early PD

	First-choice option	Symptom control	Possible risk of side effects	
			Motor complications	Other adverse events
Levodopa	✓	+++	↑	↑
Dopamine agonists	✓	++	↓	↑
MAOB inhibitors	✓	+	↓	↑
Anticholinergics	×	Lack of evidence	Lack of evidence	Lack of evidence
Beta-blockers	×	Lack of evidence	Lack of evidence	Lack of evidence
Amantadine	×	Lack of evidence	Lack of evidence	Lack of evidence

+++ = Good degree of symptom control.
++ = Moderate degree of symptom control.
+ = Limited degree of symptom control.
↑ = Evidence of increased motor complications/other adverse events.
↓ = Evidence of reduced motor complications/other adverse events.

7.2.2 Levodopa

The standard symptomatic therapy for PD for more than 30 years has been levodopa. This is the precursor of dopamine which is deficient in PD. Levodopa is readily converted into dopamine by dopa decarboxylase. To reduce peripheral metabolism of levodopa, it is combined with a peripheral dopa decarboxylase inhibitor (ie carbidopa or benserazide). This increases the amount of levodopa that crosses the blood-brain barrier.

However, levodopa preparations contribute to the development of motor complications in PD. These comprise abnormal involuntary movements or dyskinesias, such as athetosis and dystonia, along with response fluctuations in which people experience 'wearing off' of the drug's effects and/or unpredictable switching between the 'on' and the 'off' state.

To avoid motor complications, the strategy of delaying the introduction of levodopa has developed. Most people with PD who commence therapy with another drug will eventually need levodopa therapy. This approach requires initial therapy with an alternative that is as effective as levodopa that does not cause motor complications. A number of drug classes have been examined for such properties.

▷ Methodology

Only one RCT[62] (ELLDOPA) was found which addressed the effectiveness of levodopa (plus a decarboxylase inhibitor) compared with placebo. The other trials found included studies on levodopa monotherapy compared with placebo and were published between 1969 and 1971. These were not reviewed, as levodopa is no longer used without a decarboxylase inhibitor.

The RCT[62] was a large multi-centre study including 361 early PD people randomly assigned to four groups, consisting of three different doses of levodopa/carbidopa (150/37.5 mg/day, 300/75 mg/day or 600/150 mg/day) or placebo.

All people included in the trial had received a diagnosis of PD within the last 2 years and no one was on any anti-parkinsonian medication at the time of enrolment. The trial duration was 40 weeks, which was followed by a 2-week withdrawal period at the end of the trial.

There were two primary outcome measures: clinical assessment using UPDRS and measurement of the dopamine transporter with ^{123}I-β-CIT SPECT.

▷ Evidence statements

With respect to clinical rating scales:[62]

- Levodopa in a dose-dependent pattern reduced the worsening of symptoms of PD.
- Changes in UPDRS scores from baseline to week 42 (versus placebo) were:
  - total score ($p<0.001$)
  - ADL component ($p<0.001$)
  - motor component ($p<0.01$)
  - mental component (non-significant).
- The UPDRS scores in the three levodopa groups worsened during the 2-week washout period but did not deteriorate to placebo levels.
- The group receiving the highest dose of levodopa had the largest improvement in UPDRS. (**1++**)

With respect to ^{123}I-β-CIT (neuroimaging) outcomes:[62]

- The percentage decrease in striatal ^{123}I-β-CIT uptake over 40 weeks was greater among participants in the levodopa than the placebo group and, although this was non-significant, 15% of people had a putaminal uptake of more than 75% of that of age-matched controls.

- Analysis of the results after exclusion of the 19 people without dopaminergic deficit on imaging showed a significantly greater decrease in uptake among those receiving levodopa than those receiving placebo (p=0.036). (**1++**)

With respect to adverse events:[62]

- Side effects were more common in the 600 mg group than with placebo for dyskinesias (p<0.001), nausea (p=0.001), infection (p=0.01), hypertonia (p=0.03), and headache (p=0.03).
- Other findings were non-significant between other levodopa doses and placebo. (**1++**)

With respect to withdrawal rates:[62]

- Of the total of 361 participants enrolled, 317 (88%) took the study medication for 40 weeks and 311 (86%) completed the 2 weeks of washout.
- The percentage of dropouts per group included: placebo (22%), 150 mg/d (15%), 300 mg/d (6%) and 600 mg/d (11%).
- The main reasons for withdrawal were worsening of symptoms and adverse events. (**1++**)

▷ From evidence to recommendations

The clinical impression that levodopa is a most effective treatment for PD has been confirmed in the large ELLDOPA trial. Short-term dopaminergic adverse effects are infrequent and usually settle with time. However, long-term levodopa therapy precipitates motor complications such as dyskinesias and motor fluctuations. Questions remain regarding the possibility that levodopa may be toxic or even protective to the remaining nigrostriatal dopaminergic neurones. Further work is required to clarify this issue.

RECOMMENDATIONS

R26 Levodopa may be used as a symptomatic treatment for people with early PD. **A**

R27 The dose of levodopa should be kept as low as possible to maintain good function in order to reduce the development of motor complications. **A**

7.2.3 Dopamine agonists

The dopamine receptor agonists mimic the effect of dopamine by binding directly with the post-synaptic dopamine receptors. They were introduced as adjuvant therapy to levodopa in later disease, but, more recently, trials have examined their effects as initial monotherapy in the hope that they may delay the onset of motor complications.

What is the effectiveness of dopamine agonists compared with placebo in the treatment of functionally disabled early PD?

▷ Methodology

Six randomised controlled trials[122–127] were found which compared the effectiveness of dopamine agonists with placebo for the treatment of people with early PD who are functionally disabled. The sample size for most of these studies was quite large (range N=55–335, mean 177).

▷ Evidence statements

The following outcomes were reported to be significantly in favour of dopamine agonists:

- UPDRS total score[122,123]
- UPDRS motor scores[122,124–127]
- UPDRS > 30% reduction in motor scores[122,124,127]
- UPDRS ADL scores[122,125,126]
- Schwab and England ADL scores[122]
- CGI 'very much improved' score[122,124,127]
- requirement of levodopa supplementation[124]
- withdrawal rates.[124] (**1+**)

The following adverse events were found to be significantly increased ($p<0.05$) in the treatment group:

- nausea[122,125,127]
- somnolence[122,125,127]
- dizziness[122,127]
- insomnia, constipation, hallucinations[125]
- anorexia, vomiting.[122] (**1+**)

The following outcomes were reported as non-significant:

- incidence of reporting adverse events[122–127]
- incidence of withdrawals.[122,127] (**1+**)

▷ From evidence to recommendation

Dopamine agonists are an effective treatment for the motor features of early PD. However, agonists generate significant dopaminergic adverse events. The latter do not lead to drug withdrawal, which suggests that they are mild and that tolerance develops. These conclusions apply to the relatively young people included in these studies. Further work on the efficacy and safety of dopamine agonists in older people is required.

Ergot-derived dopamine agonists (bromocriptine, cabergoline, lisuride and pergolide) are well known to cause rare serosal reactions such as pleural, pericardial and peritoneal effusion and/or fibrosis.[128] Recently, two echocardiographic series have suggested that pergolide can also cause a cardiac valvulopathy.[129,130] As a result of these reports, the pergolide Summary of Product Characteristics has been changed to include the following.

- Pergolide is to be used as second line after a non-ergot dopamine agonist.
- The dose of pergolide should not exceed 5 mg per day.
- An echocardiogram must be obtained before initiating therapy and should be repeated regularly thereafter to monitor for valvulopathy.
- Pergolide is contraindicated in anyone with anatomical evidence of cardiac valvulopathy.

Reports of serosal reactions with non-ergot dopamine agonists (pramipexole and ropinirole) are few and these are possibly due to previous exposure to ergot-derived agonists. However, the patient-years of exposure to these newer agonists is low, so firm conclusions cannot be reached.

RECOMMENDATIONS

R28 Dopamine agonists may be used as a symptomatic treatment for people with early PD. **A**

R29 A dopamine agonist should be titrated to a clinically efficacious dose. If side effects prevent this, another agonist or a drug from another class should be used in its place. **D (GPP)**

R30 If an ergot-derived dopamine agonist is used, the patient should have a minimum of renal function tests, erythrocyte sedimentation rate (ESR) and chest radiograph performed before starting treatment, and annually thereafter.* **D (GPP)**

R31 In view of the monitoring required with ergot-derived dopamine agonists, a non-ergot-derived agonist should be preferred in most cases. **D (GPP)**

7.2.4 Monoamine oxidase type B inhibitors

MAOB inhibitors block the metabolism of dopamine, thereby increasing its level in the striatum. MAOB inhibitors do not cause a reaction after consumption of tyramine-rich foods ('tyramine' or 'cheese' effect) and are therefore safer to use than non-selective inhibitors.

MAOB inhibitors were introduced as a symptomatic therapy in later PD. After encouraging pre-clinical and one retrospective clinical trial[131] they were used for a time in early PD in the hope that they might have a neuroprotective effect in addition to a symptomatic effect (see Chapter 6).

What is the evidence that MAOB inhibitors are an effective and safe symptomatic treatment in early PD?

▷ Methodology

Two meta-analyses[120,121] and two RCTs[132,133] which addressed the effectiveness of MAOB inhibitors in treating people with early PD were included.

One meta-analysis[120] included 3,525 people with PD from 17 randomised trials; 13 trials were on selegiline, three trials were on lazabemide and one trial was on rasagiline therapy. Although only selegiline and rasagiline are licensed for use in the UK, the results of the lazabemide studies were consistent with the results of the other two therapies. Thus, the meta-analysis, which combined the results of all MAOB inhibitor trials, was included in the evidence base. All of the selegiline trials used the standard oral preparation rather than the lyophilised buccal preparation selegiline (Zelapar®). The other meta-analysis[121] was a Cochrane review with a similar authorship. This included 2,422 people with PD from 10 trials where treatment duration or follow-up was 1 year or longer. Nine trials were on selegiline and one was on lazabemide. Several trials were included in both meta-analyses.

One RCT[133] consisted of 15 people with PD. The small sample size could explain the non-significant results, when compared with the large meta-analysis. The other RCT[132] consisted of 56 people with PD, divided into three rasagiline dose groups (1, 2 or 4 mg/d) and a placebo group. The authors of this study reported that the trial was inadequately powered for assessing anti-parkinsonian efficacy of the study drug.

*Full details of the restrictions on pergolide use and monitoring are available in the Summary of Product Characteristics.

▷ Evidence statements

The large DATATOP study accounted for over 65% of the people with PD analysed for UPDRS scores and over 79% of people with PD in the MAOB inhibitor versus placebo comparison. The combined results from the other two studies of MAOB inhibitor compared with placebo were consistent with those from DATATOP and were significant independently (p=0.004).[120] (**1++**)

With respect to clinical rating scales, one meta-analysis[120] reported:

- UPDRS scores at 3 months from six trials (all used selegiline for MAOB inhibitor intervention) were:
  - total score: treatment difference 2.7 (95% CI 1.4 to 4.1, p=0.00009)
  - motor score: treatment difference 1.8 (95% CI 0.8 to 2.7, p=0.0004)
  - ADL score: treatment difference 0.9 (95% CI 0.5 to 1.4, p=0.00007).
- All of the above quoted outcomes favoured selegiline over controls.

The Cochrane review[121] also found that MAOB inhibitors significantly improved these UPDRS scores. (**1++**)

The randomised crossover trial[133] reported no significant differences on the Webster rating scale (total scores) for people with PD on co-beneldopa/selegiline compared with people with PD on co-beneldopa/placebo. (**1++**)

The other RCT[132] reported:

- Total UPDRS score during 10-week period ($p<0.05$) for rasagiline 2 mg but not for 1 mg and 4 mg groups compared with placebo.
- A responder analysis showed that 28% of people (12/43) receiving rasagiline had an improvement in total UPDRS score of more than 30%, compared with none of the people receiving placebo ($p<0.05$).
- No evidence of drug effect was noted with respect to the Clinician's Global Impression of Change (CGIC) scale, Hoehn and Yahr stage, Schwab and England ADL scale, or BDI. (**1++**)

With respect to need for levodopa therapy, the meta-analysis[120] found the following:

- Eight trials reported data on the need for levodopa (MAOB inhibitor versus placebo). The combination of these trial results showed a highly significant reduction in need for levodopa in people with PD randomised to a MAOB inhibitor compared with placebo (0.57, 95% CI 0.48 to 0.67, $p<0.00001$).

The Cochrane review[121] found a similar significant reduction in the requirement for levodopa, although it was noted that all patients were receiving levodopa after 4 years of follow-up. (**1++**)

With respect to motor complications, one meta-analysis[120] found five trials. The combined results showed:

- 25% reduction in motor fluctuations in MAOB inhibitor group, treatment difference 0.75 (95% CI 0.59 to 0.95, p=0.02)
- no significant difference in the incidence of dyskinesia between treatment groups compared with non-MAOB inhibitor group.

The Cochrane review[121] found very similar results. However, with regard to motor fluctuations, they found that the result was dependent on the adjusted results of one study (the UK-PDRG study) and if the unadjusted figures were used the overall result became insignificant. Additionally,

results were not reported for a number of patients in these studies and a modified worst-case sensitivity analysis also made the results non-significant. (1++)

The meta-analysis[120] found more side effects were reported in:

- people with PD randomised to an MAOB inhibitor, treatment difference 1.36 (95% CI 1.02 to 1.80, p=0.04).

The Cochrane review[121] also found more adverse events with MAOB inhibitors; however, this was not a statistically significant difference. (1++)

The RCTs[132,133] found minimal or no side effects reported in either treatment group. (1++)

One meta-analysis[120] found more people in the MAOB inhibitor group withdrew due to adverse events than in the non-MAOB inhibitor group; treatment difference 2.16 (95% CI 1.44 to 3.23, p=0.0002). Similarly, the Cochrane review found significantly more withdrawals with MAOB inhibitors.[121] (1++)

One meta-analysis[120] found more deaths occurred in the MAOB inhibitor patients compared with controls but this was not a significant difference, while the Cochrane review[121] found a non-significant increase in deaths among patients treated with MAOB inhibitors compared with controls. (1++)

▷ From evidence to recommendation

The trial evidence supports the ability of MAOB inhibitors in PD to improve motor symptoms, improve activities of daily living and delay the need for levodopa. The evidence on them delaying motor complications is unclear. This is at the expense of more dopaminergic adverse events and, as a result, more withdrawals from treatment. There was no conclusive evidence of any increase in mortality on selegiline.

It is not possible from the evidence available to decide whether the lack of amphetamine metabolites with rasagiline confers any clinical benefit compared with selegiline.

RECOMMENDATION

R32 MAOB inhibitors may be used as a symptomatic treatment for people with early PD. **A**

7.2.5 Beta-adrenergic antagonists (beta-blockers)

Beta-adrenergic antagonists (eg propanolol and oxprenolol) are well established in the treatment of the tremor seen in essential tremor and thyrotoxicosis.

Are beta-adrenergic antagonists effective in reducing the symptoms of PD?

▷ Methodology

A Cochrane systematic review[134] included four randomised controlled trials. Only 72 people with PD were included in these studies. All trials were randomised double-blind crossover studies.

Three of the crossover trials[135,136,137] in the systematic review did not present data from the end of the first arms. Since there is a carry-over risk, the systematic review did not analyse the data from these trials. One trial did report data from the first arm;[138] however, the trial did not state baseline scores, numbers of patients in each group, or standard deviations.

▷ Evidence statements

The systematic review was methodologically sound and hence it could technically be given a grading of 1++/1+. However, the methodological limitations of individual studies contained within the review meant that there were insufficient robust data from which to derive evidence statements.

The only evidence reported by the review was from a single trial[138] which found no significant difference between oxprenolol and placebo in mean total score for tremor.

Details of the data analysis were not given so it was not possible for the systematic review to determine whether the non-significance was based on comparison between the first and second arms (which could have been affected by a possible crossover effect) or between the therapy and placebo groups at the end of each arm.

▷ From evidence to recommendation

There is insufficient trial evidence for the efficacy or safety of beta-adrenergic antagonists in PD. However, the GDG felt that for selected people with PD with postural tremor they could be useful and safe.

RECOMMENDATION

R33 Beta-adrenergic antagonists may be used in the symptomatic treatment of selected people with postural tremor in PD, but should not be drugs of first choice. **D (GPP)**

7.2.6 Amantadine

Amantadine was initially investigated as an anti-viral agent but found to be effective in PD by chance. The mechanism(s) of action of amantadine in PD are unclear.

What evidence is there to support the use of amantadine in early PD?

▷ Methodology

A Cochrane systematic review[139] was found which compared the effectiveness of amantadine versus placebo or levodopa in the treatment of people with early PD who are functionally disabled. The review included six studies, with a total sample size of 215 people with PD.

An additional randomised crossover trial[140] was found but excluded due to the following methodological limitations: methods of randomisation and allocation concealment not stated, limited patient characteristics given, no intention-to-treat analysis, and no power calculations provided for the small sample size (N=29).

Due to inadequate reporting of trial data, only two of the six trials within the systematic review had results that could be examined. However, in these two trials[141,142] only data for the trials' 'means' were given and thus no statistical analysis of the significance of the changes due to amantadine could be undertaken.

▷ Evidence statements

The systematic review was methodologically sound and hence it could technically be given a grading of 1++/1+. However, the methodological limitations of individual studies contained within the review meant that there were insufficient robust data from which to derive evidence statements.

▷ From evidence to recommendation

There are limited trial data to document the efficacy and safety of amantadine in early PD. This can be explained by its development in the 1970s, when trial design was in its infancy. The GDG concluded that, while amantadine should be available for the treatment of mild PD symptoms, other drug classes (ie levodopa, dopamine agonists) are more appropriate treatments for the early stages of the disease.

RECOMMENDATION

R34 Amantadine may be used as a treatment for people with early PD but should not be a drug of first choice. **D (GPP)**

7.2.7 Anticholinergics

Anticholinergics have been used to treat PD for over 100 years. They were introduced in the late 19th century after Charcot's work with hyoscine (scopolamine). In the mid-20th century, the selective centrally active muscarinic receptor antagonists were developed which had fewer peripheral side effects. These agents proliferated in the absence of more effective pharmacotherapy, but the most commonly used for PD are trihexyphenidyl (benzhexol) and orphenadrine.

What is the evidence that selective muscarinic antagonists are effective and safe treatments for PD?

▷ Methodology

A Cochrane review[143] and an additional RCT[144] were found which addressed the effectiveness of anticholinergics in early PD.

One study[145] was excluded on the basis that the methodology did not constitute a randomised design between anticholinergic and levodopa treatment groups.

The Cochrane review included nine double-blind randomised crossover trials, with a total of 221 people. All of the trials compared the effectiveness of anticholinergics with placebo or no treatment. The RCT[144] was a single-blind study with a total of 82 people randomised to three groups: anticholinergics, levodopa and bromocriptine.

The Cochrane review authors highlighted that the outcome measures varied widely among the trials and the scales used to measure effectiveness were either the authors' own or no longer in current clinical use. The numerous methodological issues associated with these trials included: rating scales not being defined in detail, incomplete reporting of methodology and results, and heterogeneous study designs which precluded any analysis of the results.

▷ Evidence statements

The RCT[144] showed that the three anti-parkinsonian medications (anticholinergics, bromocriptine and levodopa) did not have qualitatively different effects upon various parkinsonian symptoms. The authors suggested that this may have been due to low level of disease severity. (**1+**)

The systematic review was methodologically sound and hence it could technically be given a grading of 1++/1+. However, the methodological limitations of individual studies contained within the review meant that there were insufficient robust data from which to derive evidence statements.

The authors of the review conclude that as monotherapy or as an adjunct to other anti-parkinsonian drugs, anticholinergics are more effective than placebo in improving motor function in PD in short-term use.

▷ From evidence to recommendation

There are insufficient data from RCTs on the efficacy and safety of anticholinergics in PD. This is particularly true of the claimed efficacy of this class in the treatment of tremor. However, the GDG concluded that anticholinergics should be available for the treatment of mild parkinsonian symptoms in people with no cognitive dysfunction. Their use should be regularly reviewed, but withdrawal can be difficult due to the re-emergence of motor impairments.

RECOMMENDATION

R35 Anticholinergics may be used as a symptomatic treatment typically in young people with early PD and severe tremor, but should not be drugs of first choice due to limited efficacy and the propensity to cause neuropsychiatric side effects. **B**

7.3 Comparisons of drug classes

While proving the efficacy and safety of a drug class in placebo-controlled trials is important, particularly from the regulatory point of view, clinicians are keen to know how each class compares with others so that evidence-based treatment recommendations can be made for individual people. Such active comparator trials are rare in PD.

Recommendations will be presented at the end of this section for all drug comparisons.

7.3.1 Modified-release compared with immediate-release levodopa

It has been suggested that levodopa induces motor complications because of its short duration of action and thus the pulsatile stimulation of dopamine receptors. To avoid this, modified- or slow-release formulations of levodopa were developed.

What is the evidence that modified-release levodopa preparations delay the onset of motor complications?

▷ Methodology

Four studies[146–149] were found which addressed the effectiveness of modified-release levodopa compared with immediate-release levodopa in the treatment of early PD.

One study[146] was excluded due to lack of important information on drug dosages, randomisation methods, method of outcomes measurement and clinical criteria for the patient group. Another study was excluded as it was an open-trial design and therefore had increased potential for bias.[148]

One of the two included studies[147] examined the efficacy of immediate-release co-beneldopa (Madopar®; levodopa and benserazide) compared with modified-release (Madopar HBS/CR®), while the other study examined immediate-release co-careldopa (Sinemet®; levodopa and carbidopa) compared with modified-release (Sinemet CR®) formulation.[149]

▷ Evidence statements

With respect to clinical rating scales and quality of life:

- the co-careldopa study[149] (N=134) found:
  - ADL scores (UPDRS scale) were in favour of the modified-release preparation ($p=0.006$ year 1; $p=0.031$ year 5).
  - Nottingham Health Profile was in favour of modified-release for emotional reaction and social isolation ($p<0.05$). (**1+**)

Both studies[147,149] found no significant differences between the treatment groups for the following outcome measures of motor impairment:

- New York University Parkinson's Disease Scale (NYUPDS)
- Northwestern University Disability Scale (NUDS)
- UPDRS
- Hoehn and Yahr scales
- Schwab and England scores. (**1+**)

One study[149] reported no significant difference between treatment groups for motor fluctuations (primary endpoint) either by diary data or by questionnaire. With respect to drug dosage, this study[149] (N=618) found the average number of daily doses was in favour of the modified-release preparation ($p<0.005$), while the other study[147] found no differences. (**1+**)

With respect to adverse effects, one study[147] reported no significant differences between the two groups. (**1+**)

With respect to withdrawal rates, one study[149] found the number of withdrawals was higher in the immediate-release group (p=0.007). (**1+**)

▷ From evidence to recommendation

This evidence suggests that there is no value in using the existing modified-release levodopa preparations to delay the onset of motor complications.

RECOMMENDATION

R36 Modified-release levodopa preparations should not be used to delay the onset of motor complications in people with early PD. **A**

7.3.2 Dopamine agonists compared with levodopa

How effective and safe are dopamine agonists compared with levodopa in the treatment of functionally disabled early PD?

▷ Methodology

Twelve RCTs[42,116,118,150–158] were found which addressed whether dopamine agonists were more effective than levodopa in treating people with early PD who are functionally disabled.

Eight of these papers were randomised double-blind studies.[116,118,150–153,155,158] One of these studies[154] was single blind and three were open-trial designs.[42,156,157] Two of the papers[116,153] included were by the same group of investigators; the more recent publication[116] reported 10-year follow-up outcomes for the same cohort of people.

The sample sizes ranged from 18 to 782 (median 82) and the trial durations ranged from 5.8 months to 120 months (median 44.4 months or 3.7 years).

▷ Evidence statements

The results from the eight trials are summarised in Table 7.2.

Table 7.2 Dopamine agonist (DA) compared with levodopa (LD) treatment (1+)

Outcome	DA versus LD
Quality of Life (PDQUALIF and EuroQol scores)	NS[158]
UPDRS total	NS[150] PPX[158]
UPDRS motor (III)	NS[151] PPX[158], RP[152]
UPDRS ADL (II)	NS[152,118] PPX[158]
Hoehn and Yahr	NS[153,154]
Columbia Score	NS[151,155] BR[153]

continued

Table 7.2 Dopamine agonist (DA) compared with levodopa (LD) treatment (1+) – *continued*

Outcome	DA versus LD
NUDS	NS[155] BR[153]
Webster scale	NS[154] BR[42]
Risk of developing motor complications	CB[118], BR[156], PPX[158]
Risk of dyskinesias	NS[118,151,155], BR[42,152,153,156], PPX[158], RP[152], BR[153], BR[42]
Risk of wearing-off	NS[151,155] PPX[158]
Risk of dystonia	NS[151,158] BR[153]
Need for supplemental levodopa	PPX[158]
Adverse events (all)	NS[118,150–152,154–156]
Somnolence, oedema, hallucinations	PPX[158]
Mortality	NS[156] BR[42]
Withdrawals	NS [118,150-152,154,157]

PPX = pramipexole; RP = ropinirole; BR = bromocriptine; CB = cabergoline; PPX/RP/BR/CB = in favour ($p<0.05$) of dopamine agonist treatment; LD = in favour ($p<0.05$) of levodopa treatment; NS = non-significant difference between treatment groups.

7.3.3 Dopamine agonists plus levodopa compared with levodopa

What is the effectiveness of dopamine agonists plus levodopa compared with levodopa monotherapy in the treatment of functionally disabled early PD?

▷ Methodology

Eight papers[115,151,154,157,159–162] were found which addressed the effectiveness of dopamine agonists combined with levodopa compared with levodopa monotherapy. Five of these studies[115,151,154,160,161] were included in a Cochrane review,[163] but these papers were reviewed independently for additional outcomes and follow-up studies.

Five of the trials[115,157,159,160,162] were open label for the majority of the follow-up, one trial[154] was single blind and one trial[151] was double blind.

The sample size ranged from 20 to 587 people (median 78) and the trial duration ranged from 12 months to 5 years.

Five articles were appraised (see Table 7.3) and met quality criteria.[164–168] No UK studies were identified.

Table 7.3 Dopamine plus levodopa compared with levodopa monotherapy (1+)

Outcome	Significance
Clinical rating scales	
UPDRS total	NS[157]
UPDRS II (activities of daily living)	NS[151,160] Li/LD[159]
UPDRS III (motor)	Li/LD[159,161], BR/LD[161]
UPDRS IV	NS[159,161]
UPDRS addendum (motor complications) scores	Li/LD[159]
On time during day	NS[161]
Hoehn and Yahr	NS[154,159,160,162] LD[161]
Webster score	NS[154] BR/LD[161]
Columbia University Rating Scale (CURS)	BR/LD[161]
Modified CURS	NS[151]
Schwab and England score	Li/LD[159]
NUDS	LD[161]
Adverse events	
All events	NS[151,154]
Mortality	BR/LD[115]
Nausea/vomiting	LD[161]
Fatigue/weakness	LD[161]
Hallucinations/confusion	LD[161]
Withdrawal rates	
Number of drop-outs	NS[151,154,157] Li/LD[159]

LD = levodopa; Li = lisuride; BR = bromocriptine; LD = in favour ($p<0.05$) of levodopa monotherapy; Li or BR/LD = in favour of ($p<0.05$) combination therapy; NS = non-significant.

▷ Health economic methodology

A US study assessed the cost-effectiveness of pramipexole compared with no pramipexole in early PD by estimating the cost per quality-adjusted life year (QALY) during a life-time horizon.[164]

One study estimated the incremental cost (IC) per QALY of initial pramipexole treatment

compared with initial levodopa treatment in early PD based on a 4-year US and Canadian multi-centre RCT.[169]

A Canadian study derived the costs per day per patient to substitute levodopa plus benserazide by ropinirole over a 5-year time horizon in a cost-minimisation analysis.[166]

A German study evaluated cabergoline compared with levodopa monotherapy by estimating the cost per decreased UPDRS score based on a Markov model with a 10-year time horizon and the ICs per additional motor complication-free patient.[167]

A Swedish study evaluated the cost-effectiveness of early cabergoline treatment compared with levodopa in the early treatment of PD by estimating the cost per year of motor complications over 5 years.[168]

A cost-minimisation analysis of dopamine agonist compared with levodopa in initial PD therapy was estimated from the perspective of the NHS over a 1-year period (Appendix E).

▷ Health economic evidence statements

In people with early PD, the incremental cost-effectiveness for pramipexole compared with no pramipexole is $8,840 in US$ 1997 (approximately £5,510) per QALY from a societal perspective and $34,420 (approximately £21,480) per QALY without including productivity gains from pramipexole.[164] However, cost-effectiveness results were sensitive to changes in the model's parameters, resulting in cost per QALYs of $3,880 (approximately £2,420) when direct medical costs are 50% higher, $46,470 (approximately £28,990) when the rate of change of UPDRS after levodopa is 0.5 (versus 1.375 baseline) and $908,310 (approximately £566,720) when no-pramipexole treatment includes pergolide as adjunct.

One study estimated the incremental cost-effectiveness of initial pramipexole treatment compared with initial levodopa treatment in patients with early PD over a 4-year time period. The incremental cost-effectiveness ratio for pramipexole was $43,000 in US$ (approximately £24,700) per QALY, using the EQ-5D health-related quality of life measure. However, the pramipexole strategy is dominated by the levodopa strategy when using the EQ-VAS to derive the health utilities.[165]

Assuming equivalent clinical effectiveness, the cost of replacing levodopa plus benserazide with ropinirole in a Canadian setting gives a net IC of $4.14 (£2.38) per patient day. From a societal perspective, productivity and caregiver utilisation savings offset the drug acquisition cost for ropinirole. Varying the key parameters (nursing home admission rates, cost of caregiver time and proportion of people with disabling dyskinesias who lost their jobs) by 15–20%, did not change the direction of the results.[166]

In people aged 60 years or over, cabergoline monotherapy was estimated to cost approximately an additional €1,030 in Euro 2002 (approximately £718) per unit decrease in UPDRS score. This value was robust to changes in the discount rate, cost data and mortality assessed in the sensitivity analysis. Levodopa monotherapy dominated cabergoline monotherapy in people under 60 years of age. Incremental costs per additional motor complication-free patient were estimated at €104,400 (approximately £72,710) in people under 60 years of age and €57,900 (approximately £40,330) in people aged 60 years or over based on subsamples of the clinical trial used for data analysis.[167]

One study estimated an incremental cost-effectiveness of €13,860 (approximately £9,660) per year of motor complications avoided with cabergoline treatment.[168]

The baseline estimates result in an IC of £2,390 for pramipexole treatment over a 1-year period. The unit cost of pramipexole had the most impact on the ICs and resulted in the widest range of all the IC estimates (£1,880 to £2,640). On the basis of equivalent quality of life between the treatments, the levodopa strategy is the less costly option (see Appendix E).

▷ From evidence to recommendation

There is a wealth of evidence from dopamine agonist compared with levodopa trials that agonists delay the onset of motor complications. However, there is some evidence that levodopa treats motor impairments and disability better. Agonists also lead to more adverse events such as somnolence, oedema and hallucinations, but this does not lead to an excess of withdrawals from the trials.

It is more difficult to interpret the generally older dopamine agonist combined with levodopa compared with levodopa monotherapy trials. There is some suggestion of combination therapy treating motor impairments and disability better than levodopa but at the expense of more adverse events such as nausea, vomiting, fatigue, hallucinations and confusion. There are few data on motor complications.

The implication is that to delay motor complications, dopamine agonists should be used initially without levodopa. However, patients' motor function will not be treated as well and they may suffer more side effects. This issue requires further clarification in trials using patient-rated quality of life as the primary outcome measure. The GDG acknowledged that the ongoing PD MED trial might provide additional data on the cost benefits of the various agents. Although useful for economic evaluations, the EQ-5D is a relatively insensitive measure of health-related quality of life. Given that no difference was detected in the PDQUALIF or EQ-VAS scales, the GDG concluded that there was no clear evidence of a clinically important difference in overall quality of life between the two treatment strategies (see Appendix E). This assumption was used in the economic model that indicated the levodopa strategy is the less costly short-term option.

7.3.4 Monoamine oxidase type B inhibitors compared with levodopa

How effective are MAOB inhibitors compared with levodopa in managing people with early PD?

▷ Methodology

Two meta-analyses[120,121] and a randomised crossover trial[133] which addressed the effectiveness of MAOB inhibitors in treating people with early PD were included.

The meta-analyses[120,121] compared MAOBs with controls (and did not differentiate between levodopa and placebo controls). In many of the included trials, the MAOB inhibitors were not given alone but were in combination with levodopa therapy. The RCT[133] also compared people on levodopa plus selegiline with levodopa plus placebo.

One meta-analysis[120] included 3,525 people with PD from 17 randomised trials while the other (a Cochrane review) included 2,422 people with PD from 10 trials.[121] The randomised crossover trial consisted of 15 people with PD. The small sample size may have underpowered the study and could be reflective of the non-significant results, when compared with the large meta-analysis.

▷ Evidence statements

With respect to clinical rating scales:

- Only one study[42] in the meta-analyses[120,121] reported mean Webster disability scores. The trial reported that the difference was non-significant between groups on levodopa plus selegiline compared with levodopa alone (no p values given). (**1+**)
- The randomised crossover trial[133] reported no significant differences between scores for the Webster rating scale (total scores) in people with PD on levodopa plus selegiline compared with levodopa alone. (**1++**)

With respect to motor complications, only one study[156] from one meta-analysis[120] reported the following:

- Motor fluctuations were more frequent among levodopa-treated people (29.7%) than selegiline-treated people (18.7%).
- People assigned to selegiline were significantly less likely to experience motor fluctuations (non-significant, no p value stated).
- Dyskinesias occurred less frequently in the selegiline group (20.7%) than the levodopa group (27.1%). (**1+**)

With respect to need for levodopa therapy, the combined trials in the meta-analysis[120] found:

- The dose of levodopa required for adequate symptom control was 67 mg lower in the selegiline arm (95% CI 14 to 119, p=0.01).
- All studies showed higher levodopa doses in the control groups than in patients treated with MAOB inhibitors (meta-analysis not performed for this outcome).[121] (**1+**)

With respect to withdrawal rates:

- Only one study[156] from one meta-analysis[120] reported data on withdrawal rates. The trial found the probability of people ceasing treatment in the selegiline group was about threefold higher than in those assigned to levodopa.
- Most of these withdrawals occurred after the first 6 months and were due to peoples' or physicians' determination of inefficacy (two people stopped because of sleep disturbance side effects). (**1+**)

With respect to mortality:

- One study[42] in the meta-analyses[120,121] reported the following between levodopa monotherapy and levodopa plus selegiline therapy:
  - for all deaths, unadjusted hazard ratio of 1.22 (95% CI 0.95 to 1.55, no p value stated)
  - first 5 years of study, unadjusted hazard ratio of 1.41 (95% CI 0.92 to 2.17, p=0.27).
- Another study[156] in one meta-analysis found no difference between rates of mortality. (**1+**)

▷ From evidence to recommendation

Selegiline delays the onset of motor complications and the need for levodopa but at the expense of more withdrawals due to lack of efficacy. There are few trial data on selegiline's effect on motor impairments and none on quality of life. The clinical experience of the GDG suggests that selegiline is less effective than levodopa in the treatment of functional impairments and disability in PD. There are no trial data or clinical experience on the comparative efficacy and safety of rasagiline. Further trials to compare MAOB therapy with levodopa are required.

7.3.5 Monoamine oxidase type B inhibitors compared with dopamine agonists

How effective are MAOB inhibitors compared with dopamine agonists in the treatment of early PD?

▷ Methodology

Only two RCTs[156,42] were found which compared the effectiveness of MAOB inhibitors and dopamine agonists in the treatment of early PD.

Both studies included a third levodopa therapy arm. Most of the disability and motor function analysis in the UK-PDRG study[42] involved the comparison of bromocriptine with levodopa. Similarly, the other trial[156] used the levodopa group as the reference group and did not provide statistical analysis of the results for the comparison of selegiline and dopamine agonists.

The UK-PDRG study[42] consisted of 782 people with PD, and compared the effectiveness of levodopa, levodopa and selegiline and bromocriptine. The other study[156] consisted of 473 people with PD, and compared the effectiveness of selegiline, levodopa and dopamine agonists (bromocriptine and lisuride). It is important to note that selegiline in the UK-PDRG trial[42] was combined with levodopa therapy, whereas the other study[156] used selegiline as a monotherapy (levodopa could be added if physician deemed selegiline alone to be ineffective).

▷ Evidence statements

In the UK-PDRG study,[42] after 9 years of follow-up, there was a non-significant difference in Webster scores (adjusted for baseline score) between the bromocriptine group and the levodopa plus selegiline group. (**1+**)

With respect to motor complications, one study[156] found no significant differences in:

- motor fluctuations
- mean time to motor fluctuation
- frequency of dyskinesias
- difference in time to dyskinesia between dopamine agonist and MAOB inhibitor groups. (**1+**)

With respect to mortality, the UK-PDRG study[42] found non-significant differences in mortality between levodopa plus selegiline and bromocriptine groups:

- unadjusted hazard ratio for overall deaths (non-significant)
- unadjusted hazard ratio in first 5 years was (p=0.27). (**1+**)

The other study[156] found no significant difference in mortality between the dopamine agonist groups and the selegiline group. (1+)

With respect to withdrawal rates, one study[156] reported the following.

- Most people with PD withdrew from dopamine agonists because of nausea/vomiting or postural hypotension or both (43/53 people).
- Most of the withdrawals in the selegiline group occurred in the first 6 months of treatment and were due to lack of efficacy.
- Combination therapy was started in 40.7% of people on dopamine agonists and 63.9% of people on selegiline.
- The initiation of levodopa therapy was delayed for a median of 30 months in dopamine agonist group and 15 months in selegiline group. (1+)

▷ From evidence to recommendation

While there was no difference in the delaying of motor complications between MAOB inhibitors and dopamine agonists, there is a suggestion that agonists are more effective than MAOB inhibitors in delaying the need for levodopa. More people with PD withdraw from MAOB inhibitors because of lack of efficacy; however, this evidence is based on just two studies and all of the data relates to selegiline.

7.4 Choice of initial pharmacological therapy in early Parkinson's disease

7.4.1 From evidence to recommendation

See Table 7.1 for a summary of the drugs covered within this section.

It was evident from reviewing the evidence base that there is no single drug of choice in the initial pharmacotherapy of early PD.

Further trials are required to compare the initial treatment of PD with levodopa, dopamine agonists and MAOB inhibitors, preferably using quality-of-life and health economics outcome measures. The UK PD MED trial will attempt to address these comparisons. More information can be found from **www.pdmed.bham.ac.uk**

RECOMMENDATION

R37 It is not possible to identify a universal first-choice drug therapy for people with early PD. The choice of drug first prescribed should take into account:

- clinical and lifestyle characteristics
- patient preference, after the patient has been informed of the short- and long-term benefits and drawbacks of the drug classes. **D (GPP)**

7.5 Later pharmacological therapy

'"Off" is unmedicated. At my stage, it can get to where I can't really speak that well and I can't inflect. I can't really use my face. I'll be shaking. And that's "off". And then "on" is a version of this, which is when the medication's working. I have "on" plus, because I have a little bit of dyskinesia, which is a function of the medication.'

(patient)[3]

7.5.1 Introduction

It was evident from reviewing the evidence base that there is no single drug of choice in the pharmacotherapy of later PD. Table 7.4 may help to guide the reader through the following section.

Table 7.4 Options for adjuvant pharmacotherapy in later PD

Adjuvant therapy for later PD	First-choice option	Symptom control	Possible risk of side effects	
			Motor complications	Other adverse events
Dopamine agonists	✓	++	↓	↑
COMT inhibitors	✓	++	↓	↑
MAOB inhibitors	✓	++	↓	↑
Amantadine	×	NS	↓	↑
Apomorphine	×	+	↓	↑

+++ = Good degree of symptom control.
++ = Moderate degree of symptom control.
+ = Limited degree of symptom control.
↑ = Evidence of increased motor complications/other adverse events.
↓ = Evidence of reduced motor complications/other adverse events.
NS = Non-significant result.

7.5.2 Levodopa

Since most people with PD will eventually need levodopa, they will all with time develop motor complications. While the latter can be mild and not interfere with a person's quality of life, for some they can be severely incapacitating. Adjuvant drugs to take with levodopa have been developed with the aim of reducing these complications and improving quality of life.

The previous section contains a statement about the methodological limitations of symptomatic therapy studies and recommendations about symptomatic pharmacological therapies for both early and later disease.

The GDG was concerned that the old practice of withdrawing PD patients from medication in the hope of improving motor complications is dangerous. Such 'drug holidays' can lead to severe immobility with secondary chest infection, neuroleptic malignant syndrome and death. This practice is rarely performed now and, because of the dangers, it should be abandoned.

▷ Modified-release levodopa

Wearing off of the effects of levodopa and peak dose dyskinesia is largely caused by pulsatile stimulation of dopamine receptors, which is related to the intermittent administration of exogenous immediate-release levodopa. One potential way to overcome this is to prolong the effect of each dose of levodopa by administering controlled or modified-release levodopa preparations. Such preparations of co-careldopa (Sinemet CR®) and co-beneldopa (Madopar HBS/CR®) have been developed.

Can modified-release preparations of levodopa reduce motor complications compared with immediate-release preparations?

▷ Methodology

Eleven randomised controlled trials[170–180] comparing the effect of controlled-release 50/500 mg levodopa with immediate-release 25/100 levodopa in later PD were found. The sample size (range 19–202, mean 57) and mean age of people (range 58–67 years, mean 62.8) varied between trials.

Most of the included studies[170–178,180] used the co-careldopa formulation of either 25/100 or 50/200 for the immediate-release and controlled-release tablets, respectively. Only one trial[179] used 25/200 for the immediate-release dosage, but administered 50/200 for controlled release. None of the included trials used the co-beneldopa formulation.

Only one trial reported a washout period between trials[179] all other trials analysed data from either the end of the trial arms or at week 2 or later in each arm.

All of the included trials started with an open-label titration phase in which the optimal anti-parkinsonian dose and inter-dose interval for each treatment were determined. In many of the trials a large percentage of people withdrew (35%,[179] 31%,[175] 26%,[170] 24%,[173] 18%,[180] 17%[171]) during the open phase because of inconsistencies with response, delayed onset of drug action or adverse events. Due to the already small sample size (average 60), lack of power calculations and intention-to-treat analysis, these studies were highly biased towards a pre-selected patient population. The trial duration was also very short with a range of 8–24 weeks.

▷ Evidence statements

The results of the trials are summarised in Table 7.5.

With respect to adverse events:

- Most common adverse events for both treatments included dizziness, dyskinesia, dystonia, headache, hallucinations, nausea, vomiting, hypotension and confusion.[171,176,177]
- There was no significant difference in the reported incidence of adverse events between the two treatment groups.[171,174,180]
- One study[177] reported people treated with controlled-release levodopa had a higher incidence of self-reported adverse events ($p<0.05$) but not a higher frequency. (1+)

Table 7.5 Controlled-release compared with immediate-release levodopa

Outcome measures	Results
Total number of trials	11
Total sample size (N)	646
Clinical rating scales	
UPDRS motor score	CR[173]
Hoehn and Yahr score	CR[175]
NYUPDS score (after 6 months' treatment)	CR[177]
SEALD score	CR[171]
Patient-rated global improvement	CR[175]
Physician-rated global improvement	CR[175]
Patient-reported helpfulness of medication and improvement in clinical fluctuations	CR[171]
Motor complications	
On time	CR[173,175,178,179] IR[173]
Off time	CR[173,177,179]
Dyskinesia duration	IR[178]
Levodopa dose	
Mean doses per day	CR[170,172,173,175,180] NS[177]
Mean interdose interval	CR[170,173,180]
Mean daily levodopa dose (mg/d)	IR[171–174,176,178–181]

CR = controlled release - favouring ($p<0.05$) CR; IR = immediate release - favouring ($p<0.05$) IR; NS = non-significant ($p>0.05$).

With respect to withdrawal rates:

- Two studies[171,172] found 52–54% of people preferred controlled release over 27–33% of people who preferred immediate release.
- Two studies found high numbers of people continuing controlled-release therapy after the completion of their trials (100%[179] and 87%[180]).
- Common reasons for withdrawal include adverse events, insufficient therapeutic response, lack of compliance and missing follow-up appointments.[176,177] (**1+**)

▷ From evidence to recommendation

The trial evidence suggests that modified-release levodopa preparations can satisfactorily reduce motor fluctuations. However, the GDG had considerable reservations about the design

of many of the trials. Subsequent clinical practice has found that switching directly from immediate- to modified-release levodopa leads to an increase in off time. This is probably due to poorer absorption of modified-release preparations from the gut. As a result, modified-release levodopa is rarely used to manage motor complications. Modified-release preparations are also more expensive than immediate-release formulations. The GDG concluded that combinations of modified- and immediate-release levodopa could be useful in a small number of people with motor complications.

RECOMMENDATION

R38 Modified-release levodopa preparations may be used to reduce motor complications in people with later PD but should not be drugs of first choice. **B**

7.5.3 Dopamine agonists

While recent trial work has concentrated on the use of dopamine agonists as initial therapy in PD, these agents were originally introduced as adjuvant therapy to reduce motor complications in later disease.

How effective and safe are dopamine agonists as adjuvant therapy in later PD?

▷ Methodology

Nine papers, which included six Cochrane reviews[182–187] and three additional RCTs,[188–190] were found that addressed the effectiveness of adding dopamine agonists compared with placebo in the treatment of motor complications in people with later PD. Sample sizes of these trials are listed in Table 7.6. No RCTs were found on lisuride's effectiveness.

There were several issues for consideration with the trials included in the Cochrane reviews,[182–187] such as:

- inclusion of phase II and III studies and unpublished papers
- additional unpublished data obtained from investigators or manufacturers sought by the Cochrane authors.

The three RCTs[188–190] that were published since the Cochrane reviews were well designed and had sound methodologies.

▷ Evidence statements

With respect to quality of life:

- two trials, one[191] included in the Cochrane review[186] and another published after the review,[188] reported the following outcomes in favour of pramipexole:
  - Functional Status Questionnaire Basic ADL
  - mental health scales
  - EuroQol Scale
  - patient diaries (impairment of daily living and severity of tremor ($p<0.0001$). (**1++**)

With respect to clinical rating scales, motor complications and levodopa dose reduction, improvement was found to be in favour of the dopamine agonists (bromocriptine, cabergoline, pergolide, pramipexole and ropinirole) in most of the included trials (Table 7.6).

Table 7.6 Dopamine agonists compared with placebo in later PD

	Bromocriptine 182(192–198)	**Cabergoline** 183(199–201)	**Pergolide** 185(202)	**Pramipexole** 186(191,203–205),188–190	**Ropinirole** 187(206–208)
Number of trials	7	3	1	7	3
Sample size (N)	400	268	376	1,228	263
Clinical rating scales					
UPDRS II	–	DA[201] NS[199]	–	DA[191,203–205,189,190]	–
UPDRS III	–	DA[201] NS[199]	–	DA[191,203,204,189,190] NS[205]	–
UPDRS IV	–	–	–	DA[203,204] P NS[191,205]	–
Hoehn and Yahr	–	NS[200,201]	DA[202]	DA[203] NS[191]	–
S & E	–	NS[199,200]	–	A[203] NS[191]	–
MCRS*	–	–	DA[202]	–	–
Global rating					
Clinician	–	DA[200]	–	DA[204,188,190]	DA
Motor complications					
Dyskinesia	LD[198]	–	LD[202]	–	LD[207]
Off time	NS[195,197]	NS[199,200]	DA[202]	DA[191,203–205,189]	DA[207]
Impairment	DA[195,196] NS[198]	–	–	–	DA[207]
Wearing-off	DA[196]	–	–	–	–
Levodopa					
Levodopa dose reduction	NS[196]	DA[201]	DA[202]	DA[191,203,205]	DA[207]
Adverse events					
Hallucinations	–	NS[199–201]	P[202]	P[191,203,204]	–
Dyskinesia	–	NS[199]	P [202]	DA[191,203,204]	P[207]
Hypotension	NS	DA[199–201]	–	NS[191,203-205]	–
Withdrawal rate					
All cause	NS	NS[199–201]	NS[202]	DA[191,203]	NS[207]
Adverse events	–	–	P[202]	–	–

DA = favouring dopamine agonist ($p<0.05$); P = favouring placebo ($p<0.05$); – = not reported; NS = non-significant ($p>0.05$).
References for papers included in Cochrane reviews.
*Modified Columbia Rating Scale including gait, tremor, ADL and motor scores.

▷ From evidence to recommendation

In people with PD and motor complications, adjuvant dopamine agonist therapy reduces off time and levodopa dose and improves motor impairments and activities of daily living. This is at the expense of increased dopaminergic adverse events including dyskinesia, hallucinations and postural hypotension. These conclusions are based on short-term trials and the long-term acceptability of adjuvant agonist therapy remains to be evaluated.

Concerns regarding serosal reactions with ergot-derived dopamine agonists have been considered earlier in this chapter.

RECOMMENDATIONS

R39 Dopamine agonists may be used to reduce motor fluctuations in people with later PD. **A**

R40 If an ergot-derived dopamine agonist is used, the patient should have a minimum of renal function tests, ESR and chest radiograph performed before starting treatment and annually thereafter.* **D (GPP)**

R41 A dopamine agonist should be titrated to a clinically efficacious dose. If side effects prevent this, then another agonist or a drug from another class should be used in its place. **D (GPP)**

R42 In view of the monitoring required with ergot-derived dopamine agonists, a non-ergot-derived agonist should be preferred in most cases. **D (GPP)**

7.5.4 Monoamine oxidase type B inhibitors

The MAOB inhibitor selegiline was first used as a symptomatic treatment for PD before it was evaluated as a possible neuroprotective therapy (Chapter 6). More recently, rasagiline has become available as another MAOB inhibitor with symptomatic effects in PD.

How effective and safe are these MAOB inhibitors in treating the motor complications of later PD?

▷ Methodology

Ten randomised double-blind placebo-controlled trials[209–218] were found which addressed the effectiveness of MAOB inhibitors as an adjunct to levodopa treatment in people with later PD and motor complications. Of these nine trials, six were parallel group studies and three were crossover trials.

All of the trials apart from three,[209,217,218] investigated the effectiveness of conventional selegiline treatment. Two RCTs[217,218] investigated the effectiveness of rasagiline, while the other[209] assessed the effectiveness of Zelapar® selegiline, a formulation that dissolves on contact with saliva and undergoes pregastric absorption.

*Full details of the restrictions on pergolide use and monitoring are available in the Summary of Product Characteristics.

A common methodological issue in all the conventional selegiline trials was the lack of sample size calculations. Most of these trials failed to demonstrate a significant difference in many of the outcomes measures investigated between active treatment and placebo. The small sample sizes (range 19–96, mean 54.6) and the short-term duration (range 3–8 weeks, mean 6.7 weeks) need to be taken into consideration.

One large (N=687) RCT (LARGO)[217] compared rasagiline with entacapone and placebo over 18 weeks. Another RCT (PRESTO)[218] with a large sample size (N=472) and duration of 26 weeks compared two different doses of rasagiline (0.5 or 1 mg) with placebo.

The Zelapar® selegiline study[209] was a (N=140) study of 12 weeks' duration. The only shortcoming of this trial was the lack of a conventional selegiline arm to directly compare the two formulations.

Most of the studies using conventional selegiline used a dose of 10 mg/day. One study[214] used a dosing sequence of 0–5–10 mg/day in a random order, another study[211] started with 5 mg/day in the first 4 weeks and increased to 10 mg/day for the final 4 weeks, and only one study[210] used 5 mg/day for the entire trial duration of 8 weeks. The rasagiline study administered a dose of 1 mg/day for 18 weeks. The study on Zelapar® selegiline used a dose of 1.25–2.5 mg/day for 12 weeks.

▷ Evidence statements

Outcomes that favoured ($p<0.05$) conventional selegiline were:

- Physician preference[211]
- Webster Rating Scale[211]
- Modified Columbia Rating Scale: 5/22 items (dressing, dysarthria, hypomimia, sialorrhoea, tremor)[212]
- Disability Scale: 2/22 items (facial expression and resting tremor)[213]
- Investigator's Global Subjective Opinion: more likely to have experienced improvement than worsened or no change.[213] (**1+**)

With respect to patient observations of conventional selegiline:

- At the end of the 6-week treatment period 76% of people reported themselves to be improved in the selegiline group and only 26% in the placebo group.[212]
- People reported the following while on selegiline treatment: dose of levodopa lasted longer, transitions between on and off periods were less abrupt, on periods were better, off periods were less severe.[216] (**1+**)

With respect to long-term follow-up:

- One study[215] performed a long-term blinded follow-up. People selected the treatment period they preferred during the randomised short-term trial and they were maintained on that preferred treatment for about 16 months on average. The follow-up study found:
  - The average levodopa dose was significantly lower ($p<0.001$) in selegiline-treated people.
  - The average dosing frequency was also lower in the selegiline group ($p<0.01$). (**2+**)

Table 7.7 MAOB inhibitor compared with placebo

Outcome	Conventional selegiline	Rasagiline	Zelapar® selegiline
Number of trials	7	2	1
Sample size (N)	169	1,159	140
Quality of life			
PDQUALIF scores	–	NS[218]	–
Clinical rating scales			
UPDRS total	–	R[217]	–
UPDRS motor (on)	–	R[217,218]	–
UPDRS ADL (off)	–	R[217,218]	–
UPDRS subscores	–	R[217,218]	–
Schwab and England ADL	–	R[218]	–
Patient diaries: proportion of people with improvement	SEL[212,213]	–	–
Clinician Global Impression Scale	–	R[217,218]	SEL[209]
Patient Global Impression Scale	–	–	SEL[209]
Motor complications			
On-off episodes	SEL[210]	–	–
On time	SEL[214]	R[217,218]	SEL[209]
Off time	SEL[214]	R[217,218]	SEL[209]
On time with dyskinesia (increased)	P[214]	NS[217] R[218]	–
Tremor	SEL[215]	R[217]	–
Daily levodopa dose			
Levodopa dose reduction	SEL[211,215,216]	R[217]	–
Adverse events and withdrawal rates			
Any adverse events	NS	NS[217]	NS[209]
All-cause withdrawal rates	NS	NS[217,218]	NS[209]

SEL = favouring selegiline ($p<0.05$); R = favouring rasagiline ($p<0.05$); P = favouring placebo ($p<0.05$);
– = not reported; NS = non-significant ($p>0.05$).

One rasagiline RCT[218] reported a significant ($p<0.05$) increase in adverse events in the treatment group:

- Dyskinesias were reported as an adverse event by 10% receiving placebo and by 18% receiving either dose of rasagiline.
- Weight loss, vomiting and anorexia were reported in 1.0 mg/day group.
- Balance difficulty and depression were reported in 0.5 mg/day group. (**1++**)

▷ From evidence to recommendation

The size and quality of the adjuvant selegiline trials was poor, so it is impossible to reach firm conclusions about its efficacy and safety in later PD. The more recent study with the buccal formulation of selegiline and two large oral rasagiline trials provide more convincing evidence for the efficacy and safety of MAOB inhibitors in later PD. However, all studies were of short duration, so no comments on the long-term benefits and drawbacks of these agents can be made.

RECOMMENDATION

R43 MAOB inhibitors may be used to reduce motor fluctuations in people with later PD. **A**

7.5.5 Catechol-O-methyl transferase inhibitors

Levodopa is now always combined with carbidopa (co-careldopa) or benserazide (co-beneldopa) to block its metabolism by dopa decarboxylase. This increases levodopa bioavailability by twofold to threefold and reduces peripheral side effects. However, only 5–10% of each levodopa dose crosses the blood-brain barrier, the rest being metabolised to 3-O-methyldopa by catechol-O-methyl transferase (COMT). The aim of COMT inhibitors is to further reduce the metabolism of levodopa and thus increase the amount crossing into the brain.

Two COMT inhibitors are available: entacapone and tolcapone. These lead to a 30–50% increase in levodopa half-life and a 25–100% increase in the levodopa concentration versus time curve (area under the curve); they do not increase the maximum plasma concentration of levodopa.[219] Most of this occurs because of peripheral inhibition, but tolcapone also has a central effect in the brain.

Tolcapone was the first COMT inhibitor to enter clinical practice in England and Wales but its European product licence was withdrawn in November 1998 after three cases of fatal hepatic toxicity. However, after further clinical experience in other markets and a forced switch from entacapone to tolcapone study, it has recently been reintroduced in Europe. It is currently licensed, at a dose of 100 mg three times per day, for people who have failed on entacapone, and requires mandatory liver function test monitoring at 2-week intervals for the first year of treatment followed by less stringent monitoring ad infinitum.

Entacapone has been combined with the levodopa plus carbidopa combination (co-careldopa) as a triple combination called Stalevo®. One study has shown that Stalevo® simplifies the taking of medication, which is more acceptable to patients.[220]

How effective are these COMT inhibitors in reducing the motor complications of later PD?

▷ Methodology

A Cochrane review[221] was found which addressed the effectiveness of the COMT inhibitors tolcapone and entacapone compared with placebo in people with PD suffering from motor complications.

Two additional RCTs[217,222] were found after the Cochrane search date. One RCT[217] compared entacapone (200 mg) with placebo (LARGO). The study[217] had a large (N=456) sample size and a trial duration of 18 weeks. The other RCT[222] compared entacapone (200 mg) with levodopa monotherapy. The study sample size was large (N=270) and the trial duration was 13 weeks. The methodological limitations of this study were lack of reported methods of randomisation and allocation concealment.

An additional RCT[223] was also found but excluded on the basis of patient characteristics. The people included in this trial could not experience end-of-dose wearing off within 4 hours of levodopa use, and had an average disease duration of 4.5 years. The results of this trial were not included due to the absence of motor complications.

The Cochrane review consisted of 14 trials (13 phase III, one phase II) and 2,566 patents with PD and motor fluctuations. Eight trials[224–231] examined entacapone compared with placebo (N=1560) and six trials[232–237] examined tolcapone compared with placebo (N=1006). Two of the included entacapone papers[229,230] were abstracts; however, the results were consistent with the full publications. The level of evidence for the Cochrane review is graded as 1++, which is based on the review's methodology and not that of the individual trials.

Issues for consideration with the Cochrane entacapone studies included: lack of randomisation and allocation concealment methods, lack of methodological detail available from the abstracts, and two studies did not state the method of data analysis. In addition, one of the entacapone studies[228] was a crossover design (N=26) without a washout period, and the results were presented as a combination of the two trial arms. The review did not use the results of this study in the meta-analysis.

▷ Evidence statements

Table 7.8 summarises the evidence for the effectiveness of COMT inhibitors compared with placebo.

The additional RCT[222] which compared entacapone with levodopa monotherapy reported the following significant ($p<0.05$) results in favour of combined therapy:

- improvement in UPDRS II (ADL) score, treatment difference –1.6 (95% CI –2.4 to –0.8, p=0.0001)
- UPDRS III (motor) scores decreased, treatment difference –1.9 (95% CI –3.7 to –0.2, p=0.03)
- mean UPDRS total score decreased, treatment difference –3.6 (95% CI –6.0 to –1.2, p=0.004)
- fluctuation sum score (UPDRS IVb) decreased, treatment difference –0.3 (95% CI –0.5 to –0.1, p=0.02)
- Global Assessment scores by study investigator increased ($p<0.001$) and the proportion of participants who improved was greater. (1+)

Table 7.8 Meta-analysis of COMT inhibitors compared with placebo[221] (1++)

	Entacapone	Tolcapone	Combined meta-analysis
Number of trials	9	6	14
Sample size (N)	2,016	1,006	2,566
Efficacy			
Levodopa dose reduction	COMT[217,224–227,230]	COMT*[232–237]	COMT
Off time (hours)	COMT[217,224–227]	COMT*[232,233,235,236]	COMT
On time (hours)	COMT[217,224–227]	COMT*[232,233,235,236]	COMT
UPDRS ADL	COMT[217,225–227,231]	COMT**[234]	–
UPDRS motor score	COMT[217,225–227,231]	COMT**[233]	–
Adverse events			
Dyskinesia	P[224–227,231], NS[217]	P*[232–237]	P
Nausea	P[224–227,231], NS[217]	P*[232–237]	P
Vomiting	P[225,226], NS[217]	P*[232–237]	P
Diarrhoea	P[224–227], NS[217]	P**[233–235,237]	P
Constipation	P[224–226], NS[217]	NS[234–237]	
Hallucinations	NS[217,224–227]	P**[232–237]	P
Withdrawal rates			
Due to adverse events	P[224–227,231], NS[217]	NS[232–237]	P
Due to all causes	P[224–227,231], NS[217]	NS[232–237]	P

COMT = favouring COMT inhibitor ($p<0.05$); P = favouring placebo ($p<0.05$); – = not reported; NS = non-significant ($p>0.05$); *Significant for 50, 100, 200 and 400 mg tds doses; **Significant for 200 mg tds doses
Numbers within the table refer to the references of the original papers.

The RCT[222] also reported the following non-significant outcomes between treatment groups:

- Parkinson's Disease Questionnaire 39 (PDQ-39) summary index scores and subscores
- SF-36 variables and EQ-5D self-rating questionnaire utility score
- patient home diaries: mean 'off' time and mean 'on' time
- UPDRS I (mentation, behaviour and mood) scores
- dyskinesia sum score (UPDRS IVA)
- severity of PD (UPDRS part V; Hoehn and Yahr staging)
- UPDRS IV (Schwab and England)
- mean daily dose of levodopa. (1+)

The RCT[222] reported the following in relation to adverse events.

- 113 (65%) entacapone and 47 (49%) levodopa monotherapy people reported adverse events.
- A total of 311 adverse events occurred in entacapone (2.8 events per participant) and 104 in levodopa monotherapy group (2.2 events per participant).
- The most frequently reported adverse events significantly ($p<0.05$) in favour of levodopa monotherapy were nausea, diarrhoea, aggravated parkinsonism and constipation.
- A frequently reported adverse event was also dyskinesia, but there was no significant difference between treatment groups. **(1+)**

The RCT[222] reported the following results in relation to withdrawal rates.

- 45 (17%) of participants discontinued prematurely (27/174 entacapone and 18/96 levodopa monotherapy).
- Reported reasons for discontinuation were: adverse events for 26 (10%) of people; an unsatisfactory response to treatment for 14 (5%) of people; a wish to discontinue for three participants (1%); and other reasons for two participants (1%). **(1+)**

▷ From evidence to recommendation

The placebo-controlled COMT inhibitor trials document the efficacy of these agents in reducing off time and levodopa dose, while improving on time, motor impairments and disability. This is at the expense of increased dopaminergic adverse events such as nausea, vomiting and dyskinesia.

Tolcapone has caused rare cases of fatal hepatic toxicity and neuroleptic malignant syndrome. As a result, it can only be used in England and Wales after a patient has failed on entacapone and its use requires intensive monitoring of hepatic function (see Summary of Product Characteristics).

RECOMMENDATIONS

R44 Catechol-O-methyl transferase inhibitors may be used to reduce motor fluctuations in people with later PD. **A**

R45 In view of problems with reduced concordance, people with later PD taking entacapone should be offered a triple combination preparation of levodopa, carbidopa and entacapone.* **D (GPP)**

R46 Tolcapone should only be used after entacapone has failed in people with later PD due to lack of efficacy or side effects. Liver function tests are required every 2 weeks during the first year of therapy, and thereafter in accordance with the Summary of Product Characteristics. **D (GPP)**

7.5.6 Amantadine

When originally introduced, amantadine was used as an early therapy for PD. It fell into disuse as more effective agents such as levodopa and dopamine agonists became available. In the last few years, amantadine has had a revival after several small trials suggested it might have an anti-dyskinetic effect in people with later PD and motor complications.

How effective and safe is amantadine in managing the motor complications of later PD?

*Trade name Stalevo® (Orion).

▷ Methodology

A Cochrane review[238] and an RCT[239] (published after the review) were found which compared the effectiveness of adding amantadine versus placebo in the treatment of people with later PD and motor complications.

The Cochrane review[238] included three studies with a total of 53 people, while the RCT[239] included a total of 40 people.

Issues for consideration included a lack of reporting: allocation concealment, washout periods in crossover design trials, clinical criteria for PD diagnosis, and intention-to-treat analysis. The trials were generally of small sample size (range 11–40) and short trial duration (range 4–6 weeks). A dose of 100–400 mg/day of amantadine was used.

The three trials[240–242] included in the review[238] were all crossover designs, in which none had reported the results of the first treatment arms. Two of the trials[241,242] did not incorporate a washout period; thus, data from these trials were not reported.

▷ Evidence statements

The RCT[239] found the results of key outcome measures changed over time (Table 7.9). (**1+**)

Table 7.9 Amantadine compared with placebo at different time points[239]

	After 15 and 30 days' treatment	After 8 months' treatment	After 1 month withdrawal
Clinical rating scale			
UPDRS items 32–34 (self-assessment)	A	NS-B	NS
Motor complications			
IGA scores of dyskinesia	NS-A	NS-B	NS
DRS total scores	NS-A	NS-B	NS

A = favours amantadine ($p<0.05$); NS-A = non-significant improvement in amantadine; NS = no differences between groups; NS-B = non-significant worsening in amantadine; IGA = Investigator Global Assessment; DRS = Dyskinesia Rating Scale.

With respect to motor complications:

- Only one trial from the systematic review[240] reported the outcome of dyskinesia severity following levodopa challenge. This trial reported that dyskinesia was reduced after oral amantadine treatment by 6.4 points (41%) when compared with placebo arm (after 2 weeks of amantadine treatment). (**1++**)

With respect to adverse events:

- Only one trial[240] from the systematic review[238] reported adverse events for patients while on amantadine medication; these included: confusion, worsening of hallucinations, reappearance of palpitations, nausea, reversible oedema, dry mouth and constipation. (**1++**)

- Only one trial[239] from the review reported adverse events following amantadine withdrawal; these included: an abrupt increase of dyskinesia to 100% of daily time, hypothermia, and severe confusion (amantadine was reintroduced). (1+)

With respect to withdrawal rates:

- Reasons for withdrawal from amantadine treatment included: mild and transient adverse events,[242] tachycardia (N=1),[239] psychosis and livedo reticularis (N=2).[239] (1++)
- Reasons for withdrawal from placebo group included: dizziness,[239] somnolence,[239] poor compliance.[241] (1++)

▷ From evidence to recommendation

While there is some encouraging trial evidence that amantadine can be used as an anti-dyskinesia agent, data on its long-term effects are lacking. The evidence from one small trial suggests that amantadine's anti-dyskinetic effect is substantially reduced after 8 months of therapy. Further work is required in this area.

RECOMMENDATION

R47 Amantadine may be used to reduce dyskinesia in people with later PD. **C**

7.5.7 Apomorphine

Apomorphine is a dopamine agonist that is not effective orally due to extensive first-pass metabolism in the liver. Early studies in PD lead to severe emesis and pre-renal failure. Its further development was facilitated by the availability of the antiemetic domperidone, which in doses of 10–30 mg tds for 72 hours before apomorphine can prevent most peripheral dopaminergic side effects.

There are currently two distinct methods of administering apomorphine: subcutaneous bolus doses and continuous infusion. People with a maximum of five or six off periods per day are suitable for intermittent bolus injections. Initially, the threshold dose of apomorphine (usual range 2–4 mg) is established as an inpatient using clinical examination and motor rating scales. The patient is then trained to use a pre-filled apomorphine injection system in which the agreed threshold dose can be dialled up more easily by the patient when in the off state.

Subcutaneous infusions of apomorphine are appropriate for PD people with so many off periods that repeated bolus injections are inappropriate. Apomorphine is administered by a portable syringe driver connected via a butterfly cannula sited in the abdominal wall or subcutaneous tissue of the thighs. The programmable pump delivers 50–120 mg of apomorphine over the waking day or the whole 24-hour period. Usually, oral medication can be reduced according to the patient's response. Considerable adjustment of the infusion dose is required once the patient is in the home environment. This can be facilitated by a PDNS.

What is the evidence that apomorphine injections and infusions are effective and safe treatments for motor complications in later PD?

7.5.8 Intermittent subcutaneous apomorphine injections

▷ Methodology

Three randomised controlled trials[243,244,245] were found which addressed the effectiveness of subcutaneous injections of apomorphine compared with placebo. The people included in these trials were all classified as later PD and had mean disease duration of 9–12 years.

All three studies[243,244,245] were placebo controlled. One was an 8-day crossover design[244] (4 days per arm), while another was a 4-week parallel design.[243] The third consisted of five N=1 trials conducted over 10 consecutive 'off periods' with each person acting as their own control[245]. The sample sizes of all three trials were relatively small (N=29,[243,244] N=22,[243,244] and N=5[245]).

No controlled trials were found which looked at apomorphine compared with standard oral treatment, and no controlled trials were found of continuous subcutaneous apomorphine infusions.

▷ Evidence statements

Table 7.10 summarises the evidence for subcutaneous apomorphine injections.

With respect to a correlation analysis:[243]

- Levodopa dose (the single dose that produced the effect to which apomorphine responses were matched) was not predictive of the required apomorphine dose.
- Total daily levodopa dose was also not predictive of apomorphine dose ($p=0.32$).
- Inpatient response was correlated with and predictive of outpatient efficacy ($p<0.001$). (1+)

With respect to clinical global impressions:[244]

- 86% of people who completed the apomorphine 8-week follow-up (maintenance phase) reported 'much' or 'very much' improvement at the last visit.
- No people reported to have worsened during the follow-up. (1+)

With respect to withdrawal rates:[243,244]

- Reasons for withdrawal included: failure to demonstrate a significant response to the levodopa challenge, adverse events (nausea and vomiting, hypotension, exanthema), lack of motivation. (1+)

With respect to adverse events:

- Common events included: injection site complaints, drowsiness, yawning, dyskinesias, nausea or vomiting, chorea, sweating and warmth, dizziness, headache, rhinitis.[243,244]
- Other events included: nausea, dyskinesia, short-lasting twinkling (sic) in legs, short-lasting worsening of tremor, warmth and sweating, lower level of motor functioning at end of clinical effect compared with basic level before the test.[245]
- There were no significant changes in other safety measures (blood tests, electrocardiography, physical examination).[243] (1+)

Table 7.10 Effectiveness of subcutaneous apomorphine injections (1+)

Outcome		Before versus after treatment
Clinical rating scales		
UPDRS (I, II, III, IV) scores		NS[244]
UPDRS motor (III) score		APO[243]
Columbia individual item (tremor, rigidity, gait, hypokinesia, stability) scores		APO[245*]
Columbia total score		APO[245*]
Timed finger/foot tapping, walking and pinboard combined test scores		APO[245*]
Patient diaries for hand-tapping test		APO[243]
Patient diaries for Webster step-seconds scores		P[243]
Motor complications		
Mean daily duration of off periods (minutes/day)	Staff rating	APO[244]
	Patient rating	APO[244]
Mean daily numbers of off periods	Staff rating	P[244]
	Patient rating	NS[244]
Distribution of severity of off periods		APO[244]
Patient diaries (out of 10 parameters):		
Off-state events aborted per patient		APO[243]
Onset latency (minutes)		APO[243]
Total time off per day		APO[243]
Incidence of dyskinesia		P[243]
Adverse events		
Yawning		P[243]
Mean daily duration of involuntary movements		P[243]
Mean daily numbers of involuntary movements		P[243]

APO = favouring dopamine agonist ($p<0.05$); *$p<0.001$; P = favouring placebo ($p<0.05$); – = not reported; NS = non-significant ($p>0.05$).

7.5.9 Apomorphine infusions

▷ Methodology

There were no randomised or controlled trials, which assessed the effectiveness of chronic apomorphine infusion in people with later PD. Ten studies, nine retrospective[246–254] and one prospective,[255] were found which investigated the benefit of chronic apomorphine treatment compared with pre-treatment evaluations.

Most of the included retrospective studies used a hospital/clinic database to identify people who had received apomorphine for the treatment of severe motor fluctuations or dyskinesia, but who were refractory to optimal oral medication. One prospective study enrolled people with motor fluctuations and dyskinesias at two sites if they were refractory to oral medication and scheduled to start continuous apomorphine infusion.[255] For included studies, the follow-up ranged from 3 months to 5 years, the sample size ranged from seven to 64 people, and the average age ranged from 56 to 65 years.

The methodological limitations of these studies included: lack of prospective protocols in most instances, non-randomisation of people, lack of control groups, small sample sizes, and lack of patient and/or investigator blinding.

▷ Evidence statements

Table 7.11 summarises the evidence for continuous apomorphine infusions.

With respect to clinical global rating scales:[250]

- Patient rating: no patient described overall worsening; three felt unchanged; six experienced slight improvement; and 16 had a clear improvement.[250]
- Physician rating: no patient worsened; two people were unchanged (the same who described themselves as unchanged); seven slightly improved; and 16 had clearly improved. (**3**)

With respect to drug dosage:[252]

- Larger doses of apomorphine produced a longer duration of anti-parkinsonian effect ($p<0.001$). (**3**)
- Two studies[253,254] looked at the anti-dyskinetic effect of monotherapy, which means these people received no oral anti-parkinsonian drug treatment from the time when the apomorphine pump was started in the morning to when it was turned off at night. There was an overlap in the patient populations included in these studies; therefore, only the results of one [253] will be reported below.

With respect to motor complications:[253]

- There was a mean maximum reduction of dyskinesia per patient of 64% ($p<0.005$).
- The mean time to achieve maximum dyskinesia improvement was 12.1 months.
- There was an increase in on time of 55% ($p<0.005$). (**3**)

With respect to treatment management:[253]

- 25% of people managed treatment independently, 50% managed with family help, 25% required nurse input.
- The success rate was greater ($p<0.05$, 81%) among people managing the pump system independently or with help from family than those requiring outside help (eg nurse). (**3**)

Table 7.11 Effectiveness of continuous apomorphine infusions (3)

Outcome	Before versus after treatment
Clinical rating scales	
UPDRS total and subscores	APO[247]
UPDRS 32 (dyskinesia duration)	APO[255*]
UPDRS 33 (dyskinesia severity)	APO[255]
Lang and Fahn	APO[255]
Hoehn and Yahr scores (off and on states)	APO[250]
Schwab and England scale (off and on states)	APO[250]
Severity and duration in diaries	APO[255*]
Motor complications	
Decrease in off time	APO[246–248,250–253, 255]
Increase in on-time duration (% waking day)	APO[255*]
Dyskinesias	NS[247,248,250]
Levodopa	
Daily dose of levodopa	APO[246–250,252,255*]
Number of levodopa doses per day	APO[252]

APO = favouring apomorphine treatment ($p<0.05$); *$p<0.01$; NS = non-significant.

With respect to neuropsychiatric problems:[253]

- There was 40% improvement (especially in people with depressive-type symptoms) ($p<0.05$). (**3**)

With respect to adverse events:[246–253,255]

- The majority of people developed subcutaneous nodules.
- Other effects were: rhinorrhoea, nausea and hiccups, recurrent diarrhoea, confusion and emotional lability, euphoria and dysarthria, worsening of dyskinesia, orthostatic hypotension, psychosis, hallucinations, intermittent illusions, confusion, sleepiness, vertigo, eosinophilia, increased appetite, increased libido, visual delusions, diurnal agitation, immune haemolytic anaemia, mild self-limiting leg oedema, positive direct anti-globulin test without associated haematological changes. (**3**)

With respect to withdrawal rates:[246,248,250–253]

- People withdrew due to side effects (psychiatric effects, insufficient therapeutic effects or adverse effects). (**3**)

With respect to effects of single-dose levodopa and apomorphine challenges before and after continuous apomorphine infusion on dyskinesias:[255]

- Levodopa reduced dyskinesias after continuous apomorphine infusion by at least 40% (AIMS and Goetz scales; both $p<0.01$).
- Apomorphine reduced dyskinesias after continuous apomorphine infusion by at least 36% (AIMS and Goetz scales; both $p<0.01$). (3)

▷ From evidence to recommendation

The evidence base for the use of both intermittent injections and continuous infusions of apomorphine is relatively poor but both techniques are licensed for use in England and Wales. The GDG considers these to be useful treatment modalities for people with severe off periods that are not responsive to changes in oral medication. However, there is a risk of triggering serious side effects such as confusion and hallucinations. In addition, the risk of injection site reactions is considerable.

Long-term continuous apomorphine infusions can dramatically reduce both off periods and dyskinesia and allow withdrawal of oral medication.

The initiation of apomorphine should be restricted to expert units with the availability of a home monitoring system by a suitably trained health professional such as a PDNS.

RECOMMENDATIONS

R48 Intermittent apomorphine injections may be used to reduce off time in people with PD with severe motor complications. **B**

R49 Continuous subcutaneous infusions of apomorphine may be used to reduce off time and dyskinesia in people with PD with severe motor complications. Its initiation should be restricted to expert units with facilities for appropriate monitoring. **D**

7.6 Comparisons of drug classes

While it is valuable to know that various drug classes are effective agents in managing the motor complications seen in later PD, clinicians are particularly keen to know whether one class or combination of classes is better than another so that clinicians can make rational decisions about the order in which adjuvant therapies are used.

7.6.1 Dopamine agonists compared with monoamine oxidase type B inhibitors

How effective are dopamine agonists compared with MAOB inhibitors in the management of later PD?

▷ Methodology

No trials were found which compared dopamine agonists with MAOB inhibitors in the treatment of people with later PD and motor complications.

▷ From evidence to recommendation

In the absence of any evidence, no firm conclusions on the comparative efficacy and safety of dopamine agonists versus MAOB inhibitors can be made. Further trials are required to compare these two drug classes.

7.6.2 Catechol-O-methyl transferase inhibitors compared with dopamine agonists

How effective are dopamine agonists compared with COMT inhibitors in the management of later PD?

▷ Methodology

One Cochrane review[256] was found which compared the effectiveness of dopamine agonists versus COMT inhibitors.

Two RCTs were included in the review. One trial[257] (N=205) compared tolcapone with pergolide and the other trial[258] (N=146) compared tolcapone with bromocriptine.

▷ Evidence statements

With respect to quality of life:[257]

- PDQ-39 improved more with tolcapone than pergolide (p=0.005).
- Sickness Impact Profile was non-significant. (**1++**)

With respect to clinical rating scales:[257,258]

- Both studies found a non-significant difference in UPDRS ADL scores and UPDRS motor scores. (**1++**)

With respect to levodopa dose reduction:

- One trial[258] found the total daily levodopa dose decreased significantly with tolcapone compared with bromocriptine (124 mg versus 30 mg, p<0.01).
- The other trial[257] found a non-significant difference between tolcapone and pergolide (mean of 108 mg versus 92 mg). (**1++**)

With respect to total on and off time:

- One trial[258] found a non-significant difference in off and on time between tolcapone and bromocriptine. (**1++**)

With respect to adverse events:

- The combined results of both trials showed more nausea (OR=0.42, p=0.0003), constipation (OR=0.26, p=0.00007) and orthostatic complaints (OR=0.24, p=0.0002) in pergolide and bromocriptine groups than in tolcapone groups. (**1++**)

With respect to withdrawal rates:

- One of the studies[257] reported, due to adverse events, a trend towards more pergolide withdrawals (Peto OR=0.34, p=0.02). Neither study showed any significant differences for all-cause withdrawal. (**1++**)

▷ From evidence to recommendation

While there is some evidence of the superiority of tolcapone over bromocriptine and pergolide, this is insufficient to recommend the use of COMT inhibitors ahead of dopamine agonists. Further trials are required to compare these classes of adjuvant therapy.

7.6.3 Dopamine agonists compared with amantadine

How effective are dopamine agonists compared with amantadine in the management of later PD?

▷ Methodology

No trials were found which compared adding dopamine agonists versus amantadine to levodopa therapy in the treatment of people with later PD and motor complications.

▷ From evidence to recommendation

In the absence of any evidence, no conclusions on the comparative efficacy and safety of dopamine agonists compared with amantadine can be made. Further trials are required to compare these two drug classes.

7.7 Choice of pharmacological therapy in later Parkinson's disease

7.7.1 From evidence to recommendation

A summary of the drugs covered in this section can be found in Table 7.4.

It was evident from reviewing the evidence base that there is no single drug of choice in the pharmacotherapy of later PD.

Further trials are required in later PD with motor fluctuations to compare adjuvant therapy with dopamine agonists, COMT inhibitors and MAOB inhibitors, preferably using quality-of-life and health economics outcome measures. The PD MED trial in the UK is just such a trial and is scheduled to continue recruitment until November 2006 (**www.pdmed.bham.ac.uk**).

7.7.2 Generic therapeutic issues in later Parkinson's disease

There are a number of generic issues concerning the prescription and administration of anti-parkinsonian medication that are crucial to good concordance. Sudden increases in off time can occur if people with later PD are not given their medication often enough when they are admitted to hospital or care homes. This may require administration at times other than the normal 'drug rounds'. This is often best achieved by allowing patients to self-medicate. It is also advisable that the anti-parkinsonian regimen of patients admitted to hospital is reviewed and, if necessary, adjusted by an expert.

In addition, there are concerns over the dangers of sudden withdrawal or changes in medication and the overuse of such medication by a minority of people with PD.

RECOMMENDATIONS

R50 It is not possible to identify a universal first-choice adjuvant drug therapy for people with later PD. The choice of adjuvant drug first prescribed should take into account:

- clinical and lifestyle characteristics
- patient preference, after the patient has been informed of the short- and long-term benefits and drawbacks of the drug classes. **D (GPP)**

R51 Anti-parkinsonian medication should not be withdrawn abruptly or allowed to fail suddenly due to poor absorption (for example gastroenteritis, abdominal surgery) to avoid the potential for acute akinesia or neuroleptic malignant syndrome. **D (GPP)**

R52 The practice of withdrawing patients from their anti-parkinsonian drugs (so-called 'drug holidays') to reduce motor complications should not be undertaken because of the risk of neuroleptic malignant syndrome. **D (GPP)**

R53 In view of the risks of sudden changes in anti-parkinsonian medication, people with PD who are admitted to hospital or care homes should have their medication:

- given at the appropriate times, which in some cases may mean allowing self-medication
- adjusted by, or adjusted only after discussion with, a specialist in the management of PD. **D (GPP)**

R54 Clinicians should be aware of dopamine dysregulation syndrome, an uncommon disorder in which dopaminergic medication misuse is associated with abnormal behaviours, including hypersexuality, pathological gambling and stereotypic motor acts. This syndrome may be difficult to manage. **D (GPP)**

8 Surgery for Parkinson's disease

8.1 Introduction

Recognition of the limitations of dopaminergic therapy and the need to treat motor complications were the prime movers in the revival of functional stereotactic surgery for PD. This was aided by technological advances in the fields of imaging and computing. The introduction of CT and MRI scanning allowed surgeons to visualise and directly target deep brain structures without the need for indirect calculations from atlases based on cadaveric dissections. Modern engineering methods and computer technology resulted in easily used and reliable stereotactic hardware. Further advances came with the development of technology for deep brain stimulation (DBS), which has become the mainstay of movement disorder surgery.

Better understanding of the pathophysiology of movement disorders and of the basal ganglia circuitry has refined the surgical targets used in movement disorder surgery.

The ventrolateral nucleus of the thalamus has been one of the commonly used target sites for surgery in PD. Cells firing at tremor frequency can be identified in the ventralis intermedius (Vim) part of the thalamus and lesions or stimulators placed at this target can dramatically improve tremor.[259]

The serendipitous observation[260] of the effects of accidental ligation of the anterior choroidal artery focused attention on the globus pallidus interna (GPi) as a target for surgery. One group[261] identified the ventral and posterior parts of the internal segment (GPi) as the optimal site for surgical ablation. This group[261] revived this procedure and it was in widespread use in the early 1990s. While pallidotomy significantly reduced dyskinesia, it had a lesser effect on tremor and akinesia. The morbidity of bilateral lesions and the introduction of subthalamic nucleus (STN) DBS reduced the use of pallidotomy. However, DBS of the pallidum has a role in dystonia and some patients with PD.

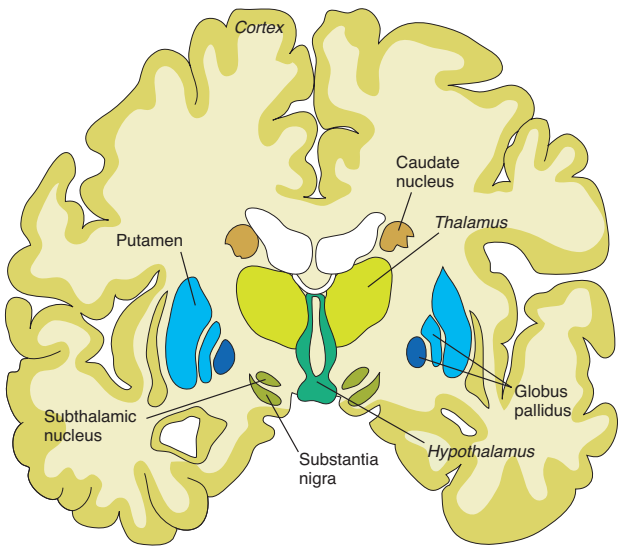

Figure 8.1 Structures of the basal ganglia[262] (reproduced with permission from publisher).

Experimental studies using the MPTP primate model showed increased cellular activity in the STN, and lesions or stimulation of the STN can reverse the cardinal features of parkinsonism.[263,264] However, surgeons were reluctant to lesion the STN in humans because of the risk of inducing hemiballismus. It was then shown that electrical stimulation of the STN-DBS[265] produced dramatic improvement in parkinsonian symptoms in PD. STN-DBS has since become the most widely undertaken surgical procedure for PD.

Surgical techniques vary between centres, but it is generally performed in three stages: radiological localisation, physiological localisation, and then either an ablation or a stimulation procedure.

Radiological localisation involves the rigid fixation to the skull under local anaesthesia of a stereotactic base ring onto which a fiducial array can be mounted. In the past, ventriculography (ie outlining the ventricles of the brain by instilling air or contrast medium) was the radiological technique used, but this has been largely replaced by CT and MRI. It is now possible to identify most of the targets on MRI, and their position in stereotactic space is calculated using sophisticated computer programs.

When the radiological data have been acquired and analysed, the patient is moved to the operating theatre and the radiological localiser is replaced with a stereotactic arc system that allows the surgeon to pass electrodes through a small opening in the skull with a high degree of precision. This is usually undertaken under local anaesthesia to allow the surgeon to evaluate responses from the patient, though some centres now carry this out under general anaesthesia and depend on recording of cellular activity for final localisation of the target. Microelectrode recording of cellular activity is widely used for physiological localisation, but there is no consensus on the added value of this technique. Evaluating the patient's response to electrical stimulation of the target usually makes further confirmation of accurate identification of the target.

When the target has been identified the options are of either using radiofrequency current for thermal ablation of the area or introducing a system for chronic electrical stimulation. Ablation has the advantage of being an inexpensive single procedure that does not require long-term follow-up for maintenance of implanted hardware. These advantages are largely negated by the irreversibility of the procedure and higher morbidity. Ablation has therefore largely been replaced by chronic DBS.

For DBS, the initial target localization is similar to that used for ablative procedures. Once the target has been identified the test electrode is replaced with an implantable quadripolar electrode, which is anchored to the skull. A period of stimulation using an external stimulator is sometimes used and when the efficacy has been confirmed the system is internalised. Under general anaesthesia fine cables are connected to the electrodes and tunnelled subcutaneously to a programmable pulse generator usually placed in the chest wall. The pulse generator is similar to a cardiac pacemaker with a high degree of programmability by an external device. It is possible to provide the patient with a degree of control of the stimulator. The pulse generator has a battery within it and depending on usage will have to be replaced in a simple surgical procedure every 3–5 years.

In view of the relative safety of stimulation procedures compared with lesioning, most surgery for people with PD today uses the former approach. The GDG felt therefore that it should confine its recommendations to STN, GPi and thalamic stimulation.

8.1.1 Methodological limitations of surgery trials

The included trials all had methodological limitations common to non-analytical study designs. Firstly, none of the included trials were randomised into surgical or non-surgical intervention groups. Secondly, none of the trials were performed under blinded conditions, either single or double. None of the trials were controlled with a cohort of non-surgical patients for longitudinal comparison over time.

There was also a general lack of inclusion/exclusion criteria, which could lead to pre-selected patient populations, lack of multi-centre comparative results analysis, and lack of sample size calculations. The mean follow-up of most trials was 7–12 months and the patient population tended to be younger with an average age of approximately 60 years.

What is the effectiveness and safety of any DBS procedure versus standard medical therapy in the treatment of motor complications in patients with PD?

8.2 Subthalamic nucleus stimulation

8.2.1 Methodology

No randomised or controlled trials were found on the effectiveness of any DBS procedure versus standard medical therapy. Therefore, the GDG agreed that large case series studies with a minimum sample size of 40 patients were to be accepted for review.

Nine papers were found which reported the effectiveness of STN-DBS versus standard medical therapy.

8.2.2 Health economic methodology

Four health economic studies met our quality criteria.[266-269] One study[267] evaluated the incremental cost-effectiveness of bilateral DBS of the STN or GPi versus best medical management. The study[267] estimated the cost per QALY of bilateral DBS of the STN or GPi (intervention) versus best medical management in the US healthcare context.

Another study[266] evaluated the incremental cost-effectiveness of STN-DBS versus drug treatment. This study[266] estimated the extra cost per additional UPDRS point gained from bilateral high-frequency STN-DBS by comparing STN-DBS and drug treatment with drug treatment alone in the German healthcare context.

One study[268] evaluated the costs of STN-DBS. The study[268] estimated the total health service cost per patient including preoperative assessment, STN-DBS and postoperative management over a 5-year period in the UK healthcare context.

Another study[269] evaluated the change in medication costs after bilateral STN-DBS. This study[269] estimated the anti-parkinsonian medication costs pre- and post-operatively at 1 and 2 years after bilateral STN-DBS in a US healthcare context.

A simplified cost-effectiveness analysis of bilateral DBS-STN was estimated from the perspective of the NHS over 5-year period (Appendix F).

8.2.3 Evidence statements

With respect to quality of life:[270]

- Parkinsonian symptoms, systemic symptoms, emotional functioning and social functioning all improved post-operatively ($p<0.001$).
- The improvement in the score of UPDRS II correlated with the improvement in total Parkinson's Disease Quality of Life (PDQL) score ($p<0.001$). (3)

With respect to efficacy, see Table 8.1.

Table 8.1 Bilateral STN stimulation (stimulator 'on')

	3 months	6 months	1 year	2 years	3 years	5 years
Quality of life						
PDQL	–	–	S[270]	–	–	–
Clinical rating scales						
Hoehn and Yahr	-	S[271,272]	S[272]	S[272]	–	–
UPDRS I$^{\int}$	–	–	NS[270]	–	B[273]	–
UPDRS II$^{\int}$	S[273,274]	S[271,272]	S[270,272–274] NS[275] B*[275]	S[272,274]	–	S[276]
UPDRS III	S[273,274]	S[271]	S[270,273–275]	S[274]	–	S[276]
UPDRS IV	S[274]	S[271]	S[274]	S[274]	–	–
SEALD$^{\int}$	S[273]	S[272]	S[270,272,273,276]	S[272]	S[276]	S[276]
BDI	–	–	S[270,273]	–	S[273]	NS[276]
Motor complications						
Tremor	S[273]	S[272]	S[272,273]	S[272]	–	S[276]
Dyskinesias (on drug)	–	S[272]	S[270,272,275] NS[273]	S[272]	–	–
Dystonia$^{\int}$	–	S[272]	S[272] NS[273]	S[272]	–	–
Akinesia and rigidity	S[273]	S[272]	S[272,273]	S[272]	–	S[276]
Axial symptoms^	–	S[271,272]	S[271,272]	S[272]	–	–
Fluctuations	–	S[271]	S[275]	–	–	–
Medication						
Levodopa dose	S[274]	S[271,272]	S[270,272,274–276] NS[273]	S[272,274]	S[276]	S[276]

S = improvement in favour of STN stimulation ($p<0.05$); NS = not-significant; B = worsening of symptoms after surgery ($p<0.05$); – = not reported; * = patients >70 years of age; ^ = axial symptoms: speech, postural stability and gait (items 18, 28, 29 and 30 of UPDRS III); $^{\int}$ = off medication.

With respect to predictive factors, the following results were observed (Table 8.2):

- One study[274] found: 'the younger the age at the moment of operation and the shorter the duration of disease, the better the clinical outcome'. Another study[271] reported: no significant correlation between age at time of surgery or disease duration and post-operative clinical outcome. (**3**)
- One study[275] found: UPDRS motor scores off medication were improved but less so in patients over 70 (<70 vs >70, p<0.02), and changes in UPDRS motor scores (on medication) worsened in patients over 70 and improved in patients under 70 (p<0.05). Another study[274] found: no significant difference between patients older and younger than 60 years of age for UPDRS II, III and IV scores, and no significant difference in mean daily levodopa dosage at follow-up. (**3**)

Table 8.2 Correlations between pre-operative and post-operative factors

Pre-operative factor	Correlation	Post-operative outcome
Age[275]	–	Improvement from stimulation (p<0.01)
Age of patients[273]	–	Frontal score (p<0.001) and initiation subset of Mattis DRS (p=0.007)
Age of patients[273]	–	Item 2 of UPDRS thought disorders (p=0.023)
Age or disease duration (p<0.005 and p<0.007 respectively)[271]	+	Motor disability score in the 'on' stimulation and 'on' drug conditions
Younger patients and shorter disease duration[271]	+	Residual ADL, motor disability and axial scores
Low motor disability and high neuropsychological status[271]	+	Improvement in motor disability *Please note: low motor disability predicting level of improvement in motor disability after surgery may be a statistical artefact (regression to mean).*
Less severe axial motor symptoms[271]	+	Improvement in axial motor disability
Levodopa challenge[275]	+	Results from STN-DBS (p<0.02)
Improvement from levodopa[275]	+	Improvement from STN-DBS (p<0.00001)
Levodopa response in an individual symptom[275]	+	Stimulation response for that same symptom (akinesia, tremor, rigidity, postural instability, gait and pull test (p<0.001))
Improvement from levodopa in Hoehn and Yahr and Schwab and England global ratings[275]	+	Improvement from stimulation in the same rating (p<0.001)

+ = Positively correlated (ie increase in factor 1 leads to an increase in factor 2); - = negatively correlated (ie increase in factor 1 leads to a decrease in factor 2)

With respect to adverse events, the following were reported following STN-DBS:

- Neuropsychological events including: confusion, mania, delusion, depression, hypomania, aggressive behaviour, hallucinations, attentional and cognitive deficit, dementia, panic attack and apathy, which in some impaired activities of daily living.
- Other adverse events including: hypophonia, transitory eye opening apraxia, thrombophlebitis, subcutaneous infection, haematomas, focal cerebral contusions, infections of the system (sic) ('the system' relates to the actual equipment used), dysarthria, disequilibrium, dystonia, weight gain, connection wound dehiscence, lead repositioning, air embolus, seizure and dyskinesias.
- Stimulator-induced events including: electrode replacement due to unsatisfactory results, local pain at the implantation site of the pulse generator, reversible stimulation-induced dyskinesias after an increase in voltage, minor intracerebral bleeding at the site of the trajectory lead, dislocation of the impulse generator from site of implantation, transient paraesthesias associated with adjustment of stimulation parameter. (3)

With respect to withdrawal rates:

- Two studies reported suicide attempts: one study reported patients with depression (three) who then attempted suicide (two)[270] and the other study reported four patients who attempted suicide post-operatively (one died).[273]
- In a third study,[277] three patients died from causes unrelated to surgery or stimulation, and in a fourth study[276] three deaths were reported (from intracerebral haemorrhage, myocardial infarction and suicide). (3)

8.2.4 Health economic evidence statements

Bilateral STN- or GPi-DBS costs an additional $49,194 in US$2000 (approximately £31,112) per QALY in comparison to best medical management.[267] The study's results suggest DBS may therefore be cost-effective if the quality of life after the procedure is improved by 18% or more compared with best medical management.

Bilateral STN-DBS costs approximately an additional DM1,800 (UK£580) in 2002 prices per unit improvement in UPDRS total score, derived from German costs and patient data.[266] However, the costs will decrease further over the long term (> 1 year study period) from reduced drug expenditure and improved patient functioning. Therefore, the direct and indirect costs need to be assessed over the long term to sufficiently evaluate the cost-effectiveness of DBS.

The total health service costs of DBS of the STN, including pre-operative assessment, surgery and post-operative management over a 5-year period, was recently evaluated in the UK.[268] The estimated total cost per patient was £32,526 for the bilateral procedure and £30,447 for the unilateral procedure (£ 2002).[268]

A US study evaluated the change in anti-parkinsonian medication costs 2 years after bilateral STN-DBS. The study found the medication costs had significantly decreased by 32% ($p \leq 0.01$) from the 1-year pre-operative costs and there was 39% reduction after 2 years.[269] Pre-operatively, the average daily cost of PD medication was $19.53 ± 10.41 in US$ 2002 (approximately £11.92 ± 6.35) per patient. Post-operatively, this fell to $13.25 ± 5.41 (approximately £8.08 ± 3.30) per patient.[269]

The economic modelling performed for this guideline (Appendix F) suggests that STN-DBS costs approximately £19,500 per QALY over a 5-year period in comparison to standard PD care in the UK (£ 1998). The results are relatively robust based on one-way sensitivity analysis.

8.2.5 From evidence to recommendation

In the absence of RCTs, any conclusions on the efficacy and safety of bilateral STN stimulation must be tentative. Most of the patients in the open-label non-controlled trials described above were relatively young (aged around 60 years) so the results may not be generalisable to all those with the condition. Follow-up was for around 12 months only, which may not record later complications.

Despite these limitations, what evidence is available supports the efficacy of this technique in reducing off time, dyskinesia and levodopa dose, improving motor impairments and disability, and improving quality of life.

There is a small but significant risk of permanent neurological disability as a consequence of this operation, due mostly to cerebral infarction or haemorrhage. In a small number of patients, this can lead to death. Most other adverse effects of surgery were transient but concern remains regarding the incidence of neuropsychiatric complications, particularly depression and suicide. It is difficult to comment reliably on such issues in the absence of a control group.

The procedure requires an experienced, well-trained multidisciplinary team.

The high cost of this type of functional neurosurgery in PD is well recognised. No long-term data from clinical trials are available. However, economic modelling over a 5-year period performed as part of this guideline suggests that bilateral STN-DBS costs £19,500 per QALY in comparison to standard PD care in the UK (£ 1998).

The National Institute for Health and Clinical Excellence (NICE) published an Interventional Procedure Statement on bilateral STN stimulation in November 2003.[23] This supported the use of the procedure provided normal arrangements for consent, audit and clinical governance are in place.

The PD SURG trial is evaluating the clinical and cost-effectiveness of STN surgery and recruitment is ongoing (**www.pdsurg.bham.ac.uk/**). The NICE Interventional Procedure Statement encouraged clinicians to consider randomising patients in this trial.

RECOMMENDATION

R55 Bilateral STN stimulation may be used in people with PD who:

- have motor complications that are refractory to best medical treatment,
- are biologically fit with no clinically significant active comorbidity,
- are levodopa responsive and
- have no clinically significant active mental health problems, for example depression or dementia. **D**

8.3 Globus pallidus interna stimulation

8.3.1 Methodology

No randomised or controlled trials were found on the effectiveness of any GPi-DBS procedure versus standard medical therapy. Therefore, large case series designs with a minimum sample size of 40 people were accepted for review.

8.3.2 Evidence statements

No trials were found which assessed the effectiveness of GPi stimulation in a case series with a minimum sample size of 40 people with PD.

8.3.3 From evidence to recommendation

While no RCTs or large case series have evaluated GPi-DBS, there are a small number of case series and comparative trials that suggest the procedure is effective (see section 8.4). However, it is likely to suffer from the same concerns regarding adverse events and costs as STN-DBS.

GPi-DBS is rarely performed for PD in the UK at present, though it is sometimes undertaken when STN-DBS is not possible.

RECOMMENDATION

R56 Bilateral GPi stimulation may be used in people with PD who:

- have motor complications that are refractory to best medical treatment,
- are biologically fit with no clinically significant active comorbidity,
- are levodopa responsive and
- have no clinically significant active mental health problems, for example depression or dementia. **D (GPP)**

8.4 Comparison of different types of deep brain stimulation

What is the most effective form of DBS procedure in the treatment of motor fluctuations and complications in patients with PD?

8.4.1 Methodology

There were no randomised or controlled trials reporting the most effective form of DBS in the treatment of patients with PD. The majority of trials were retrospective case series, which compared the results of different techniques. Due to the lack of comparative trials in this area, the GDG agreed studies with a sample size minimum of 10 patients per arm should be reviewed.

Five trials[278–282] were found which compared the before and after surgery results of STN-, GPi- and Vim thalamic DBS.

The majority of the patient population received bilateral implantation, though results were not reported separately from the unilateral implantation results.

8.4.2 Evidence statements

With respect to clinical efficacy

- The following criteria were significantly ($p<0.05$) in favour of both STN- and GPi-DBS:
  - UPDRS I, II (off and on), III (off and on), IV[278,279,281,282]
  - time in off state (UPDRS item 39)[282]
  - Hoehn and Yahr scores[281]
  - levodopa equivalent daily dose[278,279,281]
  - dyskinesia scores[278,279]
  - patient and physician global assessments
  - Schwab and England scale[282]
  - home diary scores (% of time with good mobility and without dyskinesia during the waking day).[279] (**3**)
- The following criteria were improved in only one DBS technique versus another:
  - Motor score improvement was more pronounced in STN patients than GPi patients (no p values stated).[281]
  - Medication could be reduced only in STN patients and not in GPi patients (no p values stated).[281]
  - Levodopa dose equivalent, though unchanged in the GPi group, was significantly reduced in the STN group ($p=0.017$).[282]
  - Trail making test ($p=0.0013$), test B ($p=0.0015$) and BDI ($p<0.0001$) improved under STN stimulation and not Gpi.[281]
  - Literal ($p=0.0018$) and total ($p=0.0002$) fluency decreased under STN-DBS and not GPi-DBS.[281]
  - Core Assessment Program for Intracerebral Transplantations dyskinesia rating scale favoured GPi ($p=0.046$) in absolute scores but percentage changes were not significant.[282] (**3**)
- Thalamic nucleus stimulation could not be compared directly to other techniques, as the outcome measures used to assess its efficacy are different from other techniques. The main outcome, tremor suppression, was found to be significantly improved with the procedure.[283] (**3**)

With respect to adverse events, the following was reported:

- No GPi-specific adverse events were reported.
- See thalamic stimulation and STN stimulation sections for events specific to these procedures. (**3**)

8.4.3 From evidence to recommendation

There is no evidence from RCTs to compare STN with GPi stimulation. However, observational studies suggest that STN stimulation may lead to greater improvement in motor scores and more reduction in levodopa dose and depression scores. In comparison, GPi stimulation may lead to less cognitive impairment. Further work is required in this area.

It is recognised that pallidal stimulation for PD is rarely performed at present, though it is sometimes undertaken when STN-DBS is not possible.

RECOMMENDATION

R57 With the current evidence it is not possible to decide if the STN or GPi is the preferred target for DBS for people with PD, or whether one form of surgery is more effective or safer than the other. In considering the type of surgery, account should be taken of:

- clinical and lifestyle characteristics of the person with PD
- patient preference after the patient has been informed of the potential benefits and drawbacks of the different surgical procedures. **D (GPP)**

8.5 Thalamic stimulation

How effective and safe is thalamic stimulation for the control of tremor in PD?

8.5.1 Methodology

Three papers[284,283,285] reported the effectiveness of chronic stimulation to the Vim thalamic nuclei. The methodological limitations of these papers are similar to those of STN stimulation (see Section 8.2).

8.5.2 Evidence statements

With respect to tremor suppression:

- All three studies[284,283,285] showed a benefit of thalamic stimulation.
- Only one study[283] reported statistical analysis and stated that the following outcomes were significantly ($p<0.05$) improved: face tremor and observed tremor, hypokinesia, rigidity and ADL score. (**3**)

With respect to adverse events, the following were reported:

- Post-operative events included: venous infarction with temporary aphasia, intraventricular haemorrhage and cardiovascular problems intra-operatively.
- Stimulation-related events that occurred considerably more frequently in patients with bilateral implants (52%) as compared with unilateral (31%)[285] included: dystonia, diplopia, sleepiness, altered mental status, paraesthesias, mild disturbance of gait and balance, mild dysarthria, increased drooling, nausea, insomnia, dysphagia, depression, wire tightness and dysarthria. (**3**)
- No mortality was reported in any of the trials.

With respect to withdrawal rates:

- Most withdrawals were due to adverse events. (**3**)

8.5.3 From evidence to recommendation

There is no evidence from RCTs of the benefit of thalamic stimulation in PD. Data from observational studies suggest that this is an effective method of reducing tremor. The operation carries a risk of serious complications such as cerebral infarction and haemorrhage. The GDG recognised that this form of surgery is rarely performed for tremor in people with PD in England and Wales, having been superseded by STN stimulation.

RECOMMENDATION

R58 Thalamic DBS may be considered as an option in people with PD who predominantly have severe disabling tremor and where STN stimulation cannot be performed. **D**

9 Non-motor features of Parkinson's disease

'I feel trapped inside my body . . . as if I'm not in control . . . almost as if someone or something else is running my life.' (patient)[2]

9.1 Introduction

The spectrum of PD includes many problems that do not directly affect motor function. These non-motor features are of crucial importance to people since they have a major impact on quality of life.[28,286]

Non-motor features comprise:

- mental health problems
- depression and dementia
- falls and potential fractures
- sleep disturbance
- autonomic disturbance and pain.

While most people are troubled by these problems in the later stages of their PD, certain non-motor conditions can develop throughout the course of the condition (eg depression, anxiety, hypersomnolence) or even precede it (eg sleep disturbance, depression, anxiety).

A recent study reported on the non-motor problems experienced by a group of 149 people with PD followed for 15–18 years.[287] They found the occurrence rates were: falls 81% (with 23% suffering fractures), cognitive decline 84% (48% fulfilling criteria for dementia), hallucinations 50%, depression 50%, choking 50%, symptomatic postural hypotension 35%, and urinary incontinence 41%.

There have previously been few therapeutic studies examining the effects of treatments for non-motor disorders. However, there is now a real desire to increase research into the non-motor features of PD as their effect on people's well-being has been recognised.[288]

The non-motor features of PD considered in the scope of this guideline and thus undergoing literature review were:

- mental health problems:
  - depression
  - dementia
  - psychosis
- sleep disturbance:
  - hypersomnolence
  - rapid eye movement sleep behaviour disorder (RBD)
  - restless legs syndrome (RLS)
  - inverted sleep-wake cycle
  - nocturnal akinesia.

Although the following non-motor features of PD were not considered within the scope of this guideline, it is recognised that they are important and should always be considered in patient care. These non-motor features include:

- mental health problems
  - anxiety
  - apathy
- falls
- autonomic disturbance
  - bowel dysfunction including constipation
  - dysphagia
  - weight loss
  - dribbling of saliva
  - bladder dysfunction
  - sexual dysfunction
  - postural hypotension
  - excessive sweating
- pain.

Depression, dementia and psychosis are frequent problems in PD and some research has been performed on their treatment. Therefore, these topics were included in the scope of this guideline.

Other important mental health issues in PD include anxiety and apathy, but little work has been done in these areas specific to PD so they were not included in the scope. Standard treatment therefore applies in these areas; see NICE guidance entitled: 'Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care'.[21]

9.2 Mental health problems

9.2.1 Depression

Depression affects around 40–50% of people with PD.[289] It is usually mild to moderate but can be severe, and symptoms of depression can predate motor manifestations.

The relationship of depression to the pathology of PD is unclear but the inconsistent relationship between mood changes and the severity of motor symptoms indicates that depression should not simply be considered a reaction to motor disability.

There are difficulties in diagnosing mild depression in people with PD as the clinical features of depression overlap with the motor features of PD.

The characteristic features of depression are low mood, loss of interest and enjoyment, and fatigue. This is accompanied by various combinations of:

- slowed mental and physical function
- motor agitation
- poor appetite and sleep
- weight loss

- other somatic symptoms
- disturbance of cognitive function and thought processes.

The disturbance of cognitive functions and thought processes may result in poor concentration and memory, excessive worry, feelings of worthlessness, hopelessness and guilt, negative views of self and life, and thoughts of suicide. Psychological and physical symptoms of anxiety are also common.

The development of depression creates an added burden for people with PD and their carers and has been shown to be an important determinant of quality of life.[290]

Factors relevant to the aetiology of depression that need to be considered are:

- previous susceptibility to depression
- neurotransmitter disturbances of PD
- effects of drug treatments
- relationship to on–off motor fluctuations
- the person's adjustment to the diagnosis of PD and their symptoms and life factors, including losses
- other stressors
- interpersonal relationships.

What is the effectiveness of antidepressant therapies versus placebo or active comparator in the treatment of depression in PD?

▷ Methodology

A Cochrane review[291] and two randomised controlled trials[292,293] (published after the review's search date) were found which addressed the effectiveness of antidepressant therapies versus placebo or active comparator. No controlled trials were found on electroconvulsive therapy or behavioural therapy for the treatment of depression in PD people.

The Cochrane review included three trials: one trial[294] compared a selective serotonin re-uptake inhibitor (SSRI) with placebo; another study[295] compared a tricyclic antidepressant (TCA) with placebo; and the third trial[296] compared the effectiveness of an SSRI versus a TCA.

These trials included small sample sizes (range 22–47). There were several methodological limitations of the included studies: lack of power calculations, lack of baseline characteristics, and no details on methods of randomisation and allocation concealment. The duration of the included trials varied from 16 to 52 weeks (with one study not reporting the trial duration).

One of the independent RCTs[292] compared the effectiveness of an SSRI with placebo. The methodological limitations of this study included unclear methods of randomisation and allocation concealment, small sample size (N=12, six in each arm) and lack of power calculations. The study reported that, because of the low recruitment, the study was terminated after 10 weeks.

The second independent RCT[293] compared repetitive transcranial magnetic stimulation (rTMS) versus an SSRI as an effective antidepressant therapy. The methodological limitations included: short trial duration (8 weeks), small sample size (N=42, 21 in each arm) and lack of power calculation.

▷ Evidence statements

The Cochrane review[291] reported the following non-significant results:

- Nortriptyline (TCA) improved depressive symptoms in the first half of a crossover trial with no deterioration in parkinsonian symptoms.
- Citalopram (SSRI) provided no additional benefit over placebo in the treatment of depressive symptoms in a parallel trial design.
- Fluvoxamine (SSRI) and amitriptyline (TCA) showed similar efficacy in an open-label trial.
- Confusion and visual hallucination were infrequently reported in people taking fluvoxamine and amitriptyline; otherwise, no other major adverse events were reported. (**1++**)

One of the independent RCTs[293] reported no significant difference between sertraline (SSRI) and placebo in terms of 'response' to treatment (defined as at least 50% reduction of the pre-treatment Montgomery-Asberg Depression Rating Scale), or UPDRS motor scores. (**1+**)

One of the independent RCTs[292] reported that the following outcomes were improved in both rTMS and fluoxetine-treated groups: the Hamilton Depression Rating Scale and BDI, ADL scores, and the Mini-Mental State Examination (MMSE), with no significant differences between groups. However, adverse events were found more frequently in the fluoxetine-treated group than the rTMS group ($p=0.03$). (**1+**)

▷ From evidence to recommendation

There is insufficient evidence from RCTs of the efficacy or safety of any antidepressant therapy in PD. This includes cognitive behavioural therapy, all classes of antidepressant medication and electroconvulsive therapy.

NICE has recently published guidelines[18] for the management of depression which include people with physical disorders. While it is tempting to adopt these guidelines for people with PD, there are a number of factors that suggest that the management of depression in PD may require different strategies:

- There are case reports suggesting that some antidepressants may make PD motor symptoms worse.[297]
- There are established, but rare, interactions between some antidepressants and dopaminergic therapy for PD (eg MAOB inhibitors and antidepressants).[298]
- Cognitive behavioural therapy is not widely available to secondary care teams looking after people with PD.

There is an urgent need for further research to establish effective and safe treatments for depression in PD.

RECOMMENDATIONS

R59 Clinicians should have a low threshold for diagnosing depression in PD. **D (GPP)**

R60 Clinicians should be aware that there are difficulties in diagnosing mild depression in people with PD because the clinical features of depression overlap with the motor features of PD. **D (GPP)**

R61 The management of depression in people with PD should be tailored to the individual, in particular, to their co-existing therapy. **D (GPP)**

9.2.2 Psychotic symptoms

Psychotic symptoms indicate a loss of reality testing; that is, the formation of beliefs and sensations without a basis in reason or external sensory stimulus. Delusions (false unshakeable beliefs that cannot be understood from the individual's sociocultural context) and hallucinations (perceptions in any sensory modality occurring without external sensory stimulus) are the most common symptoms of psychosis.

Psychotic symptoms may occur at any stage in PD. Up to 50% of people with the condition may develop psychotic symptoms[299] and 30% may experience hallucinations within the first 5 years.[300] Although visual hallucination is the most frequent psychotic symptom, a degree of auditory hallucination is found in 40%.[300] Delusions may involve themes of persecution, infidelity and jealousy but these are much less common.

The aetiology of psychotic symptoms in PD is complex. They may arise from the neurotransmitter disturbances of PD but can be caused by any of the drugs used to treat motor symptoms.

The appearance of psychotic symptoms requires careful evaluation. Psychotic symptoms may also occur as part of delirium (caused by other physical illness or drug treatments) or dementia, or may indicate the development of a co-morbid mental illness.

Psychotic symptoms are distressing and may be frightening to people with PD and their carers who may not appreciate that they are symptoms of illness. It is essential to explain the nature of these symptoms to people with PD and their carers.

What is the effectiveness of atypical antipsychotic therapies versus placebo or active comparator in the treatment of psychotic symptoms in PD?

▷ Methodology

Five RCTs[301–305] were found which addressed the effectiveness of atypical antipsychotic therapies versus placebo or active comparator in the treatment of psychosis.

Three trials[306–308] were found that compared two atypical antipsychotic drugs, and these were excluded as within drug class comparisons.

The methodological limitations for some of the included studies involved: lack of randomisation and allocation concealment methods, lack of multi-centre comparative results analysis, lack of power calculations, small sample sizes (N=31[309], 160[303], 30[302] and 60[304]) short trial duration and no intention-to-treat analysis protocols.

▷ Evidence statements

With respect to psychiatric outcomes:

- Trials which looked at the effectiveness of clozapine versus placebo found the following outcomes in favour of active drug treatment:
  - CGI scale (p=0.002)[301], (p=0.001)[304]
  - Brief Psychiatric Rating Scale (BPRS) score (p=0.002)[301]
  - BPRS-Modified score (p=0.003)[301]
  - Scale for the Assessment of Positive Symptoms (p=0.01)[301]
  - Positive and Negative Syndrome Scale positive subscore (p<0.001).[304] **(1+)**
- Trials which looked at the effectiveness of olanzapine versus placebo found no significant differences between groups on a battery of neuropsychological tests.[302,303] **(1+)**
- One trial which looked at quetiapine versus placebo found no significant difference between groups on the Baylor PD Hallucination Questionnaire, the BPRDS, and a battery of neuropsychological tests.[305] **(1+)**

With respect to motor outcomes:

- One trial which looked at clozapine versus placebo reported a beneficial effect of clozapine on UPDRS tremor subscore (p=0.02).[301] **(1+)**
- Other trials which looked at olanzapine versus placebo reported that the following outcomes worsened with drug treatment:
  - UPDRS total (p=0.007 and p=0.024)[303]
  - UPDRS motor scores (p=0.023 and p=0.039),[303] (p<0.05)[302]
  - subscores gait (p<0.001) and hypokinesia (p<0.05)[302]
  - timed tapping scores (p<0.05)[302]
  - UPDRS ADL scores (p=0.004 and p=0.009).[303] **(1+)**
- The trial that looked at quetiapine found no differences between placebo and active drug groups on UPDRS ADL or motor scores. There was also no difference found on the Goetz Dyskinesia Rating Scale scores.[305] **(1+)**

With respect to adverse events:

- The following events were reported as significantly increased in people receiving clozapine treatment:
  - increased mean resting heart rate (p=0.046)[301]
  - increased body weight (p=0.005)[301]
  - increased somnolence (53% vs 18%) and worsening of parkinsonism (21.8% vs 4%) (p values not stated).[304] **(1+)**
- The following events were reported as significantly increased in people receiving olanzapine treatment:
  - extrapyramidal syndrome (p=0.003)[303]
  - hallucinations (p=0.013)[303]
  - increased salivation (p=0.026)[303]
  - no case of agranulosytosis reported.[304] **(1+)**
- There were no significant differences in adverse events reported in the study on quetiapine versus placebo. The study did report that no people on the active drug dropped out secondary to related adverse events, which included sedation (N=9, 43%), and subjective worsening in PD (N=4, 19%).[305] **(1+)**

With respect to withdrawal rates:

- Trials on clozapine efficacy reported that most withdrawals were due to either treatment failure[304] or adverse events.[301] (**1+**)
- Trials which assessed the effectiveness of olanzapine reported:
  - significantly more people receiving olanzapine discontinued (p=0.029), and mostly due to adverse events (p=0.003), compared with placebo.[303] (**1+**)
- The trial that assessed quetiapine effectiveness reported no significant differences in withdrawal rates. The study found that 81% of the active drug group completed the study, with four patients withdrawing due to serious unrelated illness or lack of effect and poor compliance. In the placebo group 80% of the participants completed the trial; reasons for withdrawal included unrelated serious illness, resulting in death.[305] (**1+**)

▷ From evidence to recommendation

Psychosis is a common problem in later PD and can be difficult to manage (Figure 9.1). It may be precipitated by intercurrent illnesses (eg infections), addition of new anti-parkinsonian medication or dementia. Correspondingly, the initial treatment of psychosis should include general medical assessment and treatment of any potential causative factor. Consideration should be given to withdrawal of any recently added medication that may have triggered a psychotic reaction. Drugs that are particularly prone to trigger psychosis, such as anti-cholinergics, selegiline and amantadine, should be withdrawn first. The patient should be evaluated for a fixed cognitive deficit that might suggest the development of dementia.

For psychosis which does not respond to the above measures, no treatment may be required if psychotic features are not troublesome to the patient or their carers.

In more severe psychosis, antipsychotic medication should be considered. Typical antipsychotics (eg phenothiazines and butyrophenones) are well known to exacerbate PD and should not be used. Various atypical antipsychotics have been evaluated in PD, but only clozapine has a licence for this indication in England and Wales:

Several randomised placebo-controlled trials have shown that clozapine can reduce psychotic symptoms in PD without exacerbating parkinsonian features. However, the use of clozapine requires intensive monitoring to detect the uncommon but potentially life-threatening complication of agranulocytosis. As a result, it is rarely used in PD.

Limited trial evidence suggests that olanzapine is not effective against psychotic features and makes parkinsonian symptoms worse.

There are concerns about the safety of olanzapine and risperidone in elderly people with dementia and risk factors for stroke.[310]

There is no evidence from RCTs of the efficacy and safety of quetiapine as an antipsychotic in PD. However, several trials are ongoing in this area. Quetiapine is thought to be relatively safe and does not require haematological monitoring. As a result, quetiapine has been widely used in PD psychosis.

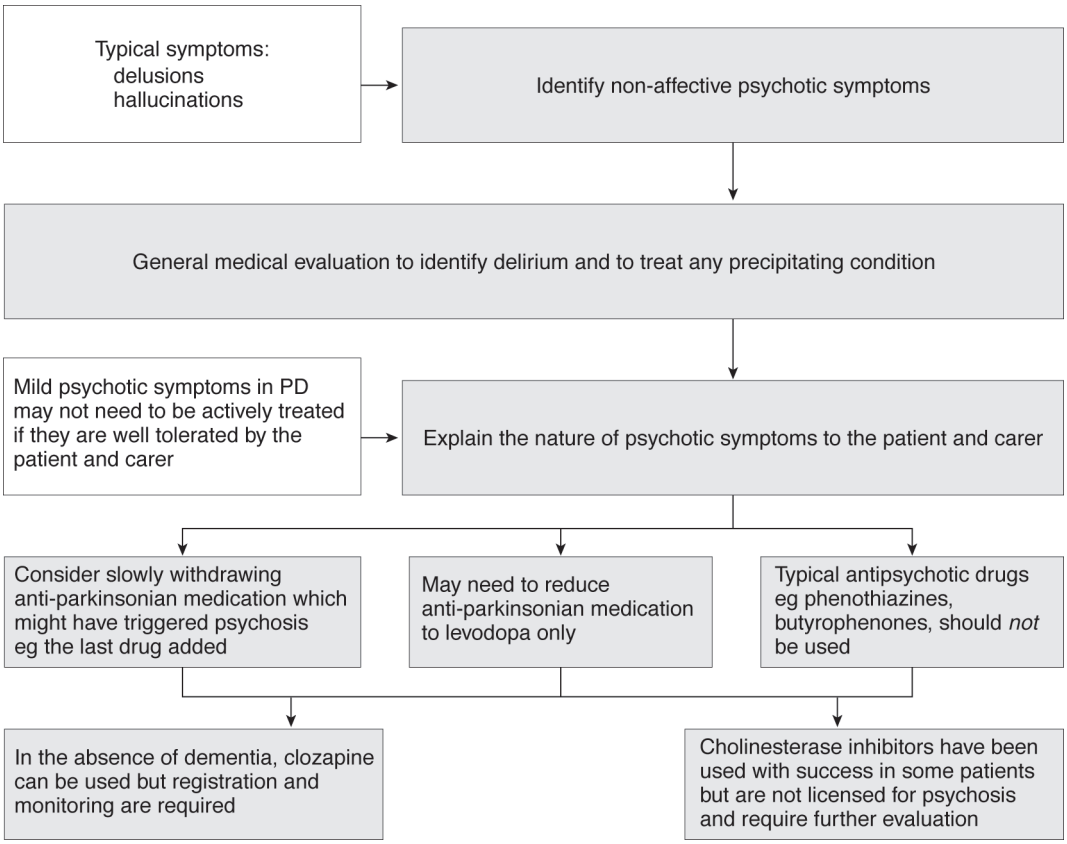

Figure 9.1 Management of psychosis in PD

RECOMMENDATIONS

R62 All people with PD and psychosis should receive a general medical evaluation and treatment for any precipitating condition. **D (GPP)**

R63 Consideration should be given to withdrawing gradually anti-parkinsonian medication that might have triggered psychosis in people with PD. **D (GPP)**

R64 Mild psychotic symptoms in people with PD may not need to be actively treated if they are well tolerated by the patient and carer. **D (GPP)**

R65 Typical antipsychotic drugs (such as phenothiazines and butyrophenones) should not be used in people with PD because they exacerbate the motor features of the condition. **D (GPP)**

R66 Atypical antipsychotics may be considered for treatment of psychotic symptoms in people with PD, although the evidence base for their efficacy and safety is limited. **D (GPP)**

R67 Clozapine may be used in the treatment of psychotic symptoms in PD, but registration with a mandatory monitoring scheme is required. It is recognised that few specialists caring for people with PD have experience with clozapine. **B**

9.2.3 Dementia

PD is associated with impairment of cognitive function. Compared with people without PD, deficits in visuospatial abilities, category learning, verbal fluency, set switching and executive functions are typically reported.

Particular attention has focused on deficits of executive function that may mediate many of the other impairments. Executive functions include working memory, mental flexibility, and the ability to initiate and suppress responses.

Dementia (the progressive loss of global cognitive function) is also common in PD; 48%[305] to 80%[311] of people may develop dementia at some point in the course of the condition.

In addition to cognitive decline, dementia leads to impairment in activities of daily living and disturbance of behaviour and other psychological functions. Dementia in PD is accompanied by reduced quality of life for people with PD and their carers.[290,312]

Other pathologies commonly causing dementia include Alzheimer's disease, vascular brain disease and dementia with Lewy bodies.

Traditionally, dementia developing more than 1 year after the onset of the motor features of PD is referred to as PD with dementia (PDD). Dementia developing within 1 year of the onset of motor features is classified as dementia with Lewy bodies. The relationship between PDD and dementia with Lewy bodies is unclear, but many consider them to be a continuum rather than discrete entities.

Since people with dementia with Lewy bodies may not develop parkinsonism, we have not considered the treatment of this type of dementia in this guideline. The GDG acknowledges that this decision may need to be revisited in the future if new evidence proves that a continuum exists between PDD and dementia with Lewy bodies.

Rarely, dementia may arise due to a treatable illness. All people with dementia require careful evaluation of their medical condition, treatment and investigations to clarify the diagnosis with attention to potentially treatable conditions. In this context, cognitive decline due to depression, often referred to as depressive 'pseudodementia', should be considered.

The assessment and management of dementia will require a range of clinical expertise that can be provided only by a multidisciplinary team.

Are cholinesterase inhibitors effective cognitive enhancement therapies in PD?

▷ Methodology

Seven papers[313–319] were found which addressed the effectiveness of cholinesterase inhibitors as cognitive enhancement therapies in PD. All levels of evidence (RCTs and case series) were selected in order to provide a comprehensive body of evidence upon which to analyse the cost-effectiveness of these treatments in people with PDD. In addition, the literature search cut-off date, for this particular section of the guideline, was August 2005 instead of February 2005.

In addition to the seven papers selected, a Cochrane review[320] which included only one RCT[321] on rivastigmine versus placebo was excluded. This paper was excluded as the patient population was defined as people suffering from dementia with Lewy bodies and not PDD.

▷ Evidence statements

Table 9.1 Effectiveness of cholinesterase inhibitors for people with PDD (1++)

	Rivastigmine		Donepezil	Galantamine
Study design	RCT	CS	RCT	CS
Level of evidence	1++	3	1+	3
Number of trials	1	1	3	1
Sample size (N=)	541[313]	28[318]	22[316], 14[317], 15[314]	16[319]
Trial duration (weeks)	24[313]	34[318]	10[316,317], 16[314]	8[319]
Key cognitive outcomes				
ADAS-cog	C[313]	C[318]	NS[316], NR[317], NR[314],	NR[319]
MMSE	C[313]	NS[318]	C[316], C[317], NS[314]	NS[319]
Motor outcomes				
UPDRS total	NR[313]	NS[318]	NS[316], NS[317], NR[314]	NR[319]
UPDRS motor	NS[313]	NS[318]	NS[316], NS[317], NR[314]	NR[319]

CS = case series; RCT = randomised controlled trial; NR = not reported; NS = not statistically significant (p>0.05); C = statistically significantly (p<0.05) in favour of treatment with cholinesterase inhibition; P = statistically significantly (p<0.05) in favour of placebo treatment.

Other cognitive outcomes reported to be in favour (p<0.05) of cholinesterase inhibitor treatment:

- Neuropsychiatric Inventory 10[313]
- Alzheimer's disease assessment scale (ADAS-cog)[313]
- Alzheimer's Disease Cooperative Study (ADCS)-CGIC[313]
- ADCS ADL[313]
- Cognitive Drug Research power of attention tests[313]
- Delis-Kaplan Executive Function System*[313]
- Ten-point clock-drawing test[313]
- Dementia Rating Scale memory subscore[314]
- CGI[316] (**1++**)
- Clinical impression of change at weeks 12 and 26[318]
- UPDRS subscore part I (mental)[318]
- Clock-drawing test.[319] (**3**)

Other cognitive outcomes reported to be improved in people treated with galantamine:[319]

- Hallucinations improved in 78% of people who experienced hallucinations at baseline.
- Cognition improved in 62% of people and declined in 31%.[319] (**3**)

*Because executive function tests were not performed at all sites, these tests included only people who actually took these tests (74% and 18% of patient population respectively).

A third case series study[315] reported the following outcomes specific to the trial's PDD population:

- In people diagnosed with PDD there was an association with increased probability of an MMSE response (p=0.02).
- PDD patients improved by a mean of 2.3 MMSE points. (**3**)

With respect to adverse events:

- In the rivastigmine-treatment group:
  - More adverse events were experienced (p<0.001).[313]
  - Parkinsonian symptoms were more frequent (p=0.002).[313]
  - The most common events included: tremor (p=0.01), nausea and vomiting (p<0.001). (**1++**)
  - 40% of people had to decrease the daily dose.[318] (**3**)
- In the donepezil-treatment group:
  - There was a non-significant difference in incidence.[314]
  - Events leading to withdrawal included: constipation, nausea and vomiting, hypersalivation, worsening of motor symptoms (gait impairment, increased number of falls, increased tremor).[314,317] (**1+**)
- In the galantamine-treatment group:[319]
  - Three people withdrew prematurely due to vomiting, worsening tremor, anorexia and nausea. (**3**)

With respect to withdrawals:

- There was no significant difference in rivastigmine trials.[313,320] (**1+**)
- The donepezil-treatment group remained in the trial 4.2 weeks longer on average (p<0.05).[314]
- 57% of donepezil group versus 11% of placebo group withdrew due to adverse events.[314] (**1+**)

▷ From evidence to recommendation

There is evidence from randomised placebo-controlled trials of the effectiveness and safety of cholinesterase inhibitors in the treatment of PDD. They are effective in treating both cognitive decline and psychosis in this context. However, not all patients respond, so regular review of the need for these agents is required.

At the time of writing, only one of the cholinesterase inhibitors has a product licence in the UK. The GDG considers that these are useful agents that are commonly used in clinical practice and that they should be available.

NICE has commissioned the guideline: 'Dementia: management of dementia, including use of antipsychotic medication in older people'. NICE is developing this guideline in collaboration with the Social Care Institute for Excellence. This guideline will cover all major forms of dementia, including Alzheimer's disease, vascular dementia, Lewy body dementia, subcortical dementia, frontotemporal dementias, and mixed cortical and subcortical dementia. Dementia encountered in the course of PD will be addressed. The guidelines will, where appropriate, address the differences in treatment and care for people with mild, moderate and severe dementia.

RECOMMENDATION

R68 Although cholinesterase inhibitors have been used successfully in individual people with PD dementia, further research is recommended to identify those patients who will benefit from this treatment. **D (GPP)**

9.3 Sleep disturbance

'He has lots and lots of nightmares when he goes to sleep, and he comes to and doesn't know where he is...' **(carer)[2]**

Sleep problems are common in PD and comprise:

- daytime hypersomnolence
- nocturnal akinesia
- restless leg syndrome (RLS) (Ekbom's syndrome)
- periodic leg movements of sleep
- REM sleep behaviour disorder (RBD)
- sudden onset of sleep
- vivid dreams and/or hallucinations
- nocturia (passing of urine frequently – three times or more – at night)
- sleep fragmentation.

They are particularly taxing to people with PD and their bed-partners because of their mixed nature comprising motor, sensory and sleep issues. In addition, if inadequate rest is gained by night, there is a high prevalence of excessive daytime somnolence that may have serious consequences on social functioning and safety.[322]

Assessment should include a thorough sleep history including:

- enquiry about the three phases of sleep: initiation, maintenance and awakening
- enquiry about leg movements – periodic leg movements in sleep, RLS
- hallucinations and vivid dreams
- questioning whether dreams are acted out, sometimes violently, indicative of RBD, which occurs in up to 15% of people with PD and may precede the diagnosis of PD.

Drug-induced hallucinations and/or vivid dreams may occur, and should be distinguished from RBD. Many centrally acting drugs may disturb sleep patterns, mainly by inducing sedation, but some may cause nocturnal alertness (eg selegiline).

One of the most common sleep disorders seen in PD is RLS. The International RLS Study Group[323] criteria for the diagnosis of RLS are:

- desire to move the extremities, usually associated with discomfort or disagreeable sensations in the extremities
- motor restlessness – people move to relieve the discomfort (eg walking, or providing a counter-stimulus to relieve the discomfort such as rubbing the legs)
- symptoms are worse at rest with at least temporary relief by activity
- symptoms are worse later in the day or at night.

Vivid dreams and nightmares may be provoked by many of the commonly used drugs in PD. A review of medication and reduction/avoidance of suspected causes is usually effective. However, RBD may also occur in which dreams are so vivid that they are acted out. When pharmacotherapy is required, a response may be seen to low doses of clonazepam.[322]

'Sudden onset of sleep' without warning has recently been described in PD people, with the potential to cause road traffic accidents.[324] While certain dopamine agonists were initially incriminated, current opinion is that all PD medications can cause daytime hypersomnolence and that all people with PD are liable to hypersomnolence and should be warned of the possibility of falling asleep at the wheel. This may be more likely in people with later PD on multiple medications and also during upwards dose titration, particularly with dopaminergic agonists. Any people so affected should not drive.

RECOMMENDATIONS

R69 A full sleep history should be taken from people with PD who report sleep disturbance. **D (GPP)**

R70 Good sleep hygiene should be advised in people with PD with any sleep disturbance and includes:

- avoidance of stimulants (for example coffee, tea, caffeine) in the evening
- establishment of a regular pattern of sleep
- comfortable bedding and temperature
- provision of assistive devices, such as a bed lever or rails to aid with moving and turning, allowing the person to get more comfortable
- restriction of daytime siestas
- advice about taking regular and appropriate exercise to induce better sleep
- a review of all medication and avoidance of any drugs that may affect sleep or alertness, or may interact with other medication (for example, selegiline, antihistamines, H_2 antagonists, antipsychotics and sedatives). **D (GPP)**

R71 Care should be taken to identify and manage restless leg syndrome (RLS) and rapid eye movement (REM) sleep behaviour disorder in people with PD and sleep disturbance. **D (GPP)**

R72 People with PD who have sudden onset of sleep should be advised not to drive and to consider any occupational hazards. Attempts should be made to adjust their medication to reduce its occurrence. **D (GPP)**

9.3.1 Daytime hypersomnolence

It has been recognised in recent years that daytime hypersomnolence is a major issue for people with PD. This may even lead to the sudden onset of sleep, which can be dangerous.

How effective is modafinil in treating daytime hypersomnolence in PD?

▷ Methodology

Three placebo-controlled, double-blind RCTs[325,326,327] were found which investigated the effectiveness of modafinil treatment for sleep disorders in people with PD. Two of the studies used a 200 mg/d dose[325,326] while the third increased the dose to 400 mg/d after 1 week.[327]

All studies were small (N=15, 21 and 40)[325,326,327] and of short duration (between 4 and 8 weeks). The mean age of the people included in these studies was 65 years, with mean disease duration of 7 years.

No RCTs were found on the specific treatment of RBD and RLS in PD.

▷ Evidence statements

With respect to the Epworth Sleepiness Scale (ESS):

- One study[325] demonstrated the change in ESS was statistically significant in favour of modafinil treatment (95% CI –8.6 to –0.2, p=0.039). (**1+**)
- Another study[327] found no significant change in ESS between modafinil and placebo groups. (**1++**)

With respect to patient-rated scales:

- The patient-rated CGI scale improved significantly on modafinil (p=0.07).[325] (**1+**)
- There was no difference between modafinil and placebo groups in terms of change in sleepiness 'much or very much improved'.[327] (**1++**)

With respect to other outcome measures:

- There were *no* significant differences between modafinil and placebo in the largest study[327] for the following:
  - UPDRS ADL and motor scores
  - Multiple sleep latency test
  - SF-36
  - Fatigue Severity Scale
  - Hamilton depression scale
  - adverse events
  - withdrawal rates. (**1++**)
- There were *no* significant differences between modafinil and placebo for the following in the two smaller studies:[325,326]
  - Maintenance of Wakefulness Test[326]
  - mean changes in sleep latency[326]
  - sleep logs (similar amounts of sleep)[326]
  - Beck depression scores[326]
  - physician-rated CGIC[325]
  - worsening/improvement of PD signs[325]
  - UPDRS scores, Hoehn and Yahr scores, timed tapping tests or patient diaries[325]
  - percentage on time[325]
  - adverse events[325,326]
  - withdrawal rates.[325,326] (**1+**)

▷ From evidence to recommendation

While there is little evidence from RCTs of the efficacy and safety of modafinil in the treatment of daytime hypersomnolence in PD, it has a product licence for use in hypersomnolence in chronic diseases. Members of the GDG have little experience in its use but acknowledged that modafinil can be useful in this clinical context.

RECOMMENDATION

R73 Modafinil may be considered for daytime hypersomnolence in people with PD. **D (GPP)**

9.3.2 Nocturnal akinesia

Turning over in bed (nocturnal akinesia) may become difficult in PD due to truncal rigidity. This can have a major impact on people with PD and can interfere with sleep and thus lead to daytime hypersomnolence.

Treatment has traditionally been with either small doses of immediate-release levodopa or controlled-release levodopa last thing at night. There is insufficient experience with dopamine agonists and COMT inhibitors in this area.

Are controlled-release levodopa preparations effective in the management of nocturnal akinesia in PD?

▷ Methodology

A double-blind RCT[328] was found which compared controlled-release levodopa and immediate-release levodopa in the treatment of nocturnal and early-morning disability.

The RCT was a multi-centre trial including 103 people from 11 centres in the UK. The mean age of people included in the study was 68 years, with average disease duration of 8 years. Controlled-release co-beneldopa or immediate-release co-beneldopa was given at a dose of 125 mg/day immediately before going to bed.

Methodological limitations included: lack of randomisation and allocation concealment methods, no washout period or first-arm results, and intention-to-treat analysis was not stated. However, carry-over effects and differences between centres were statistically analysed and produced no significant differences.

▷ Evidence statements

With respect to controlled-release levodopa versus immediate-release levodopa, one study[328] reported the following outcomes:

- There were no significant differences in nocturnal and early morning disability. (**1+**)

▷ From evidence to recommendation

There is insufficient evidence from RCTs to support the use of controlled-release levodopa preparations in the treatment of nocturnal akinesia in PD. However, the GDG had considerable experience of their use in this context and were able to support their value.

There is also some experience in using long-acting dopamine agonists, especially cabergoline, for nocturnal akinesia, although such ergot-derived agonists are used less frequently in view of the risk of serosal reactions.

RECOMMENDATION

R74 Modified-release levodopa preparations may be used for nocturnal akinesia in people with PD. **D (GPP)**

9.4 Falls

Falls are common in PD; two-thirds of people with PD fall each year, with most eventually becoming fallers.[12,329,330]

Early onset of falls may indicate an alternative diagnosis to idiopathic PD such as PSP.[331]

Predictors of falls specific to PD include:[12,329,330,332]

- longer disease duration
- more advanced disease
- dyskinesia
- motor fluctuations
- atypical parkinsonism
- postural instability
- small steps
- freezing
- stride-to-stride variability
- altered step and stance width
- loss of arm swing.

Predictors of falls in PD similar to those in the general population include:[12,333]

- old age
- previous falls
- use of sedative drugs
- depression
- dementia.

The clinical impact of falls is considerable, often leading to injury requiring healthcare services, an incapacitating fear of renewed falls, anxiety and depression.[334] The associated costs for society are substantial in terms of finances as well as stress on the patient and their support network.

9.4.1 Assessment and prevention of falls

People with PD require a multidisciplinary assessment of the specific and non-specific predictors of falls together with the intrinsic and extrinsic factors that contribute to falls. In common with other people with repeated falls the assessment and prevention of falls in PD

requires multifactorial assessment and intervention by a professional with understanding of PD. The NICE clinical guideline no. 21 'Falls: assessment and prevention of falls in older people'[16] provides a framework for this process. The 'Quick Reference Guide'[335] (Appendix D) of this guideline is applicable to all people with PD.

RECOMMENDATION

R75 For all people with PD at risk of falling, please refer to *Falls: assessment and prevention of falls in older people*. NICE clinical guideline no. 21. (Available from **www.nice.org.uk/CG021**) (**NICE 2004**)

9.5 Autonomic disturbance

Autonomic dysfunction is common in PD due to the underlying pathophysiology of the condition affecting the catecholaminergic neurones of the autonomic nervous system.

While symptoms due to autonomic disturbance are common, and while this area has not undergone a systematic search for treatment trials, several crucial issues specific to PD were identified by the GDG as Good Practice Points.

9.5.1 Gastrointestinal dysfunction

▷ Weight loss

Unintended weight loss is common in PD, occurring in over 50% of individuals, with 20% losing over 12 kg in one study.[336] A larger proportion of women than men with PD may experience weight loss. Moderate or severe dyskinesia is the strongest correlate of under-nutrition in PD, although the reasons for weight loss are likely to be more complex than simply 'burning off' more calories.[337] Similarly, the weight gain commonly observed after bilateral DBS has not yet been adequately explained.

When significant weight loss occurs, the following general points should be considered:

- other medical causes for weight loss (eg malignancy, endocrine causes)
- investigation of swallow[338]
- review of anti-parkinsonian medications if dyskinesias are problematic
- dietary supplements
- referral to a dietitian.

▷ Dysphagia

Dysphagia is an impairment of swallowing. It is a complex process with risks of asphyxiation, aspiration pneumonia, malnutrition and dehydration. Swallowing difficulties in PD usually relate to disease severity and may affect all phases of the swallow process (oral, pharyngeal and oesophageal). Abnormalities are often detected on video fluoroscopy (modified barium swallow).

One group[339] studied 75 people at different stages of PD and showed that up to 94% had problems with swallowing. In Hoehn and Yahr stages I–III the problems were often not noticed

by the person with PD. However, abnormalities are often detected on modified barium swallow testing. In advanced PD, swallowing difficulties can be severe and are usually obvious to patients and their carers. There is a high incidence of silent aspiration in PD,[340] putting the person at risk of developing recurrent chest infections if not properly investigated. Infected oral secretions are a prime cause of pneumonia and this may be caused by poor oral hygiene due to reduced motor movement in the mouth. Pneumonia is a leading cause of death in later stages of PD.[341]

Dysphagia in PD results from catecholaminergic degeneration and Lewy body formation in the brainstem and within the pharyngeal muscles. It does not respond fully to optimisation of dopaminergic medication.[342]

Dysphagia poses a major problem to the taking of medications which are critical in the successful management of PD. Reduced tongue control leads to difficulty manipulating and clearing tablets from the mouth. Pharyngeal pooling and dysmotility may lead to retention of pills in the valleculae and pyriform fossae; consequently, delivery of medications may be erratic.

The management of dysphagia in PD may involve the following generic issues:

- There should be early referral to a speech and language therapist for assessment, swallowing advice and, where indicated, further instrumental investigation (eg videofluoroscopy or fibreoptic endoscopic examination of swallow safety (FEES)).
- Videofluoroscopy/FEES should be considered to exclude silent aspiration.
- The problems associated with eating and swallowing should be managed on a case-by-case basis. Problems should be anticipated and supportive measures employed to prevent complications where possible.
- Enteral feeding options may need to be considered. This may involve short-term nasogastric tube feeding to re-establish a suitable drug regimen, or placement of a longer-term feeding system such as a percutaneous endoscopic gastrostomy.
- Cricopharyngeal (CP) myotomy has been reported to be successful in some cases with specific CP deficits. However, treatment must be based on physiology, which is best revealed with videofluoroscopy. CP myotomy may put people with PD at high risk of laryngeal penetration and pulmonary aspiration if oral and pharyngeal dysphagia is present.[343,344] CP myotomy also puts people at high risk of aspiration of reflux from the stomach.

▷ Constipation

Colonic dysmotility and anorectal dysfunction are common in PD, occurring in up to 30% and 60% of cases, respectively.[345] Lewy body degeneration occurs within the myenteric plexus of the colon in PD, leading to slow transit times and, occasionally, megacolon, intestinal pseudo-obstruction and volvulus. A combination of disordered contraction and relaxation of the muscles of defecation, which may in part be dystonic, leads to excessive straining, pain, and a sense of incomplete evacuation. Faecal incontinence, when it occurs in PD, is usually due to overflow around faecal impaction.

The management of constipation due to colonic dysmotility in PD should follow a staged, or stepladder, approach:[345]

- increasing dietary fibre and fluid intake (at least eight glasses of water per day) and avoiding bananas

- increasing exercise
- fibre supplements such as psyllium[346] or methylcellulose
- stool softener (eg docusate)
- osmotic laxative (eg lactulose)
- polyethylene glycol electrolyte-balanced solutions[347]
- occasional enemas when required.

For further details on nutrition support in adults, please refer to the NICE guideline on 'Nutrition support in adults' available from **www.nice.org.uk/page.aspx?o=292900**

▷ Genitourinary dysfunction

Urinary dysfunction

Up to 75% of people with PD develop bladder problems. Nocturia is the earliest and most common urinary problem, although daytime urgency and frequency may also be troublesome. Urinary incontinence is common in PD. Detrusor overactivity of neurogenic origin appears to result from disinhibition of the ponto-mesencephalic micturition centre.[348]

Where there are refractory or persistent bladder problems, referral to a person with urological expertise should be considered.

Other management approaches include:

- excluding urinary tract infection where there is an abrupt change in voiding pattern
- excluding diabetes mellitus where frequency and polyuria are prominent
- use of anticholinergic agents (tolterodine, oxybutynin, propiverine, solifenacin), although, since these drugs cross the blood-brain barrier, they must be used with caution as they may induce a toxic confusional state. Other drugs may be available which do not cross the blood-brain barrier (eg trospium chloride).

▷ Sexual dysfunction

Erectile dysfunction is more common in PD (60–70%) than in age-matched controls (38%).[349,350] Men with PD may also experience sexual dissatisfaction and premature ejaculation. In women, difficulties with arousal, low sexual desire and anorgasmia are common.[349]

Dopaminergic therapy may also induce hypersexuality, even when there is erectile dysfunction.

In the management of erectile dysfunction the following should be considered:

- co-morbid endocrine abnormalities (eg hypothyroidism, hyperprolactinaemia)
- 'latent' depression
- discontinuation of drugs associated with erectile dysfunction (eg alpha-blockers) or anorgasmia (eg SSRIs)
- type V cGMP-specific phosphodiesterase inhibitors (eg sildenafil)
- intracavernous injections or transurethral suppositories of alprostadil (a synthetic prostaglandin E_1).

9.5.2 Orthostatic hypotension

Orthostatic hypotension (OH) occurs in 48% of people with PD in the community[351] but is asymptomatic in up to 60%.[352] It may be defined as a drop in systolic blood pressure after standing greater than or equal to 20 mmHg or to less than 90 mmHg.[353] The aetiology of OH in PD is multifactorial and includes Lewy body degeneration in the hypothalamus, brainstem and peripheral nervous system. Symptoms of OH include fatigue, pre-syncope and syncope, while OH may also contribute to falling. Persisting or troublesome OH may warrant referral to a unit with expertise in falls and syncope.

The management of OH in PD should follow a stepladder approach:

- eliminate or reduce antihypertensive medications; reduce or change anti-parkinsonian drugs
- increase dietary salt and fluid intake, avoid caffeine at night; eat frequent, small meals and avoid alcohol
- elevate head of bed by 30–40°
- salt-retaining steroid (eg fludrocortisone)
- direct-acting sympathomimetic (eg midodrine, only available on named-patient basis).

9.5.3 Excessive sweating

Severe sweating may occur as an end-of-dose off phenomenon or while in the on motor state, usually associated with dyskinesias.

The management approach to excessive sweating should exclude a comorbid medical problem (eg chronic infection, thyrotoxicosis), or the post-menopausal state.

9.5.4 Sialorrhoea

Excessive saliva or drooling occurs in 70–80% of people with PD and may be more common in men.[354,355] It may result from oropharyngeal dysfunction, including reduced swallow frequency. Apart from social embarrassment and soiling of clothing, sialorrhoea may also be associated with perioral infection.

General management measures may include:

- referral to a speech and language therapist for full assessment of swallowing ability
- advice and trial of behavioural management techniques to encourage regular saliva swallows
- use of a portable metronomic brooch as a reminder for saliva swallows[356]
- lip seal and swallow exercises
- sublingual 1% atropine ophthalmic solution twice daily[357]
- injection of salivary glands with botulinum toxin A.[358]

RECOMMENDATION

R76 People with PD should be treated appropriately for the following autonomic disturbances: **D (GPP)**

- urinary dysfunction
- weight loss
- dysphagia
- constipation
- erectile dysfunction
- orthostatic hypotension
- excessive sweating
- sialorrhoea.

9.6 Pain

Pain is defined as an unpleasant or distressing sensory experience.[359] Pain occurs in around 40% of people with PD but is rarely a major feature of the disorder.

Pain in PD has been classified[359] as:

- musculoskeletal – often secondary to parkinsonian rigidity and hypokinesia (eg frozen shoulder)
- dystonic – associated with dystonic movements and postures which often occur in the off period in the feet
- primary or central – burning or paraesthetic pain outwith a dermatome or root territory which is not explained by a musculoskeletal or dystonic cause
- neuropathic – pain in the distribution of a root or nerve with associated signs
- akathisia-related – inner feeling of restlessness leading to inability to keep still.

Little research has been done in this area and the management of many of these types of pain is generic rather than being specific to PD. Therefore, the GDG elected not to undertake a literature search in this area. The GDG did recognise the importance of dystonic pain which is often responsive to dopaminergic medications (see Chapter 7).

10 Other key interventions

'Never has anybody said to us, "Do you think you need a physiotherapist, a speech therapist, or an occupational therapist – do you need these services?" That's something we have gone out to find ourselves and I think too late.' (carer)[2]

10.1 Introduction

In previous chapters, consideration has been given to the evidence for pharmacological treatments and surgical interventions. People with PD may also benefit from interventions provided by a range of health disciplines. This chapter addresses the effectiveness of specific interventions that are part of:

- PD specialist nursing
- physiotherapy
- occupational therapy
- speech and language therapy.

Because service issues lie outside the scope of this guideline, evidence has been sought for the effectiveness of the interventions that are part of a discipline and recommendations made accordingly. It should be noted that some interventions, particularly those related to maintaining independence, may, in practice, be carried out by professionals from a number of disciplines.

10.1.1 Methodological limitations

When reviewing the evidence of the interventions delivered by health professionals the following methodological limitations should be considered:

- variations in location of therapy (home, outpatient clinic, in hospital)
- lack of reporting the intensity of therapy given
- variations in therapy regimen between trials
- unclear qualifications and experience of person delivering the intervention
- short trial duration and lack of long-term follow-up
- small sample sizes without power calculations provided
- lack of reporting methods of randomisation or allocation concealment
- lack of reporting drop-outs from trials
- lack of intention-to-treat analysis.

10.2 Parkinson's disease nurse specialist interventions

PDNS care has been pioneered in the UK over the last 10 years supported by the UK PDS. A PDNS's role is defined[360] as a specialist practitioner with essential skills in:

- communication (see Appendix C)
- patient and carer assessment

- symptom management
- medicines management
- providing ongoing support and advice
- referral to other therapists
- education.

A recent report from the UK PDS (2004)[361] identified the key roles and responsibilities of the PDNS in the UK as:

- making and receiving referrals directly to create an integrated and responsive service for people with PD
- admitting and discharging people for specified conditions and within agreed protocols
- managing caseloads
- providing information, education and support to people in their homes, in clinics and in hospitals
- prescribing medicines and treatment and monitoring the effectiveness of changes in medication and treatment
- using the latest information technology (IT) to triage people with PD to the most appropriate health professional
- using IT to identify people at risk and speed up responses to crises.

What is the effectiveness of PDNS care versus standard medical care in the management of people with PD?

10.2.1 Methodology

Three RCTs[362,363,364] were found which addressed the effectiveness of PDNS or other non-consultant care. The specific intervention of 'nursing care', the comparator and the sample size varied between the studies limiting the ability to draw general conclusions. The three studies and their variables are listed below:

- the effects of community-based PDNS care versus GP care in 1869 people with PD[362]
- the effects of nurse practitioner care versus 'standard care' in a population of 40 people with PD recruited from a specialist neurology unit[363]
- the effects of substituted consultant care versus PDNS care in a population of 185 people with PD attending hospital clinics.[364]

Only one study provided data on statistical power.[362] Another study[364] involved only 58% of the 185 enrolled participants who completed the trial, and in a third study[363] the sample size was small (N=40).

The study environment varied considerably between trials. In one study,[362] 438 GP practices were involved from nine randomly selected English health authorities. The practices recruited people who represented the PD population of England and Wales. In another study,[364] clinics in London and Hull with established PDNS services were selected to participate. This study had large numbers of crossovers (ie people receiving care from both consultants and PDNSs), which makes interpretation difficult. Finally, a third study[363] considered only people recruited from the National Hospital for Neurology and Neurosurgery in London. The lack of random patient and centre selection methods in the latter studies limits their generalisability to care provided elsewhere in the UK.

10.2.2 Health economic methodology

Three economic studies of PDNS care were critically appraised[362,364,365] and one met quality criteria.[362] One study[364] did not meet quality criteria in the health economic analysis, but was included in the clinical efficacy analysis. The reason for the exclusion here is due to a 42% loss of people during follow-up, which may have led to bias in the economic results. The third study[365] was also excluded as the trial did not consider all costs relevant to the provision of PDNS care to reflect true cost-saving estimates.

The one study[362] that met quality criteria evaluated community-based PDNS care with GP care versus standard GP care in an RCT in the UK.

As part of the guideline development process, we have evaluated the cost-effectiveness of PDNS care in comparison to standard care over a 1-year period from the NHS perspective. Full details of this analysis are shown in Appendix G.

10.2.3 Evidence statements

The PDNS versus GP care study[362] evaluated the results of the Global Health Questionnaire at the end of a 2-year period and found only one significant outcome measure (out of approximately 20 measures) which favoured PDNS care (treatment difference –0.23, 95% CI –0.4 to –0.06, p=0.008). (**1+**)

This study also reported non-significant results for the following outcome measures: 2-year and 4-year mortality, stand-up tests, bone fracture, mean best hand score, EuroQol tariff, dot-in-square score, PDQ-39 measures, physical functioning (SF-36) and general health (SF-36). (**1+**)

The trial also found that PDNS care enabled more rapid implementation of what was then thought to be good prescribing practice:

- The proportion of people with PD taking controlled-release levodopa increased significantly more in the nurse group (p=0.016).
- People in the nurse group had a greater tendency after 2 years to discontinue their use of selegiline (p<0.001).[362] (**1+**)
- After 1 year, another trial[364] found that substituted consultant care produced the following outcomes (out of 22 measures):
  - one significant outcome in favour of PDNS care: the communication score on the PDQ-39 questionnaire (p=0.05)
  - two significant outcomes favouring the consultant care group: physical functioning on SF-36 (p=0.02) and general health on SF-36 (p=0.02). (**1+**)
- The nurse practitioner versus standard care RCT[363] assessed people with PD and dystonia over 6 months. For the psychosocial outcome measures, no significant differences were found between the intervention and control groups. (**1+**)

In addition, the results from an independent assessment[363] of patient satisfaction, in just the intervention group arm, showed that:

- The most common information provided by the nursing intervention concerned practical issues such as income support and mobility allowance.
- The mean rating for the nursing intervention was 8.5 on a scale of 1–10 (one-half rated the contact as 10, ie 'very useful').

- The aspect of the intervention most highly ranked in terms of usefulness was 'the opportunity to talk to someone about the illness and the problems caused by it'.
- 89% considered the home visits the most useful aspect of the intervention.
- 81% thought that the duration of contact with the PDNS needed to be prolonged.
- 58% thought that the PDNS intervention would be useful to other people with PD (mean 9.0 on scale of 1–10). (**3**)

10.2.4 Health economic evidence statements

The RCT[362] found no significant difference in mean increase in annual costs between groups (p=0.47) from the year before the study to the second year of the study. This mean annual cost estimated the provision of nurse specialist care to cost £200 per person per year and excluded the cost of apomorphine. The mean annual cost in the specialist nurse group increased from £4,050 to £5,860 (£ 1996) and from £3,480 to £5,630 in the control group based on 1,859 people from 438 general practices in nine randomly selected health authority areas of England.

It is not always clear whether PDNS care is substituting some or all of the consultant care or is serving as additional care.[364] By varying the cost-savings of other health professional costs by PDNS care, costs for 1 year of PDNS care range from an additional cost of £3,289 to cost-savings of £4,564. Full details of these analyses are shown in Appendix G.

10.2.5 From evidence to recommendation

Most of the benefits derived from PDNS interventions have been shown to relate to the overall patient care experience and the delivery of services such as the monitoring of medication and provision of information. The communication issues for people with PD and their carers are further addressed in Chapter 4.

There has only been limited evidence showing improvements in direct measures of outcome.

The evidence indicates the cost-effectiveness of PDNS care is inconclusive.

RECOMMENDATION

R77 People with PD should have regular access to the following: **C**

- clinical monitoring and medication adjustment
- a continuing point of contact for support, including home visits when appropriate
- a reliable source of information about clinical and social matters of concern to people with PD and their carers,

which may be provided by a Parkinson's disease nurse specialist.

10.3 Physiotherapy

Physiotherapy or physical therapy can be defined as: 'A health care profession which emphasises the use of physical approaches in the promotion, maintenance and restoration of an individual's physical, psychological and social well-being, encompassing variations in health status'.[366]

Physiotherapy primarily addresses the physical components of rehabilitation, essentially to maximise the functional capacity of a person and their role within society.

Where people receiving physiotherapy have a longer-term condition, such as PD, physiotherapy is generally regarded as an active, ongoing process and one that should be client-focused in its approach and regularly reviewed.

Physiotherapy might incorporate only education and advice ensuring maintenance of a current level of fitness and ability, or involve exercises specific to the needs of the person with PD to regain movement, prevent falls, maximise respiratory function or reduce pain. It also has a role alongside medical and surgical intervention to enhance the person's potential with these interventions.

In addition to physiotherapy, other physical adjuncts to therapy may include approaches such as the Alexander Technique, yoga, Conductive Education or Pilates – techniques which not only promote movement, but also are linked with social well-being.

The principles of physiotherapy are:[367]

- early implementation of exercise programme to prevent de-conditioning and other preventable complications
- utilisation of a meaningful and practical assessment procedure to allow monitoring and identification of rehabilitation priorities
- the identification of deterioration and timely, appropriate intervention
- the opportunity for targeted therapy for restoration or compensation of function
- the involvement of patients and carers in decision-making and management strategies.

What is the effectiveness of physiotherapy interventions versus standard therapy in the care of people with PD?

10.3.1 Methodology

A Cochrane systematic review[368] and an RCT[369] were found which addressed the effectiveness of physiotherapy versus standard therapy or placebo in the treatment of PD. Another study[370] was found which addressed the effectiveness of the Alexander Technique versus no therapy or massage therapy.

The physiotherapy RCT[369] (N=8) investigated the effect of a 16-week aerobic exercise programme on aerobic capacity and movement initiation time for PD.

The Alexander Technique RCT[370] (N=88) randomised participants to three groups: controls (N=30) or Alexander Technique (N=29) or massage group (N=29). The massage group received two massage sessions per week for 12 weeks (the massage group was used as control for touch and attention). The Alexander Technique consisted of two 40-minute lessons per week for 12 weeks, then 5 weeks after completion the participants received a short audio tape that led them through a 20-minute lying down exercise.

The Cochrane review[368] included 11 randomised trials; four of these trials[371–374] reported significant outcomes in relation to physiotherapy treatment for people with PD, with a total of 280 people. The participants in these trials received physiotherapy directed to trunk and limb functions and were treated for 8–30 hours over 3–52 weeks. The method of physiotherapy was usually described in a very broad manner; even the time spent by the therapist with the patient was not specified in half of these trials.

10.3.2 Evidence statements

For a summary of the effectiveness of physiotherapy techniques see Table 10.1 below.

Table 10.1 Effectiveness of physiotherapy techniques (1+)

Outcomes	(N)	Follow-up	p value
Conventional physiotherapy techniques			
Activities of daily living[374]			
Barthel Index	20	Post-intervention	0.05
		5 months	0.045
NUDS		Post-intervention	NS
		5 months	0.018
Functional Index Measure		Post-intervention	0.048
		5 months	0.016
Clinical rating scales			
Total UPDRS[374]	20	Post-intervention	<0.001
		5 months	<0.001
Webster rating scale[374]		Post-intervention	NS
		5 months	0.011
Parkinson's Home Visiting Assessment Tool (5/53 items)[373]	30	8 months	<0.05
Motor impairments			
Walking velocity[372,374]	44	Post-intervention	≤0.002
		5 months	0.006
Stride length[372,374]		Post-intervention	≤0.016
		5 months	0.044
Spinal rotation[371]	51	Post-intervention	0.019
Exercise outcomes[369]			
Aerobic capacity	8	Post-intervention vs controls	0.013
Power output		Post-intervention vs controls	0.037
Movement initiation		Post-intervention vs controls	0.003

continued

Table 10.1 Effectiveness of physiotherapy techniques (1+) – *continued*

Outcomes	(N)	Follow-up	p value
Conventional physiotherapy techniques			
Alexander technique[370]			
SPDDS 'at best'	88	Post-intervention vs controls	0.04
SPDDS 'at worst'		Post-intervention vs controls	0.01
		6 months vs controls	0.04
		6 months vs controls	0.01
BDI scores		Post-intervention vs controls	0.03
		6 months vs controls	NS
Attitudes to Self Scale		Post-intervention vs controls	NS
		6 months vs controls	0.04

The references cited in this table refer to individual papers within the Cochrane review.[368]

With respect to medication changes:[370]

- The rate of medication change was statistically in favour of Alexander Technique treatment compared with control (p=0.001).
- Fewer participants in the Alexander Technique group changed their medication and yet were not experiencing worsening symptoms (p=0.047). (1+)

10.3.3 From evidence to recommendation

There is encouraging RCT evidence of the effectiveness of some of the physiotherapy interventions for people with PD. However, further definitive trials are required to confirm these findings. Additional work is necessary to define what physical therapy interventions are effective in the different stages of the disease. The GDG acknowledge that physiotherapists would not use many of the outcome measures reported in the trial evidence (see Table 10.1). The GDG agree that there is a need for quality-of-life evaluation rated by the patient.

In addition to this evidence, the experience of the GDG members supports the use of physiotherapy interventions in people with PD.

RECOMMENDATIONS

R78 Physiotherapy should be available for people with PD. Particular consideration should be given to: **B**

- gait re-education, improvement of balance and flexibility
- enhancement of aerobic capacity
- improvement of movement initiation
- improvement of functional independence, including mobility and activities of daily living
- provision of advice regarding safety in the home environment.

R79 The Alexander Technique may be offered to benefit people with PD by helping them to make lifestyle adjustments that affect both the physical nature of the condition and the person's attitudes to having PD. **C**

10.4 Occupational therapy

Occupational therapy (OT) is a profession concerned with promoting health and well-being through occupation. The primary goal of OT is to enable people to participate in the activities of everyday life. Occupational therapists achieve this outcome by enabling people to do things that will enhance their ability to participate or by modifying their environment to better support participation.[375]

Occupational therapists have expertise in assisting people who have disabilities to manage the practical aspects of everyday life. Referral to an occupational therapist can enable people with PD to maximise their current abilities, retain independence for as long as possible and develop their own coping strategies to deal with future problems.[376]

The principles of OT are:

- early intervention to establish rapport, prevent activities and roles being restricted or lost and, where needed, develop appropriate coping strategies
- client-centred assessment and intervention
- development of goals in collaboration with the individual and carer with regular review
- employment of a wide range of interventions to address physical and psychosocial problems to enhance participation in everyday activities such as self-care, mobility, domestic and family roles, work and leisure.

Current UK practice emphasises functional goals centred around independence, safety and confidence, including activities such as transfers, mobility and self-care.[377]

A wide variety of interventions are used in PD. Owing to the individualised nature of the therapeutic process, these may include practising skills, cognitive and sensory cueing strategies, problem solving, advice, education, provision of equipment and environmental adaptations.[378]

What is the effectiveness of occupational therapy versus standard medical therapy in the management of PD?

10.4.1 Methodology

A Cochrane review[379] was found on the effectiveness of OT versus placebo (or no interventions) in people with PD. The review included two randomised, parallel group trials, with a total of 84 people (N=64[380] and N=20[381]).

There were significant differences between the methodologies of the two studies. One trial[380] conducted 20 hours of treatment over 5 weeks with 1-year follow-up while the other trial[381] conducted 12 hours of treatment over 1 month with no follow-up. The methodological limitations of these studies are covered in section 10.3.

Due to the lack of RCT evidence, papers with lower-level study designs (eg non-randomised and/or uncontrolled trials) were also included in the search, but no further papers were found which addressed the effectiveness of OT in the treatment of people with PD.

10.4.2 Evidence statements

With respect to clinical outcome measures:[380]

- Barthel Index score, an assessment of ADL, was maintained over 1 year in those treated with occupational therapy.
- The group without the OT intervention lost an average of 4.6 points (out of a total score of 100) (p values not available).
- The other study[381] reported small differences in mean changes between groups on all outcome measures (motor impairment, activities of daily living, and quality-of-life measures) (p values not available).

10.4.3 From evidence to recommendation

In view of the methodological flaws in the trials and the small numbers of randomised participants, and only one outcome measure reported from one trial, there is insufficient evidence to support the efficacy of OT interventions in PD. However, the GDG support the value of many of the aspects of this therapy, particularly with respect to the provision of aids and adaptations to maintain functional independence in people with PD. There is evidence to support this from one trial where there was maintenance of ADL scores in the treated group but a decline in those not treated. Further trials are required to evaluate the role of different aspects of OT.

Despite this lack of evidence, the experience of the GDG members supports the use of OT interventions in people with PD. It is recognised that, in practice, some of these interventions may be carried out by health professionals other than occupational therapists.

RECOMMENDATION

R80 Occupational therapy should be available for people with PD. Particular consideration should be given to: **D (GPP)**

- maintenance of work and family roles, home care and leisure activities
- improvement and maintenance of transfers and mobility
- improvement of personal self-care activities such as eating, drinking, washing and dressing
- environmental issues to improve safety and motor function
- cognitive assessment and appropriate intervention.

10.5 Speech and language therapy

Deterioration in speech is a common manifestation of PD that increases in frequency and intensity with the progress of the disease.

The specific dysarthria resulting from PD is known as hypokinetic dysarthria and it is characterised by:

- monotony with reduced loudness and pitch range
- difficulties in initiating speech
- variable rate

- short rushes of speech
- imprecise consonant
- breathy or harsh voice.

Treatment programmes have focused on specific components of the dysarthria such as respiratory exercise[382] and prosodic exercises.[383] These treatments can be used with individuals or in groups.[384]

Lee Silverman Voice Treatment (LSVT) is a speech therapy programme developed specifically for individuals with PD. It focuses on improving voice loudness with immediate carry over into daily communication. The intensive nature of the programme helps individuals with PD to recognise that their voice is too soft, convince them that a louder voice is within normal limits and makes them comfortable using the new louder voice. It is now provided by certified clinicians in England.

Some people with PD may benefit from use of augmentative and alternative communication devices, which can include the use of:

- alphabet boards
- pacing boards
- voice amplifiers
- digitised speech output systems
- recorded voice messages
- delayed auditory feedback[385]
- microcomputer-based wearable biofeedback device.[386]

What is the effectiveness of speech and language therapy versus standard medical therapy or control in the treatment of speech disturbance in PD?

10.5.1 Methodology

A systematic review[387] was found which addressed the efficacy of speech and language therapy versus standard medical therapy in people with PD.

The review included three RCTs,[384,388,389] with a total sample size of 63. One of these trials used the LSVT technique,[389] whereas the rest used the more conventional speech and language therapy techniques. No raw numerical data were available from one of these studies,[384] so data on only 41 participants were available from the review's[387] analysis. Another included study[388] showed the intervention groups differed significantly from one another at baseline on a number of outcome measures, but no further analysis was provided.

There were significant differences in the intensity of the speech and language therapy intervention between studies. One trial[388] treated participants for 10 hours over 4 weeks, another trial[389] provided treatment for 16 hours over 4 weeks and a third trial[384] treated people for 35–40 hours over 2 weeks.

10.5.2 Evidence statements

With respect to the assessment of speech impairment:

- One study[388] found total impairment with the Frenchay Dysarthria Assessment improved in the intervention group compared with the placebo ($p<0.05$), showing an overall

improvement in the dysarthria score, while all participants in the untreated group showed lower scores with a significant deterioration ($p<0.05$).

- Another study[384] reported that the scores of the Dysarthria Profile were comparable at baseline, but immediately after therapy the scores were significantly higher in the treatment group ($p<0.05$).

With respect to vocal loudness:

- In two trials objective loudness improved by 11 dB[388] and by 5.4 dB[389] ($p<0.005$) immediately after therapy.
- This gain was reduced by 3.5 dB[389] after 6 months but was still significantly in favour of therapy ($p<0.05$).[389]
- Mean objective loudness of speech when the participants were asked to describe a picture improved by 5.2 dB ($p<0.025$) and this improvement was maintained over 6 months (4.2 dB, $p<0.02$).[389]
- The reading loudness of participants receiving LSVT was more than the placebo group immediately after therapy ($p<0.001$) and improvement was mostly maintained ($p<0.005$) at 6 months.[389]
- Mean objective loudness improved when people were asked to give a prolonged 'a' (12.1 dB, $p<0.001$) and this was mostly maintained (9.4 dB, $p<0.001$) at 6 months.[389]
- Maximum vocal loudness increased after therapy[388] by 16 dB ($p<0.01$).
- Mean pitch range increased in the therapy group by 66 Hz (162.7 to 228.3) and remained virtually static in the placebo group.[388]

10.5.3 From evidence to recommendation

Although there is good preliminary evidence of the efficacy of speech and language therapy for speech disorders in PD, this is based on data from only 41 people with maximum follow-up of only 12 weeks. Much of the positive data concerns the unique North American therapy LSVT. While some therapists in England and Wales have attended the mandatory training programme for this intervention, it is not widely available at present. The GDG was also concerned about the practicalities of 16 1-hour treatment sessions in the context of the NHS financial climate.

There is little evidence comparing speech and language therapy to standard medical therapy or control. The GDG were aware of a body of evidence that addresses use of LSVT compared with other speech and language therapy techniques.[390–393] In addition to this, the experience of the GDG members supports the use of speech and language therapy intervention in people with PD.

In the section on dysphagia (Chapter 9) the potential contribution that could be made by speech and language therapist interventions is discussed.

RECOMMENDATION

R81 Speech and language therapy should be available for people with PD. Particular consideration should be given to:

- improvement of vocal loudness and pitch range, including speech therapy programmes such as LSVT **B**
- teaching strategies to optimise speech intelligibility **D (GPP)**
- ensuring an effective means of communication is maintained throughout the course of the disease, including use of assistive technologies **D (GPP)**
- review and management to support the safety and efficiency of swallowing and to minimise the risk of aspiration. **D (GPP)**

11 Palliative care in Parkinson's disease

11.1 Introduction

In the absence of any curative treatment, the management of PD remains largely palliative despite the huge advances that have been made in medical knowledge. The principles of palliative care should be applied throughout the course of the disease and not limited to the terminal end-of-life period.

Palliative care can be defined in the following way:

> *The active total care of patients whose disease is not responsive to curative treatment. Control of pain and other symptoms and of psychological, social and spiritual problems is paramount.*

The goal of palliative care is achievement of the best quality of life for patients and their families.[394]

Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness. It does not necessarily mean the use of specialist care services but should focus on prevention and relief of suffering with early identification, impeccable assessment, and treatment of pain and other physical, psychological and spiritual problems.

The issues common to malignant and non-malignant conditions, that are the focus of palliative care, can be categorised[395] as:

- physical: pain, breathlessness, anorexia, immobility and constipation
- social: loss of employment, role change, fear for dependants
- psychological: depression, fear and anxiety, uncertainty, guilt
- existential: religious, non-religious, meaning of life, why?

11.2 The palliative phase of Parkinson's disease

The needs of patients in the palliative care stage of PD are not always identified or satisfied.[396] Over time, progression of the underlying disease process makes interventions less effective and they may be associated with intercurrent illnesses. As a result, patients become increasingly disabled and dependent. This physical disability is often combined with cognitive dysfunction and depression.

The 'palliative phase' in PD has been defined by:[397]

- inability to tolerate adequate dopaminergic therapy
- unsuitability for surgery
- the presence of advanced comorbidity.

The duration of time spent in each of the stages of PD is variable. From an audit of 73 patients undertaken in Cornwall[398] the mean duration of disease was 14.6 years. The time spent in the four stages was: diagnosis 1.5 years; maintenance 6 years; complex 5 years, and palliative care

2.2 years. This reinforces the view that 'palliative care' in PD does not equate with imminent end of life, but that the emphasis of care will shift from a 'therapeutic' pharmacological approach to one that places greater emphasis on quality of life issues. This is in recognition of the shortened remaining lifespan of the patient and the inadequacy of current medications to meet the increase in needs.

The care of people with PD is best undertaken in a multidisciplinary way throughout each stage of the disease. The palliative care approach should be utilised by all health professionals throughout these stages. It should also be possible to seek advice from specialist palliative care teams, not just at the end of life, but at any stage after diagnosis with the main aims of care to provide symptom relief, prevent complications, minimise distress, maintain patient dignity and provide counselling. With more complex difficulties, the specialist palliative care team may, on agreement, become temporarily or regularly involved with input for the patient or their family, and in supporting the usual professional carers.

The NSF for Long-term (Neurological) Conditions (2005)[14] focuses on the palliative care needs of patients with chronic disabling conditions such as PD in 'Quality requirement 9: palliative care'.

11.2.1 Palliative care and carers

Management of the palliative stage must always be in the context of the patient and the family/caregiver. Recognising the needs of carers of people with PD at an early stage will help enable patients to be maintained at home for as long as possible. Many will have been in the role of carer for a significant number of years and have become 'experts' in PD themselves. Realistic goals need to be agreed jointly by the patient/family and the multidisciplinary team caring for the patient. Respite periods, both for short and longer periods and to meet planned and emergency needs, are particularly important. The White Paper 'Your health, your care, your say' highlights the need for carer support. It may also be useful to refer to a carer care pathway to recognise some of the problems carers may experience. When looking at specific information and support for carers, the PDS provides useful information sheets for carers.[399,400]

11.2.2 Care homes

While the majority of people with PD will cope at home for many years, increasing dependency in the palliative stage, when the care needs exceed the ability of their family or community to cope, will frequently lead to admission into care home settings. This may be due to increased disability or the result of a combination of disability and social factors when the burden of caring becomes too great. In particular, PD studies suggest[401,402] that care home admission is often provoked by hallucinations. Admission of patients into care homes carries with it a greater mortality.[401,402] These trials found that all PD patients admitted into care homes died within 2 years of admission. PD may affect 5–10% of nursing home residents.[403] Guidance on caring for people in care homes in the palliative stage is available.[404–406]

11.2.3 Social costs

Social services will play an increasingly greater role in palliative care stages; in particular to address issues that may arise from increased disability and dependency. Results from a study[10] looking into the economic impact of PD showed that:

- Total social services costs accounted for 34% of total costs and tended to increase with increasing age.
- Total NHS costs accounted for 38% of total costs and tended to fall with increasing age.
- Total annual direct costs were £4,189 for patients living at home; £15,355 for patients whose time was divided between home and an institution; and £19,338 for patients in full-time institutional care.

Wherever the patient resides, their condition should be monitored to ensure comfort and quality of life is maintained. However it may be difficult to assess their needs in a hospital outpatient environment. Day hospital attendance may be easier or a PDNS or other key worker may visit at home. Visiting in the home environment is less stressful for the patient, carer and care staff, and allows time for more detailed discussion, advice, education and counselling.

11.2.4 Withdrawal of drugs

In later stages of PD there may be the need to withdraw dopaminergic drugs due to lack of drug efficacy and increasing sensitivity to unwanted effects such as hallucinations. As a general guide, medication withdrawal should be managed with help from the specialist clinician and PDNS. Where possible drug withdrawal should be gradual in order to achieve the best balance between relief of symptoms and minimal side effects. Patients and carers at this stage will often agree to reduce medications, exchanging greater levels of physical disability for increased mental clarity. This situation should however be reviewed on an ongoing basis as frequent adjustments may be required to maintain this balance.

11.2.5 Pressure ulcers

Immobility in the palliative care phase of PD places individuals at risk of pressure ulcer development, and an assessment of risk for pressure ulcers should be a priority. Most pressure ulcers occur over a bony prominence, but if contractures of the limbs have developed with immobility and the altered body shape of PD, this may result in pressure sores appearing in more unusual locations.

Carers will require support and education in understanding how to move and handle patients safely. Additional information can be found in:

- NICE documents:
  - Pressure relieving devices guidelines[407]
  - Pressure ulcer risk assessment and prevention guidelines[408]
- Royal College of Nursing documents:
  - Clinical practice guidelines on pressure ulcer risk assessment and prevention: implementation guide and audit protocol.[409]

11.2.6 End-of-life issues

In July 2004 the Department of Health (England) started an initiative so that all adult patients nearing the end of life, irrespective of diagnosis, will have access to high-quality specialist palliative care. The focus was to train and equip healthcare professionals with the knowledge and skills to support patients to live and die in the place of their choice. Three key documents make up the basis of this 'End of Life Initiative':

- Preferred Place of Care Plan[410]
- Gold Standards Framework[411]
- Liverpool Care of the Dying Pathway.[412]

Increasingly, initiatives such as these have resulted in district general hospitals (DGHs), primary care and care homes achieving:

- increased advance care planning
- greater choice for patients in where they wish to live and die
- decreased emergency admissions of patients who wish to die at home
- decreased number of older people transferred from a care home to a DGH in the last week of life.

What are the end-of-life palliative care needs of PD patients and what treatments are available? These aspects are currently being explored within the neurological conditions policy group of the National Council for Palliative Care, working closely with the PDS.
www.ncpc.org.uk/policy_unit/neuro_pg.html

11.2.7 Methodology

No trials were found which addressed end-of-life palliative care needs of PD patients and what treatments are available.

11.2.8 From evidence to recommendation

The needs of patients in the palliative care stage of PD are often under-recognised and considered too late in their care. Better understanding of the complexity of the manifestations of the disease, its innate variability, and the roles of the extended team members, which may or may not include the palliative care team, can help to improve care and reduce distress. Care needs to be supported by good care planning since many problems can be predicted or avoided with appropriate strategies.

RECOMMENDATIONS

R82 Palliative care requirements of people with PD should be considered throughout all phases of the disease. **D (GPP)**

R83 People with PD and their carers should be given the opportunity to discuss end-of-life issues with appropriate healthcare professionals. **D (GPP)**

11.3 Ethical issues

Patients and their families need to be allowed to have time to come to terms with the fact that the disease has reached a stage where no more can be done. Decisions may need to be made about management and treatment in the future, and end-of-life decisions (ie do-not-resuscitate policies and advance directives (living wills)). These are never easy issues to discuss but they can provide an opportunity for the person with PD to state treatment preferences should they lose

their capacity for decision making in the future. They derive their authority from the principle of informed consent and the promotion of personal autonomy and should be considered before mental or physical disability precludes their completion.

Additional information that may be of help includes the British Geriatrics Society Compendium advance directives section (**www.bgs.org.uk**), and the BMA (**www.bma.org.uk**).

12 Research recommendations

12.1 Future research recommendations

The questions below are not in order of priority.

▷ Question 1: Do any of the agents with preclinical neuroprotective properties in PD models have any clinically worthwhile protective effects in PD?

Population	People with early PD: some trials with patients on no medication; other trials may randomise patients stabilised on symptomatic medication Any gender, age, ethnic group Trials performed in secondary care.
Intervention	Systematic reviews in the USA have identified 12 agents that require study (Table 6.2). The UK could contribute to the raft of ongoing studies that are funded by the National Institute for Neurologic Disorders and Stroke (NINDS) and the Michael J Fox Foundation Support should also be given to innovative surgical approaches to neuroprotection
Comparison	Each putative neuroprotectant versus placebo in double-blind parallel design or delayed-start design trial
Outcome	Total UPDRS change

Table 6.2 NINDS selected candidate neuroprotective drugs in Parkinson's disease[100]

Caffeine
Co-enzyme Q_{10}*
Creatine*
GM-1 ganglioside
GPI-1485*
Minocycline*
Nicotine
Oestrogen
MAOB inhibitors (rasagiline§ and selegiline)
Dopamine agonists (ropinirole§ and pramipexole§)

*In phase II or III studies in North America.
§Further neuroprotection trials may be performed by manufacturer.

Explanatory paragraph

At present there is no agent that slows the progression of PD. Patients want such a 'cure' for their condition. The NHS requires neuroprotectants to reduce the burden of disability caused by PD, thereby reducing the direct and indirect costs of caring for an increasing number of people with the condition.

While the pharmaceutical industry is trying to develop new putative neuroprotectants, 12 existing agents have been identified which may slow PD progression (Table 6.2). A systematic trial programme examining these agents is ongoing in the USA (Net-PD) funded by the NINDS and the Michael J Fox Foundation. Agents are being screened in small 'futility studies' using historical control data for decline in total UPDRS scores. Agents that delay progression by more than 30% will go through to larger definitive studies.

The first futility study showed that both minocycline and GPI-1485 significantly delay decline in total UPDRS by more than 30%. However, a small placebo comparator group also showed a similar effect, raising doubts about the use of historical controls.

Future Net-PD trials may use patients already established on symptomatic therapies. There are many more such patients than those who are untreated thereby allowing future neuroprotection trials to be much larger.

The recent rasagiline delayed-start design trial versus placebo (see section 6.5) raised the possibility that this may be a useful trial design to examine neuroprotection. Further pharmaceutical industry trials using this design are planned. This would be another option for UK neuroprotection trials.

UK investigators have recently carried out neurorestoration trials with intra-putaminal infusion of GDNF, although these have now been stopped. Support for further surgical approaches to neuroprotection in PD should be considered.

▷ Question 2: Which people with PDD benefit from cholinesterase inhibitor drugs and/or memantine, and is the use of these agents cost-effective?

Population	Patients with PD of more than 2 years' duration (to exclude dementia with Lewy bodies patients) and dementia defined according to DSM-IV criteria or new MDS Task Force criteria for PDD (due mid-2006) Patients stratified according to pattern and severity of cognitive impairment and neuropsychiatric burden (eg visual hallucinations) Concomitant use of stable atypical antipsychotic regimen will be permitted Any sex, age, ethnic group Trials performed in secondary care
Intervention	Donepezil/rivastigmine/galantamine/memantine
Comparison	Cholinesterase inhibitor/memantine versus placebo in RCT design
Outcome	Change in cognition according to validated scales (eg ADAS-cog, new MDS Task Force instrument for PDD – due mid-2006) Neuropsychiatric Inventory Caregiver stress scales Health economics using disease-specific models

Explanatory paragraph

A recent systematic review indicates that 24–31% of PD patients have dementia, and that 3–4% of the dementia in the general population is due to PDD. The estimated prevalence of PDD in the general population aged 65 years and older is 0.2–0.5%. PDD is associated with increased mortality, caregiver stress and nursing home admission.

A large RCT of rivastigmine in PDD showed improvements in primary and secondary end-points but the clinical significance of these benefits is uncertain. It is likely that the modest mean improvements reflect heterogeneity of response, with some patients responding far better than others; this is supported by expert opinion via open-label prescribing. In addition, health economic analysis has not been performed in trials of cholinesterase inhibitors in PDD using disease-specific models.

Identifying responsive subgroups of patients with PDD with demonstrable cost-effectiveness would focus effective targeting of cholinesterase inhibitors and/or memantine. The process of identifying these patients would also lead to the development of protocols for prescribing and assessment, together with robust guidelines regarding whether drug usage is maintained or discontinued.

▷ Question 3: Is treating mild to moderate depression in PD with an antidepressant cost-effective?

Population	People with any stage of PD with mild to moderate depression according to a depression rating scale. Patients with severe depression will be excluded, as treatment is mandatory Any sex, age, ethnic group Trials performed in secondary care
Intervention	Any SSRI class of antidepressant
Comparison	SSRI antidepressant versus no treatment in a pragmatic open-label design
Outcomes	Quality of life rated by disease specific (PDQ-39) and generic (SF-36, EuroQol) measures Health economics Depression scores on accepted depression rating scale

Explanatory paragraph

Cross-sectional studies have shown that depression affects around 40% of patients with PD and has a major impact on quality of life. In most cases depression is mild to moderate in severity and is often missed by the clinician caring for the patient.

The GDG recommends a study that would screen secondary care PD clinic populations for mild to moderate depression. Participants would then be treated with any SSRI class antidepressant or no such treatment in an open-label fashion. This would be a large-scale pragmatic trial.

If screening for and treating mild to moderate depression is cost-effective, this will add to the evidence base for the management of depression in PD and may have considerable impact on the next update of this guideline.

▷ Question 4: Are supportive therapies in PD cost-effective?
(a) Is physiotherapy in PD cost-effective?

Population	People with any stage of PD Any sex, age, ethnic group Trials based in secondary care with primary care support
Intervention	Best practice NHS physiotherapy
Comparison	Pragmatic parallel design trial comparing no treatment with physiotherapy
Outcome	Quality of life rated by disease-specific (PDQ-39) and generic (SF-36, EuroQol) measures Health economics Disease-specific and therapy-specific outcomes including: gait, balance, posture, transfers, and reaching and grasping

Explanatory paragraph

The evidence to support the use of physiotherapy in PD is limited and yet patients feel that it is effective. Many patients are referred for such therapy in the NHS with little idea of its value or whether it has any long-term benefits. In contrast, many other patients cannot access such therapy due to limited provision of service.

The GDG recommends a pragmatic trial performed in units that already have access to physiotherapy services. This is likely to be in the elderly care setting because neurologists have limited access to such treatments. An NHS subvention will be required to ensure adequate therapy resources are available for the trial.

Many prevalent cases of PD will have already received such therapies, so the trial will recruit incident cases. This will require a long recruitment period, a large number of centres or both.

A large trial of cueing therapy (The Rescue Project) in PD has recently been completed but is yet to report.[413] The data from this can act as pilot material for the new trial.

If physiotherapy is cost-effective, the provision of service needs to be increased. If it is not cost-effective, services can be diverted to other conditions.

Future trials will then need to examine which components of physiotherapy are effective and whether it is effective in the earlier stages of the disease.

▷ (b) Is OT in PD cost-effective?

Population	People with any stage of PD Any sex, age, ethnic group Trials based in secondary care with primary care support
Intervention	Best practice NHS occupational therapy
Comparison	Pragmatic parallel design trial comparing no treatment with OT
Outcome	Quality of life rated by disease-specific (PDQ-39) and generic (SF-36, EuroQol) measures Health economics Secondary outcomes to include disease-specific and therapy-specific measures

Explanatory paragraph

The evidence to support the use of OT in PD is limited and yet patients feel it is effective. Many patients are referred for such therapy in the NHS with little idea of its value or whether it has any long-term benefits. In contrast, many other patients cannot access such therapy due to limited provision of service.

The GDG recommends a pragmatic trial performed in units that already have access to occupational therapy services. This is likely to be in the elderly care setting because neurologists have poor access to such treatments. An NHS subvention will be required to ensure adequate therapy resources are available for the trial.

Many prevalent cases of PD will have already received such therapies, so the trial will recruit incident cases. This will require a long recruitment period, a large number of centres or both.

A pilot study of OT in PD is underway in Birmingham. This will provide invaluable data upon which to plan the substantive trial.

If OT is cost-effective, the provision of service needs to be increased. If it is not cost-effective, services can be diverted to other conditions.

Future trials will then need to examine what components of OT are effective.

▷ (c) Is NHS speech and language therapy in PD cost-effective?

Population	People with any stage of PD who have developed speech problems as defined by the observing clinician Any sex, age, ethnic group Trials based in secondary care with primary care support
Intervention	Best practice NHS speech and language therapy
Comparison	Pragmatic trial comparing NHS speech and language therapy with no treatment
Outcome	Quality of life rated by disease-specific (PDQ-39) and generic (SF-36, EuroQol) measures Health economics Measures of intelligibility Secondary outcomes to include disease-specific and therapy-specific measures

Explanatory paragraph

The evidence to support the use of speech and language therapy in PD is limited and yet patients feel that it is effective. The provision of this service in the NHS is patchy with some patients not receiving speech and language therapy when it may be appropriate.

The GDG recommends a trial that is preceded by survey work to identify current and best practice speech and language therapy for PD in the UK. Similar work has already been performed for physiotherapy and OT to prepare for analogous trials.

In this pragmatic trial, standard NHS speech and language therapy would be compared with no treatment. While most PD units will have access to some speech and language therapy service, this may be insufficient for trial purposes so an NHS subvention would be required.

It is likely that a pilot study will be required to assess issues concerning availability of services, recruitment rates, etc.

If speech and language therapy is cost-effective, the provision of service needs to be increased. If it is not cost-effective, services can be diverted to other conditions.

Future trials will then need to examine what components of speech and language therapy are effective.

▷ Question 5: Which diagnostic investigations for PD and potential biomarkers of its progression are clinically useful and cost-effective?

Population	People with suspected PD Any sex, age, ethnic group Trials performed in secondary care
Interventions	(1) Development of existing and novel diagnostic tests to differentiate PD from (a) non-parkinsonism (ie normality and essential tremor) and (b) other parkinsonian disorders (ie PSP, MSA, corticobasal degeneration) (2) Development of biomarkers to follow the progression of PD, mainly to be used in neuroprotection trials
Comparison	Diagnostic accuracy of test versus UK PDS Brain Bank Criteria or ^{123}I-FP-CIT SPECT
Outcome	Well-designed diagnostic studies using receiver-operator characteristic curves were appropriate to establish standard diagnostic clinimetrics of investigations (eg sensitivity and specificity).

Explanatory paragraph

The diagnosis of PD remains clinical. ^{123}I-FP-CIT SPECT may be of additional help in a small proportion of clinically uncertain cases. The diagnostic error rate on presentation may be as high as 10% in expert hands, which may lead to inappropriate therapy and distress following revision of the diagnosis.

A systematic approach led by university researchers and funded by the government would expedite the evaluation of existing and new diagnostic techniques.

The considerable debate surrounding biomarkers to measure the progression of PD has highlighted the need for further studies in this area. More work on existing techniques (eg SPECT and PET) is required and the development of new potential markers of progression is urgently required.

12.2 General research recommendations

These general research recommendations are in addition to the prioritised research recommendations covered in the preceding section. These were gaps in the evidence base that were identified by the GDG when reviewing the literature for the guideline. The GDG recognises that there are many areas of ongoing research activity in the diagnosis, treatment and management of PD. The following were agreed as broad areas for future research development.

Methodology

There were methodological limitations in many of the studies reviewed in the guideline. The GDG agreed that there was a need to make some general recommendations on the design of future research trials in PD.

The following issues should be considered in future trial design:

- Sample size calculations should be performed before the study to ensure large enough numbers of patients are included to prevent false-negative conclusions.
- UK Brain Bank diagnostic criteria should be used to ensure all trial participants have idiopathic PD.
- Trials should attempt to include a more representative spectrum of patients with PD, particularly the elderly and those with comorbidity.
- Outcome measures should include patient-rated quality-of-life instruments and health economics evaluations.
- Patients should be followed for prolonged periods.
- An intention-to-treat analysis of the data from all randomised participants should be performed.
- All reporting of results should be to CONSORT standards.[414]

Diagnosis

In the development of diagnostic tests for PD in the future, study designs should be improved to include, for example:

- blinding of investigators
- assessment of established cases then assessment of newly diagnosed cases with prospective follow-up
- reporting of appropriate statistics (including sensitivity, specificity, positive and negative predictive values).

More research is needed in the use of MRI, magnetic resonance volumetry, MRS, PET, MIBZ-SPECT, IBZM-SPECT, transcranial ultrasound and smell testing as diagnostic tools to accurately differentiate PD from controls, those with essential tremor and those with other parkinsonian conditions before further conclusions can be reached regarding their value.

Many of these investigations are expensive with limited availability. It would be particularly useful to develop inexpensive tests for PD based on serum or cerebrospinal fluid biomarkers or more sophisticated bedside tests; for example, olfaction, eye movements, neuropsychological testing and detailed movement analysis.

Studies should be done to examine the possibility of combining two or more diagnostic tests to improve accuracy. This is particularly applicable to less expensive investigations. In addition, studies should also compare promising diagnostic tests directly (eg SPECT scanning with objective smell identification).

Neuroprotection

Careful consideration must be given to the design of neuroprotection trials in PD in the future to avoid the mistakes of the past.

A systematic approach to the development of neuroprotection trials in PD should be adopted in England and Wales along the lines of, and possibly in collaboration with, the NINDS in the USA. From a societal perspective, it would be more cost-effective to slow or halt the progression of PD than to continue to treat it symptomatically.

The UK has recently led neurorestoration trials using intra-putaminal GDNF infusions in PD. Support for similar trials in the future will be imperative.

Methods to improve neuroprotection trial design include:

- Washout of drug at the end of the trial should be prolonged or trial should be done in patients not requiring symptomatic medication (ie very early disease)
- Future longitudinal clinicopathological studies are required to evaluate the ultimate diagnosis and prognosis of patients bearing an initial clinical diagnosis of PD who are found to have normal SPECT and/or PET images.
- Misdiagnosis must be taken into account when sample size calculations are performed.
- Larger and longer studies may be able to show more clinically meaningful effects.
- Standardisation of imaging methodology with blind evaluation of results should be better.
- There should be repeated imaging after dose titration and after drug withdrawal at end of trial.
- If the predicted therapeutic effect is mild or slight, trials need to be much larger (ie thousands of patients).
- Large explanatory trials in early disease should be rolled on into pragmatic long-term trials reflecting real-life practice with quality-of-life and health economics outcomes.

Symptomatic therapy

Future clinical trials examining the effectiveness of symptomatic therapies in PD should be longer and larger than those in the past to provide more reliable evidence of the long-term effects of treatments. Such trials should use robust clinical criteria for the diagnosis of PD. Results should be reported on an intention-to-treat basis using CONSORT reporting guidelines. Crossover trials should report the results of the first half of the study separately from the overall results and should have a sufficiently long washout period to prevent carry-over effects.

More data on the comparative efficacy and safety of the most commonly used symptomatic therapies for early PD are required. In particular, we need more information on the relative merits of levodopa, dopamine agonists, amantadine, anticholinergics and MAOB inhibitors in terms of quality-of-life and health economics outcomes.

Clinicians require more data on the comparative efficacy and safety of adjuvant therapies for later PD once levodopa has been commenced and motor complications have developed. There is insufficient information on which to base a decision whether to add a dopamine agonist, a COMT inhibitor or an MAOB inhibitor.

The PD MED trial is comparing levodopa, dopamine agonists and MAOB inhibitors in early PD and adjuvant therapy in later PD with dopamine agonists, COMT inhibitors and MAOB inhibitors using quality-of-life and health economics outcomes.

Non-motor features

Depression is common in PD, but further work is required to:

- develop suitable ways to screen for mild depression in clinic populations
- obtain information on the value of cognitive behavioural therapy
- obtain more trial data on the efficacy and safety of SSRIs and other modern classes of antidepressant in PD.

Further work is needed to evaluate the role of electroconvulsive therapy in drug and cognitive behavioural therapy-refractory depression.

Additional trials should be performed with memory-enhancing agents in PDD. Trials are needed to compare the effects of atypical antipsychotics with those of memory-enhancing agents in PDD.

Further research is required to evaluate treatments for daytime hypersomnolence, constipation, bladder disturbance, autonomic dysfunction, and RBD associated with PD.

Other key interventions

In the development of evidence to support physiotherapy intervention, future research should include large, well-designed trials to investigate:

- the optimal stage in the condition for referral to a physiotherapy practitioner
- the benefit of exercise for people in the different stages of the condition in relation to maintenance of their movement capability and function
- the role of optimising physical capacity to delay the onset and manifestation of disability
- the benefit of physiotherapy in preventing falls in people with PD
- the benefit of physiotherapy in maintaining confidence to move in people with PD
- the benefit of multi- and interdisciplinary intervention (including physiotherapy) in enabling a good quality of life in people with PD and their family and carers
- physiotherapy as an adjunct to change in medical and surgical intervention.

Further large, well-designed trials are required to evaluate the impact of occupational therapy for people with PD, including large, well-designed trials to investigate:

- the optimal stage for referral to OT
- the benefit of OT in maintaining or optimising safety and independence in transfers, mobility and personal care, and in reducing risk/ frequency of falls
- the benefit of OT in maintaining or optimising work, family, leisure and recreational roles and activities, according to the specific wishes and needs of the individual with PD
- the value of OT in the management of anxiety and depression
- the benefit of provision of information and advice about assistive aids, equipment and wheelchairs, and about practical and financial support and services
- the benefit of OT in improvement of hand function, including handwriting/management of micrographia
- the value of education and advice about the self-management of symptoms, especially where these are experienced in 'a pre-drug management phase', where symptoms are drug resistant or where drug side effects limit their use
- the value of a multi-interdisciplinary intervention (including OT) in enabling a good quality of life in people with PD, their families and carers.

Further research is required into the impact of speech and language therapy intervention for people with PD, including large, well-designed trials to investigate:

- different therapy programmes and their impact on features such as vocal loudness and overall communication competency/intelligibility
- treatment for dysphagia
- trials of different intensities of treatments and their impact on communication over time
- the optimal timing for intervention
- the benefit of using assistive augmentative communication devices for people with PD
- the benefit of speech and language therapy intervention on quality of life, such as feelings of social isolation
- the impact of communication difficulties on family and carers and whether this can be reduced with intervention.

APPENDICES

Appendix A: The scope of the guideline

Guideline title

Parkinson's disease: diagnosis, management and treatment of Parkinson's disease in primary and secondary care

Background

The National Institute for Health and Clinical Excellence (NICE or 'the Institute') has commissioned the National Collaborating Centre for Chronic Conditions to develop a clinical guideline on Parkinson's disease (PD) for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government (see below). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost-effectiveness.

The Institute's clinical guidelines will support the implementation of national service frameworks (NSFs) in those aspects of care where a framework has been published. The statements in each NSF reflect the evidence that was used at the time the framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the framework.

Clinical need for the guideline

Parkinson's disease is a progressive neurodegenerative condition leading to death of the dopamine-containing cells of the substantia nigra. The 'cardinal signs' of the disease are rest tremor, rigidity, and hypokinesia. Postural instability and falls occur later during the course of the condition. Additional common findings are asymmetric onset of symptoms and symptomatic response to L-dopa (levodopa). Although predominantly a movement disorder, cognitive impairments including dementia do occur. All of these problems lead to significant disability and handicap with impaired quality of life for both patients and their carers and increased healthcare costs.

Parkinson's disease is one of the commonest neurological conditions. It is estimated to affect up to 160 per 100,000 of the general population with an annual incidence of 15–20 per 100,000. Many population studies have shown the rising prevalence with age (up to 2% of the population aged 80 and over). Around 1 in 7 cases are diagnosed below the age of 60 years.

The costs of treatment have been estimated at between £560,000 and £1.6 million per 100,000 of the population. Significant cost drivers include the onset of motor fluctuations, psychiatric symptoms, and institutional care. Parkinson's disease is a frequent cause of falls, fractures, and hospital admission and is therefore a costly disease, especially in the later stages.[10,362,415]

The guideline

The guideline development process is described in detail in three booklets that are available from the NICE website (see 'Further information'). *The guideline development process: information for stakeholders*[13] describes how organisations can become involved in the development of a guideline.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health and Welsh Assembly Government (see below).

The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered:

- both sexes over 20 years of age
- diagnoses: Parkinson's disease and parkinsonism
- treatment: idiopathic Parkinson's disease only.

Groups that will not be covered:

- juvenile onset Parkinson's disease (<20 years)
- pregnant females
- treatment: parkinsonism (a neurological disorder that manifests with hypokinesia, tremor, or muscular rigidity) and other tremulous disorders (eg essential tremor) – except for accurate differential diagnosis.

Healthcare setting

The guideline will cover the care received from primary, secondary and tertiary NHS care settings.

Clinical management

The guideline will cover the following aspects of management.

Diagnosis and monitoring:

- clinical expert diagnosis (using UK PDS Brain Bank Criteria)
  - versus non-expert diagnosis
  - versus post-mortem gold standard
- other diagnostic tests (eg acute levodopa and apomorphine tests, radionuclide imaging: PET and SPECT, magnetic resonance imaging, magnetic resonance volumetry, magnetic resonance spectroscopy, growth hormone stimulation test).

Communication and education:

- communication of the diagnosis and patient understanding
- patient education (self-help), both specific and generic issues, including falls prevention

Pharmacotherapy:

- prevention of progression – the use of neuro-protective therapy (eg dopamine agonists, MAOB inhibitors, amantadine, co-enzyme Q_{10}, vitamins).
- functional disability – treatment of early disease with:
  - immediate-release levodopa
  - modified-release levodopa

  - dopamine agonists
  - MAOB inhibitors
  - amantadine
  - anticholinergics
  - beta-blockers.
- adjuvant pharmacotherapy:
  - dopamine agonists
  - COMT inhibitors
  - MAOB inhibitors
  - amantadine
  - intermittent apomorphine injections and continuous infusion
  - treatment of non-motor symptoms (eg sleep disturbance).

Non-pharmacological management:

- current surgical options (eg deep brain stimulation)
- physiotherapy
- speech and language therapy
- occupational therapy
- Parkinson's disease nurse specialists

Neuropsychiatric conditions

- psychosis management specific to PD
- depression management specific to PD
- dementia management specific to PD.

Palliative care:

- end-of-life issues specific to PD.

The guideline will not cover the following aspects of intervention/management.

- radical therapies that do not form common clinical management: fetal cell transplantation; stem cells; genes that code protein responsible for producing dopamine; drugs that block the action of glutamate; GDNF; viral transfection
- comorbidities in Parkinson's disease (except where treatment will differ from treatment of these comorbidities in patients without Parkinson's disease)
- generic health problems where the care for people with Parkinson's disease does not differ to that of the general population (eg constipation).

Audit support within guideline

The guideline will include Level 1 clinical audit criteria.

Referral from the Department of Health and Welsh Assembly Government

The Department of Health and the Welsh Assembly Government asked the Institute in May 2002:

> 'To prepare clinical guidelines for the NHS in England and Wales for the diagnosis, management and treatment of Parkinson's disease in both primary and secondary care settings, including examination of the evidence for the effectiveness of management of the condition by physiotherapy, speech, language and occupational therapies, self-help, drug therapies and surgery.'

Appendix B: Details of questions and literature searches

Table B1 Details of questions and literature searches

Question ID	Question wording	Study type filters used	Database and year
DIAG1	How effective is clinical expert diagnosis (using UK PDS Brain Bank Criteria) vs non-expert diagnosis in diagnosing patients with Parkinson's disease?	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
DIAG2	How effective is clinical expert diagnosis (using UK PDS Brain Bank Criteria) vs the post-mortem gold standard in diagnosing patients with Parkinson's disease?	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
DIAG3	How effective is acute levodopa testing and apomorphine testing vs long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
DIAG4a	How effective is magnetic resonance imaging vs long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
DIAG4b	How effective is magnetic resonance volumetry vs long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
DIAG4c	How effective is magnetic resonance spectroscopy vs long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
DIAG6	How effective is positron emission tomography vs long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
DIAG7	How effective is single photon emission computed tomography vs long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome? * Redone to include differential diagnosis of PD.	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
DIAG8	How effective is objective smell testing vs long-term clinical follow-up in determining an accurate diagnosis in patients with suspected Parkinson's disease?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005

continued

Table B1 Details of questions and literature searches – *continued*

Question ID	Question wording	Study type filters used	Database and year
MON1	What is the most appropriate frequency of follow-up after the initial diagnosis of Parkinson's disease?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
COMM1	What approach to patient engagement best aids patient understanding on diagnosis of Parkinson's disease?	All study types including qualitative	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005 BNI 1985–2005 PsycInfo 1887–2005
TxNP1	Is MAO-B vs placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxNP2	Are dopamine agonists vs placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxNP3	Is co-enzyme Q10 vs placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005 AMED 1985–2005
TxNP4	Are specific vitamins vs placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005 AMED 1985–2005
TxMN1	What is the effectiveness of MAO-B vs placebo or levodopa in the treatment of early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxMN2	What is the effectiveness of dopamine-agonists vs placebo or levodopa in the treatment of functionally disabled early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxMN3	What is the effectiveness of amantadine vs placebo or levodopa in the treatment of functionally disabled early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 2000–2005 Embase 2000–2005 *Cochrane 2000–2005 CINAHL 2000–2005 *Cochrane search update only

continued

Table B1 Details of questions and literature searches – *continued*

Question ID	Question wording	Study type filters used	Database and year
TxMN4	What is the effectiveness of MAO-B vs dopamine agonists in the treatment of early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxMN5	What is the effectiveness of immediate-release levodopa vs placebo in the treatment of functionally disabled early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxMN6	What is the effectiveness of modified-release levodopa vs immediate-release levodopa in the treatment of early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxMN9	What is the effectiveness of anticholinergics vs placebo in the treatment of functionally disabled early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxMN10	What is the effectiveness of beta-blockers vs placebo in the treatment of functionally disabled early Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxCM1	What is the effectiveness of adding MAO-B vs placebo in the treatment of later Parkinson's disease patients with motor complications?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxCM2	What is the effectiveness of adding dopamine-agonists vs placebo in the treatment of later Parkinson's disease patients with motor complications?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxCM3	What is the effectiveness of adding amantadine vs placebo in the treatment of later Parkinson's disease patients with motor complications?	Systematic reviews, RCTs and comparative studies	Medline 2000–2005 Embase 2000–2005 *Cochrane 2000–2005 CINAHL 2000–2005 *Cochrane search update only
TxCM4	What is the effectiveness of adding dopamine agonists vs MAOB inhibitors in the treatment of later Parkinson's disease patients with motor complications?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxCM5	What is the effectiveness of adding dopamine-agonists vs amantadine in the treatment of later Parkinson's disease patients with motor complications?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005

continued

Table B1 Details of questions and literature searches – *continued*

Question ID	Question wording	Study type filters used	Database and year
TxCM6	What is the effectiveness of adding dopamine-agonists vs COMT inhibitors in the treatment of later Parkinson's disease patients with motor complications?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxCM7	What is the effectiveness of adding COMT inhibitors vs placebo in the treatment of later Parkinson's disease patients with motor complications?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxCM8	What is the effect of controlled-release levodopa vs immediate-release levodopa in the treatment of later Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
TxCM9	What is the effectiveness of apomorphine vs standard oral treatment in later Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
SURG1	What is the effectiveness and safety of any deep brain stimulation procedure vs standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
SURG2	Which is the most effective form of deep brain stimulation in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005
AHP1	What is the effectiveness of physiotherapy vs standard medical therapy or placebo in the treatment of Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005 AMED 1985– 2005
AHP2	What is the effectiveness of speech and language therapy vs standard medical therapy or placebo in the treatment of speech disturbance in Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005 AMED 1985–2005
AHP3	What is the effectiveness of occupational therapy vs standard medical therapy or placebo in the treatment of Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005 AMED 1985–2005

continued

Table B1 Details of questions and literature searches – *continued*

Question ID	Question wording	Study type filters used	Database and year
AHP4	What is the effectiveness of Parkinson's disease nursing specialist care vs standard care or placebo in the treatment of Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005 AMED 1985–2005 BNI 1985–2005
PSYC1	What is the effectiveness of antidepressant therapies vs placebo or active comparator in the treatment of depression in Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 2001–2005 Embase 2001–2005 *Cochrane 2001–2005 CINAHL 2001–2005 PsycINFO 2001–2005 *Cochrane search update only
PSYC2	What is the effectiveness of atypical antipsychotic therapies vs placebo or active comparator in the treatment of psychosis in patients with Parkinson's disease?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005 PsycINFO 1887–2005
PSYC3	Is cognitive enhancement therapy effective in dementia in Parkinson's disease and Lewy body dementia?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 CINAHL 1982–2005 PsycINFO 1887–2005

Note: The final cut-off date for all searches was 28 February 2005.

Appendix C: Parkinson's Disease Society Communication Table

Table C1 ***Communicating with people with Parkinson's and their carers*** **(2005) (Adapted from Parkinson's Disease Society report[33])**

Principle	Comment
General	
Maintain a good knowledge of Parkinson's disease including the symptoms, comorbidities, care and treatment.	All staff who come into contact with people with Parkinson's need to have training and updating on the core symptoms, pharmacology and care.
Use clear language and avoid medical jargon when communicating with people with Parkinson's.	Essential.
Check if the person has understood information provided.	Essential.
Give the person extra time to respond to questions.	Essential.
Ensure information is appropriate, accessible and available in a range of formats.	Essential.
Provide an appropriate setting to communicate, eg a quiet room without interruptions or distractions.	Essential.
Diagnosis	
Communicate the diagnosis in a manner that is sensitive to the needs of the individual, ie if the person wants more information, make this available; if they demonstrate shock or bewilderment, offer a follow-up appointment for further discussion of the symptoms and treatment.	Essential.
Allow extensive opportunities for questions and discussion.	The consultation time should be sufficient to allow for this.
Offer a follow-up discussion.	Essential.
If the consultation reveals a demand for additional specialist information, the person should be referred promptly to the relevant professional (eg Parkinson's nurse, psychiatrist, speech and language therapist, counsellor).	Essential.
Offer written information to supplement the diagnosis. This should include details of specialist organisations such as the Parkinson's Disease Society (PDS).	Essential.
Put the person in contact with specialist support, eg Parkinson's nurse, PDS community support worker. This should include multidisciplinary support (speech and language therapy, physiotherapy, occupational therapy, social workers).	Essential.

continued

Table C1 *Communicating with people with Parkinson's and their carers* (2005). (Adapted from Parkinson's Disease Society report.[33]) – *continued*

Principle	Comment
Diagnosis – continued	
Provide information for carers.	Important but not in all circumstances – the needs of the patient should come first.
Maintenance	
Provide the person with a point of contact for further information.	The PDS recommends that all people with Parkinson's should have access to a PDNS.
Ensure the person has relevant and current information about the condition and treatment specific to their needs and stage of the condition. Provide them with information about all their options, eg medications, home care, therapy.	Essential. Frequency of reviews varies according to the individual but is optimally 6 months. Consultation can take place additionally and in the interim via telephone and email contact.
Consult the person regularly about their physical and emotional needs and financial needs.	Essential.
Consult the carer about the physical and emotional needs of the person they are caring for, and their own support needs.	Essential.
If/when the person goes into hospital, ask them whether they are self medicating, and, if so, facilitate this with access to their drugs at the times prescribed for them.	Essential.
Offer the person access to self-management resources, eg the Expert Patient Programme, if appropriate.	Essential.
Advanced stage care	
Ensure that people and carers receive regular information about the condition, the medications, the financial support and the support networks.	These should be available in a variety of formats, such as print, audio and/or video.
Ensure that staff are aware of the complexities of this stage of the disease and care for their holistic needs and those of their carers including emotional, spiritual and psychological needs.	Essential.

Appendix D: NICE Falls Quick Reference Guide: The assessment and prevention of falls in older people

Key priorities for implementation

▷ Case/risk identification

Older people in contact with healthcare professionals should be asked routinely whether they have fallen in the past year and asked about the frequency, context and characteristics of the fall.

Older people reporting a fall or considered at risk of falling should be observed for balance and gait deficits and considered for their ability to benefit from interventions to improve strength and balance. (Tests of balance and gait commonly used in the UK are detailed in the full guideline.)

▷ Multifactorial falls risk assessment

Older people who present for medical attention because of a fall, or report recurrent falls in the past year, or demonstrate abnormalities of gait and/or balance should be offered a multifactorial falls risk assessment. This assessment should be performed by healthcare professionals with appropriate skills and experience, normally in the setting of a specialist falls service. This assessment should be part of an individualised, multifactorial intervention.

Multifactorial assessment may include the following:

- identification of falls history
- assessment of gait, balance and mobility, and muscle weakness
- assessment of osteoporosis risk
- assessment of the older person's perceived functional ability and fear relating to falling
- assessment of visual impairment
- assessment of cognitive impairment and neurological examination
- assessment of urinary incontinence
- assessment of home hazards
- cardiovascular examination and medication review
- multifactorial interventions.

▷ Multifactorial interventions

All older people with recurrent falls or assessed as being at increased risk of falling should be considered for an individualised multifactorial intervention.

In successful multifactorial intervention programmes the following specific components are common (against a background of the general diagnosis and management of causes and recognised risk factors):

- strength and balance training
- home hazard assessment and intervention
- vision assessment and referral
- medication review with modification/withdrawal.

Following treatment for an injurious fall, older people should be offered a multidisciplinary assessment to identify and address future risk, and individualised intervention aimed at promoting independence and improving physical and psychological function.

▷ Encouraging the participation of older people in falls prevention programmes including education and information giving

Individuals at risk of falling, and their carers, should be offered information orally and in writing about what measures they can take to prevent further falls.

▷ Professional education

All healthcare professionals dealing with patients known to be at risk of falling should develop and maintain basic professional competence in falls assessment and prevention.

Appendix E: Economic modelling – dopamine agonists

Background

Levodopa (LD) remains the mainstay of treatment for PD but with long-term use it causes abnormal involuntary movements (dyskinesias) and fluctuations in motor performance (end-of-dose deterioration and unpredictable 'on/off' fluctuations). To avoid these motor complications, oral dopamine agonists have been used to treat early PD on their own (ie monotherapy).

However, dopamine agonists cost in the region of three times as much as levodopa per year (GDG). The incremental cost-effectiveness of this approach has not been considered in the UK. The large pragmatic PD MED trial will examine the cost effectiveness of these two approaches in the management of early PD.

Aim

The aim of the model was to perform a cost-minimisation analysis based on the assumption of equivalent effectiveness of dopamine agonist versus levodopa therapy in early PD over a 1-year time horizon.

Methods

A cost-minimisation model was constructed from the perspective of the NHS. The effectiveness outcome measure used quality of life. The data sources of the costs and benefits are described in further detail in Tables E1 and E2. No discount rate was used over a 1-year time horizon in accordance with standard practice. A one-way sensitivity analysis was run to assess the impact of variables on the incremental cost of dopamine agonists.

$$\text{Incremental cost} = (C_1 - C_2)$$

Where:

C_1 = Estimated cost of dopamine agonist treatment

C_2 = Estimated cost of levodopa treatment

Data sources and assumptions

Tables E1 and E2 list the baseline cost parameters along with the sources of data. Assumptions and methods of calculating estimates are described in further detail below.

Costs

One study suggests medication costs over a 4-year period are the only cost categories assessed in which there was a statistically significant difference by treatment group (mean = $8,938 per patient for the pramipexole arm and $5,399 for the initial levodopa arm, $p<0.001$).[169] The other cost categories assessed included acute hospitalisations, outpatient provider visits, diagnostic procedures, test and surgeries, emergency department visits, nursing home care,

rehabilitation hospital care, durable medical devices, lost wages and home health aid service. Therefore, it was assumed all other cost factors were similar between the alternatives and only the cost of medications were used to compute the incremental costs of dopamine agonist over the levodopa strategy.

Table E1 Mean total daily dosage[158]

	Levodopa group (N=150)	Dopamine agonist group (N=151)
Experimental dosage	427 ±112 mg (LD)	2.78 ± 1.1 mg/d (salt)
Supplemental LD dosage	274 ± 442 mg	434 ± 498 mg/d

The mean total daily dosage in each alternative was derived from a 4-year RCT comparing pramipexole versus levodopa in initial treatment for PD.[158] In this study, carbidopa/levodopa was taken as 12.5/50 mg or 25/100 mg capsules or matching placebo capsules and pramipexole was taken 3 times per day as 0.25 mg, 0.5 mg or 1 mg salt tablets or matching placebo tablets. Therefore, these tablet sizes were used to derive the unit costs of the medications. The choice of pramipexole as the dopamine agonist was based solely on the clinical reason that it is representative of the class.

The daily cost of the experimental drug therapy and supplemental levodopa was estimated by multiplying the daily dosages in mg with the cost per mg. Total daily cost was the sum of the experimental drug cost and supplemental levodopa cost. Total cost of therapy over one year was calculated as total daily cost multiplied by 365 days.

Additional cost of dopamine agonist treatment

The additional cost of dopamine agonist treatment over a 1-year period was calculated by subtracting the cost of levodopa treatment from the cost of dopamine agonist treatment.

Table E2 Unit costs of medications

Medication	Cost per mg (£ 2004)	Source	Type	Pack size
Pramipexole	2.467	BNF	180 micrograms base = 250 micrograms salt (0.25 mg)	30-tab pack = £18.50, 100-tab pack = £61.67
	1.963		700 micrograms = 1 mg salt (1 mg)	30-tab pack = £58.89, 100-tab pack = £196.32
Levodopa	0.002	BNF	carbidopa 12.5 mg (as monohydrate), levodopa 50 mg	90-tab pack = £7.03
	0.001		carbidopa 25 mg (as monohydrate), levodopa 100 mg	90-tab pack = £10.05

Effectiveness

The mean change of quality of life scores on both the PDQUALIF and the EuroQoL VAS were not significantly different between the dopamine agonist group and levodopa group and there were no significant treatment differences in the seven subscales of the PDQUALIF in the 4-year randomised control trial.[158] The GDG agreed there was no clear clinically important difference between the two treatment strategies as many dyskinesias are mild and non-disabling and therefore well tolerated by patients. After 4 years of treatment, there is only one additional moderately disabling dyskinesia (1.0%), two mildly disabling dyskinesias (2.0%) and 17 non-disabling dyskinesias (16.8%) in 101 individuals in the levodopa group versus the pramipexole group, whereas the mean improvements in total, motor and activities of daily living UPDRS scores were greater in the levodopa group versus the pramipexole group.[158]

Results

Table E3 Mean total daily cost

	Levodopa group (£ 2004)	Dopamine agonist group (£ 2004)
Experimental dosage	0.7839 (LD)	6.8573
Supplemental LD dosage	0.3060	0.4846

Table E4 Mean total cost over 1-year period

Alternative	Cost (£ 2004)
Pramipexole	2,680
Levodopa	286
Incremental cost	2,394

Under the base-case analysis, the additional cost of dopamine agonist treatment versus levodopa over one year is £2,394.

Sensitivity analysis

The estimates used in the model are subject to uncertainty. Therefore, a one-way sensitivity analysis was carried out to assess the impact of key variables using the model. A one-way sensitivity analysis varies one parameter while maintaining the other parameters at base-line values. The variables included are:

(1) unit cost of levodopa
(2) unit cost of pramipexole
(3) mean total daily dosage of experimental levodopa in levodopa treatment
(4) mean total daily dosage of supplemental levodopa in levodopa treatment

(5) mean total daily dosage of experimental pramipexole in pramipexole treatment and
(6) mean total daily dosage of supplemental levodopa in pramipexole treatment.

Results for the upper and lower estimates are given in Table E5. The higher range of the unit cost of levodopa was derived from the higher unit cost of alternative pack size and the lower range was estimated as minus 10%. The lower range of the unit cost of pramipexole was derived from the lower unit cost of alternative pack size and the higher range was estimated as plus 10%. The ranges of the mean total daily dosages were estimated as $\pm$ two standard errors derived from the standard deviations and population size in the study.

Table E5 One-way sensitivity analysis

Variable	Baseline value	Range evaluated	Incremental cost with lower range estimate (£ per year)	Incremental cost with higher range estimate (£ per year)
Unit cost of levodopa	0.0011	0.0010–0.0016	2,405	2,351
Unit cost of pramipexole	2.4667	1.963–2.713	1,883	2,644
Mean daily dosage of experimental levodopa	427	409–445	2,402	2,387
Mean daily dosage of supplemental levodopa	274	202–346	2,424	2,365
Mean daily dosage of experimental pramipexole	2.78	2.60–2.96	2,233	2,555
Mean daily dosage of supplemental levodopa	434	353–515	2,361	2,427

The unit cost of pramipexole had the most impact on the ICER and resulted in the widest range of all the incremental cost estimates (£1,883 to £2,644). The mean daily dosage of experimental levodopa had the least impact on incremental cost.

Discussion

The baseline estimates result in an incremental cost (IC) of £2,394 for pramipexole treatment over a 1-year period.

All baseline values were assessed within ranges of uncertainty. The unit cost of pramipexole had the most impact on the IC and resulted in the widest range of all the IC estimates (£1,883 to £2,644). All other variables resulted in a range of incremental costs with an approximate difference of £322 or less between the upper and lower estimates.

This study assumed all other costs, such as acute hospitalisations etc (see 'Costs' under 'Data Sources and assumptions' in this appendix), were similar between the pramipexole and levodopa groups based on the results of an American 4-year study.[169] Evidence of this in the UK setting awaits further research. The study also assumed the quality of life measures are sufficiently sensitive to reflect benefit differences between the alternatives. This study compared initial dopamine agonist therapy with levodopa therapy; however, combination therapy was not included as an alternative.

The model was developed from one RCT based on pramipexole on the basis of available evidence. Other dopamine agonists are currently available and may or may not have similar incremental costs. This is an important consideration as the unit cost of pramipexole had the most impact on the incremental cost.

Conclusion

The baseline estimates result in an incremental cost of £2,394 for pramipexole treatment over a 1-year period. The unit cost of pramipexole had the most impact on the IC and resulted in the widest range of all the IC estimates (£1,883 to £2,644). On the basis of equivalent quality of life between the treatments, the levodopa strategy is the less costly option. The analysis is specific to pramipexole and does not consider the broader range of dopamine agonists available. This model is a simplified version of the costs and benefits of dopamine agonist versus levodopa therapy and a variety of assumptions have been used in the baseline analysis. Therefore, the results should be interpreted with caution.

Appendix F: Economic modelling – surgery

Background

Bilateral subthalamic stimulation has become established for the management of moderate to severe motor complications in the later stages of PD that are unresponsive to changes in medical therapy.

A literature review was performed and four economic studies met quality criteria.[266–269] The economic results are presented along with the clinical evidence of deep brain stimulation.

Whilst conclusive evidence on the cost effectiveness of this procedure awaits the results of ongoing large pragmatic trials in the UK (PD SURG) and US, the GDG considered the topic valuable for further consideration in this guideline.

Aim

The aim of the model was to compare the additional cost of bilateral deep brain stimulation of the subthalamic nucleus (DBS-STN) therapy to the benefits in quality of life gained by this procedure. Treatment option 1 is the intervention: DBS-STN and post-operative care over a 5-year period. Treatment option 2 is standard therapy over a 5-year period. The cost per quality-adjusted life year (QALY) gained was calculated.

Methods

A cost-effectiveness model was constructed from the perspective of the NHS. The effectiveness outcome measure used was quality-adjusted life years (QALYs) and the cost per QALY was calculated. The data sources of the costs and benefits are described in further detail in Tables F1–F4. Costs and benefits were discounted at 3.5% in accordance with current NICE recommendations. A one-way sensitivity analysis was run to assess the impact of variables on the incremental cost-effectiveness ratio (ICER).

$$\text{Incremental cost per QALY} = (C_1 - C_2)/(Q_1 - Q_2)$$

Where:

C_1 = Estimated cost of DBS-STN procedure and post-operative care
C_2 = Estimated cost of standard care
Q_1 = Estimated quality-adjusted life years after DBS-STN
Q_2 = Estimated quality-adjusted life years with no DBS-STN.

Data sources and assumptions

Tables F1–F4 list the baseline cost and effectiveness outcomes along with the sources of data. Assumptions and methods of calculating estimates are described in further detail below.

Table F1 Costs of standard care of PD patients

Cost	Value (£ 1998)	Source
Annual cost of care per patient in Hoehn and Yahr stages III–IV	6,216	Ref 10
Total costs for 5-year period with 3.5% discount	28,066	Estimate

Table F2 Costs of DBS-STN procedure[416]

Item	Minimum (£)	Maximum (£)	Baseline (£)	Quantity
DBS-STN (including device)	12,740	14,450	13,595	1
Follow-up appointment	70	376	223	4
Annual follow-up appointment+	582	582	582	5
Inpatient follow-up for adjustment of stimulator including batteries+	3,000	6,000	4,500	5
Total procedure costs with 3.5% discount+	29,193	45,672	37,432	

+A 3.5% discount rate applies to these figures

Table F3 Costs of post-operative medication

Item	Value	Source
Annual post-operative drug costs per patient	£1,414	Ref 10
% of patients with no medication after DBS-STN	26.19%	Ref 276
Total costs for 5-year period assuming 26.19% with no medication after DBS-STN and 3.5% discount	£4,712	Estimate

Table F4 Benefits after DBS-STN with annual 3.5% discount rate

Year after DBS-STN	Per cent increase in quality of life from initial	Quality of life	Source
Initial	0	0.488	Ref 270
1st year	43	0.673	Ref 270
2nd year	43	0.651	Estimate
3rd year	43	0.629	Estimate
4th year	43	0.607	Estimate
5th year	43	0.587	Estimate
Total potential		3.147	
Total including 7% mortality rate		2.927	

Explanation of assumptions and data used

▷ Costs

Standard care

The annual cost of care per patient with Parkinson's disease in the UK without undergoing DBS-STN was derived from one UK study that estimated the annual cost of care in 1998. The study indicated that Hoehn and Yahr stage significantly influenced cost by stage ($p<0.001$). Therefore the annual NHS costs in Hoehn and Yahr stages III–IV were averaged to derive the annual standard cost of care of patients with moderate to severe motor complications in the later stages of PD.

To calculate the total cost of care per patient over a 5-year period, the annual cost of care per patient per year is considered stable for the 5-year period and was adjusted by a 3.5% discount rate.

DBS-STN procedure

The cost of the DBS-STN procedure per patient was estimated from cost data obtained from 7 of the 17 centres in the UK offering DBS-STN at the time of the study.[416] Costs of annual follow-up appointment and inpatient follow-up for adjustment of stimulator including batteries after year 1 were discounted at an annual rate of 3.5%. This resulted in a figure similar but conservatively higher (£37,432 (1998) vs £32,526 (2002)) than an estimate in a study assessing the total health service costs of deep brain stimulation of the subthalamic nucleus, including pre-operative assessment, surgery and post-operative management over a 5-year period based on one centre in the UK.[268]

Post-operative medication

The annual post-operative drug costs were derived from the same study used to estimate the cost of standard care.[10] In the study, drug costs were lower in older age groups. The highest drug cost per patient per year in the under 65-year-old age group was used as a conservative estimate in favour of standard care.

The study that estimated the 5-year follow-up of DBS-STN found 11 of the 42 patients no longer required levodopa.[276] Therefore 26.19% (11/42) was used as the baseline value for the percentage of patients no longer requiring medication.

To calculate the cost of post-operative medication per patient over a 5-year period, the annual cost of care per patient per year is considered stable for the 5-year period and was adjusted by a 3.5% discount rate. 26.19% of this cost was subtracted from the result to give the total cost of post-operative medication over the 5-year period.

Total DBS-STN costs

The total cost of the DBS-STN was the sum of the DBS-STN procedure and post-operative medication costs over the 5-year period.

Additional costs of DBS-STN

The additional cost of DBS-STN therapy over a 5-year period was calculated by subtracting the cost of standard care from the cost of DBS-STN therapy.

▷ Quality-adjusted life-years

Standard care

As a conservative estimate in favour of standard care, the study assumed there is no change in quality of life from the initial value over the 5-year period. Quality-adjusted life-years (QALYs) were discounted at 3.5%.

DBS-STN therapy

The initial quality of life and the quality of life 12 months after DBS-STN was derived from one study assessing the quality of life of 60 patients before DBS-STN surgery and 12 months after using a disease-specific quality of life instrument, the PD Quality of Life (PDQL) scale.

There are limited data on the quality of life after DBS-STN beyond the first 12 months and very limited data for converting quality of life outcomes of Parkinson's disease health states, such as UPDRS, into quality-adjusted life-years. Therefore, as UPDRS III has been found to correlate with improvements in QOL,[270] for years 2 through 5, it was assumed that per cent changes in UPDRS III scores correspond with improvements in quality of life. The QoL study found UPDRS III (motor functions) improved by 55% and UPDRS II (activities of daily living) improved by 45% after 12 months. A second study found UPDRS III improved by 54% and UPDRS II improved by 49% after 5 years.[276] Therefore, it was assumed that the quality of life improvements found after 12 months would also remain improved at its 43% increase from baseline after 5 years.

In the UPDRS study[276] over a 5-year follow-up, there was a 7% (3, N=42) rate of mortality, 5% rate of dementia (2, N=42), 19% with eye-lid opening apraxia (8, N=42) and other side effects. To include the 7% mortality, only 93% of the total possible QALY gain was included. The other side effects were assumed to be captured in the quality of life assessment. Total QALY gain in each year was added with a 3.5% annual discount rate.

▷ Results

Table F5 DBS-STN therapy

Cost	£42,144
QALY	3.147
QALY including 7% mortality	2.927

Table F6 Standard therapy	
Cost	£28,066
QALY	2.203

Table F7 Incremental results of baseline values	
Incremental cost	£14,079
Incremental QALY	0.944
Incremental QALY including 7% mortality	0.723
Incremental cost-effectiveness ratio (ICER)	£14,900 per QALY
ICER including 7% mortality	£19,500 per QALY

Note: Differences due to rounding.

Under the base-case analysis including 7% mortality, the additional cost is £19,500 per QALY gained.

Sensitivity analysis

The estimates used in the model are subject to uncertainty. Therefore, a one-way sensitivity analysis was carried out to assess the impact of key variables used in the model. A one-way sensitivity analysis varies one parameter while maintaining the other parameters at baseline values. The variables included are:

(1) cost of DBS-STN (including device)
(2) cost of follow-up appointment
(3) cost of inpatient follow-up for adjustment of stimulator including batteries
(4) total costs of DBS-STN procedure with 3.5% discount
(5) drug costs after DBS-STN
(6) total costs of standard care
(7) total QALY gains in standard care
(8) total QALY gains in DBS-STN therapy.

Results for the upper and lower estimates are given in Table F8. The ranges of DBS-STN procedure component costs were derived from the minimum and maximum values given in the cost data literature. The range of the total costs of standard care were estimated from $\pm$ two standard errors (867) from the standard deviation (6,235) and sample size of 207 of the annual cost of care. The range of the total DBS-STN procedure cost was estimated as half (× 0.5) and twice (× 2.0) the value. The range of the QALY gains were estimated as $\pm$ two standard errors (0.04), from a standard deviation of 0.16 of the per cent increase in quality of life and sample size of 60.

Table F8 One-way sensitivity analysis

Variable	Baseline value	Range evaluated	ICER lower range estimate	ICER higher range estimate	ICER lower range estimate and 7% mortality	ICER upper range estimate and 7% mortality
Cost of DBS-STN (including device)	13,595	12,740–14,450	14,014	15,826	18,282	20,646
Cost of follow-up appointment	223	70–376	14,271	15,568	18,618	20,310
Cost of inpatient follow-up for adjustment of stimulator including batteries	4,500	3,000–6,000	7,743	22,097	10,101	28,826
Total DBS-STN procedure costs with 3.5% discount	37,432	18,716–74,865	6,188	23,652	8,073	30,854
Drug costs after DBS-STN	4,712	3,192–6,384	13,309	16,692	17,362	21,775
% of patients after DBS-STN with no medication	26.19%	50%–0%				
Total costs of standard care	28,066	24,152–31,979	19,067	10,773	24,874	14,054
Annual cost of standard care	6,216	5,349–7,083				
Total QALY gains in standard care	2.203	2.023–2.384	12,523	18,451	15,575	25,940
Total QALY gains in DBS-STN therapy	3.147	2.966–3.328	18,451	12,523		
Total QALY gains in DBS-STN therapy with 7% mortality	2.927	2.759–3.095			25,350	15,796

The total DBS-STN procedure costs with 3.5% discount had the most impact on the ICER and resulted in the widest range of all the ICER estimates (£8,073 to £30,854 per QALY). The cost of DBS-STN (including device) and cost of follow-up appointment had the least impact on the ICER.

Discussion

When possible, the model used conservative estimates that favoured standard care. With these estimates, the ICER value of £19,500 per QALY falls within an accepted range of cost effectiveness. This result is lower than the cost per QALY estimated in the American study –

$49,194 (US$ 2000) per QALY[267] – attributable to methodological and pricing differences between the countries.

Due to the assumptions of UPDRS III and quality of life and the exclusion of side-effects and mortality, the estimate of the QALY gains are associated with the most uncertainty. Nevertheless, the high and low estimates in the sensitivity impact on the ICER resulted in a range of £15,575 to £25,940 per QALY varying QALYs in standard care and £15,796 to £25,350 per QALY varying QALYs after DBS-STN, still falling within a normally accepted range. Even if the improvement in QALY is less than the observed improvement in UPDRS III used to estimate the QALY gain, with the baseline incremental cost of approximately £14,079, only an increase in 0.4693 (achieved by year 3 in baseline analysis) or greater from DBS-STN over a 5-year period would be required to achieve a cost per QALY of £30,000 or less. Doubling the incremental cost of DBS-STN (£28,158) would require an increase in only 0.9386 (achieved by year 5 in baseline analysis) in quality of life or greater to achieve a cost per QALY of £30,000 or less. Therefore, unless the actual total net QALY gain over a 5-year period is less than 0.4693, DBS-STN is still arguably likely to be cost effective.

The benefits in this model are assessed only for a 5-year period. This means that any benefits from DBS-STN accrued after 5 years are not accounted for in the model. This makes each benefit in the 5-year period cost more than it would over time, assuming further benefits after 5 years. Therefore, cost effectiveness may improve over greater lengths of time, but with only small improvements in the ICER. Additionally, the benefits over time are limited by increases in costs of care after DBS-STN as PD progresses and by mortality.

The sensitivity analysis indicates the higher the costs of care of standard therapy, the more favourable the ICER. This may indicate that using DBS-STN in patients with higher costs of care, potentially those with greater severity of PD, is more cost effective, but only if the QALY gains remain the same. Since the higher cost patients may or may not gain on average the same benefits, the sensitivity analysis results do not help to identify those patients better suited to DBS-STN therapy. The lower the cost of the DBS-STN procedure, the more favourable the ICER. This suggests that ICER values will improve if the technology becomes available at lower costs in the future.

Conclusion

Bilateral deep brain stimulation of the subthalamic nucleus is a clinical alternative to standard care for the management of moderate to severe motor complications in the later stages of PD that are unresponsive to changes in medical therapy. Costs and benefits of DBS-STN accrued over greater lengths of time (5 years) in comparison to standard care indicate the potential for cost-effective use of the technology in particular individuals with the clinical potential to benefit from the procedure. The estimate suggests DBS-STN therapy costs approximately £19,500 per QALY over a 5-year period in comparison to standard PD care in the UK (£ 1998). The results are relatively robust based on one-way sensitivity analysis. This model is a simplified version of the costs and benefits of DBS-STN therapy versus standard care and a variety of assumptions have been used in the baseline analysis. Therefore, the results should be interpreted with caution.

Appendix G: Economic modelling for Parkinson's disease nurse specialist care

Background

The Parkinson's Disease Society is encouraging the development of Parkinson's disease nurse specialists (PDNS) across the UK. There are in the region of 180 nurses already in post with plans to increase this to 240 over the next few years (GDG).

A literature search was performed to identify economic evaluations of PDNS care. One study met quality criteria[362] and is presented along with the clinical evidence of Parkinson's disease nurse specialist intervention.

In practice there may be interactions between PDNS care and standard care, which makes it difficult to separate the costs and benefits discretely between the interventions. The GDG considered monitoring medications, as opposed to diagnosing, which is an appropriate example of where PDNS care may substitute standard care with equivalent outcomes. Therefore, the GDG felt it was of value to investigate in this guideline the cost implications of PDNS care based on equivalent effectiveness of completely substituted activities.

Aim

The aim was to estimate the costs and costs saved with equivalently effective and completely substituted PDNS care in comparison to standard care over a 1-year period from the NHS perspective. The additional costs of PDNS care and the cost savings per home visit, per clinic consultation and per hospital-based visit were calculated.

Methods

The annual cost per PDNS was estimated using the sum of the annual salary and training costs discounted at 3.5%. Additional costs of PDNS care were estimated using the unit costs of other professionals' time used in discussing patient care.

Cost savings were estimated from the perspective of the NHS. Estimates were derived from unit costs and discounted at 3.5% (Table G1). Savings were calculated for PDNS care by (a) home visit (b) clinic consultation and (c) hospital-based visit. To calculate savings per intervention, the unit costs of standard care were used to estimate the resources saved by PDNS care.

The net cost of PDNS care over 1 year was calculated as the sum of the annual salary, training costs and additional costs of PDNS care minus the cost savings.

Data sources

Table G1 Unit costs derived from *Unit costs of health and social care 2004*[418]

Intervention	Unit cost (£ 2004)
GP home visit lasting 13.2 minutes (plus 12 minutes travel time)	65
District nurse home visit (A–F)	20
GP clinic consultation lasting 12.6 minutes	28
Nurse practitioner in primary care surgery consultation	14
Hospital-based consultant: per patient-related hour (A–F)	114
Hospital-based staff nurse, 24-hour ward per hour of patient contact	41
Expected annual cost of training at 3.5% discount rate (district nurse)	5,149
Salary per year of district nurse	25,362
Additional cost per visit to GP by PDNS to discuss patient care	28
Additional cost per visit to carer to discuss patient care	0
Additional cost per visit to consultant to discuss patient care	38

A–F: See Ref 418 for definition.

Table G2 Nurse activity – assessing patients[362]

	Average number or per cent of patients assessed
Per week	13.7
At home	75%
At GP	14%
At hospital consultant clinics	11%

Table G3 Nurse activity – discussing patients[362]

	Number of visits per week
To GPs	5
To carers	2
To consultants	1

Assumptions

The main assumptions to this costing approach are as follows:

- PDNS care substitutes for standard care for ongoing monitoring of treatment at equivalent effectiveness.
- Nurse activity reflects substituted activities.
- PDNS care is provided at the unit costs and includes the costs for consultant time spent discussing patient care.
- Consultant time is costed per 20-minute visit.

- Healthcare resources for patients by PDNS, such as medication, are similar to standard care.[362]
- Administration activities are included in salary.
- Cost of visit to GP to discuss patient care = cost of nurse time included in salary + cost of GP time = £28.
- Cost of visit to carer to discuss patient care = cost of nurse time included in salary = £0.
- Cost of 20-minute visit to consultant to discuss patient care = cost of nurse time included salary + cost of consultant time = £38.

The results from a randomised control trial suggest PDNS care maintains clinical effectiveness and improves patients' sense of well-being.[362] This supports the assumption that PDNS care has at least equivalent effectiveness to consultant care.

It is not always clear whether PDNS care is substituting some or all of the consultant care or is serving as additional care.[364] In this analysis, consultant care is face-to-face contact with a consultant for PD care needs by a patient. Therefore, the cost-saving estimates pertain only to situations where care is a substitution, such as monitoring medications, and not where the care may be additional to standard care or duplicating standard care.

Results

Table G4 Net cost of PDNS over 1-year period with 3.5% discount rate

Item	Costs (£ 2004)
Cost of training per year	+5,149
Cost of salary per year	+24,504
Additional costs of other health professionals' time discussing patients in one year	+8,974
Cost savings of other health professionals' costs from assessing patients in one year	–39,264
Net cost of PDNS care over one year	–637

Table G5 Additional costs of nurse activity – discussing patient care

	Number of visits per year to discuss patient care[+]	Costs per year (£ 2004)
To GPs	261	7,305
To carers	104	0
To consultants	52	1,983
Total costs		9,288
Total costs at 3.5% discount rate		8,974

[+]Estimated from Table G3 with 1 year = 52.2 weeks.

Table G6 Cost savings of PDNS care when substituting standard care

	Average number of patients assessed[+]	Costs per year (£ 2004)
Per year	714	
At home	536	34,848
At GP	100	2,802
At hospital consultant clinics	79	2,988
Total		40,638
Total costs at 3.5% discount rate		39,264

[+]Estimated from Table G2.

Sensitivity analysis

The estimates used in the model are subject to uncertainty. Therefore, a one-way sensitivity analysis was carried out to assess the impact of key variables used by the model. A one-way sensitivity analysis varies one parameter while maintaining the other parameters at baseline values. The variables included are: (a) cost of training per year, (b) cost of salary per year, (c) additional costs of other health professionals' time discussing patients in one year, and (d) cost savings of other health professionals' costs from assessing patients in one year. Plus or minus 10% was used as an estimate of the variability of the parameters.

Table G7 One-way sensitivity analysis

Variable	Baseline value (£)	Range evaluated	ICER lower range estimate	ICER higher range estimate
Cost of training per year	5,149	4,634–5,664	–1,152	–123
Cost of salary per year	24,504	22,054–26,955	–3,087	+1,813
Additional costs of other health professionals' time discussing patients in one year	8,974	8,076–9,871	–1,535	+260
Cost savings of other health professionals' costs from assessing patients in one year	39,264	35,338–43,190	+3,289	–4,564

– = cost savings
+ = additional cost.

The cost savings of other health professionals' costs had the most impact on the ICER, ranging from an additional cost of £3,289 to cost savings of £4,564. Increasing and decreasing the cost of PDNS training by 10% resulted in cost savings of PDNS. However, by altering the other three parameters, costs range from cost savings to additional costs implying the model is not robust to changes in the assumptions.

Discussion

Based on the average nurse activity in the randomised controlled trial in the UK (Tables G2 and G3),[362] for one year of one PDNS, approximately £640 is saved. Cost savings appear when PDNS care is substituting for standard care. However, in practice there may be variability in the interactions between types of care. There may be substituted care, additional care, duplication of care or a combination of these.[364] Nevertheless, the more PDNS care substitutes for standard care in a practice, the greater the potential for the outcomes to approach these average cost savings. How much PDNS care substitutes, duplicates or increases benefit for the same cost in comparison to standard care is not known. As the sensitivity analysis indicates, the cost savings from other health professionals' costs had the most impact on the ICER ranging from cost savings of £4,564 to an additional cost of £3,289. The costing of other health professionals reflects the average activity of PDNS. Therefore, how much PDNS care is substituting standard care at equivalent effectiveness needs to be assessed in further studies to improve cost estimates.

Only unit costs were used to assess the benefit of PDNS care versus standard care in terms of cost savings. However, unit costs may not fully represent all costs and benefits. This may have under-estimated the benefit of PDNS care. There may be increased patient benefits gained from a greater responsiveness of PDNS care to emerging scientific evidence, such as the earlier reduction in selegiline use found in nurses versus doctors[362] or improved access to care. There may be an improved sense of patient well-being while maintaining clinical effectiveness.[417] There also may be interactions of care as an additional benefit to PDNS care working in standard care that has not been measured. Currently, however, there is insufficient evidence available to measure such benefits.

On the other hand, the unit costs may underestimate the costs of PDNS care. The resources used in PDNS care are assumed to be equivalent to those used in standard care. However, PDNS care may use more or less or higher or lower cost resources resulting in higher or lower costs that are not reflected in the estimate. The RCT is the only study that gives an indication of the cost components in PDNS care versus standard care[362] and suggests that these are similar between the groups. However, apomorphine was excluded from the total cost of healthcare. Therefore, further evidence on the costs of resources used is needed to inform cost-effectiveness analyses.

The initial cost of establishing PDNS care will be incurred by the NHS. Therefore it would be helpful to evaluate whether initial costs can be recovered over time to warrant the initial investment. However, this is also contingent on the resource implications of the care. This cost-savings estimate is based on one PDNS with average nurse activity. While activity with less substitution of standard care or higher resources used would reasonably decrease the cost savings and potentially result in a net cost, it has not been determined how having more than one PDNS would affect costs and cost savings. The net estimate should not be interpreted as the complete indication of the benefit of PDNS care, nor do the estimates provide an indication of

the appropriate amount of PDNS care that should be available. Instead, the net estimates suggest on average the cost savings of one PDNS based on average nurse activity.

A sensitivity analysis was performed to investigate changes to the cost inputs used in this analysis on the net cost. Increasing and decreasing the cost of PDNS training by 10% was the only parameter that maintained cost savings of PDNS. Increasing the cost of salary per year and the additional costs of other health professionals' time discussing patients and reducing the cost savings of other health professionals' costs from assessing patients by 10% resulted in additional costs. This suggests that further data are needed to assess the cost effectiveness of PDNS. The baseline analysis pertains to average PDNS care across the UK; however, this does not limit the applicability of the methods to individual centres to assess differences in both costs and cost-savings estimates.

The incremental costs compared with the incremental benefits was not estimated due to the difficulty in separating PDNS care from standard care and the limited evidence on measurable benefits. One study estimated PDNS care costs of £200 per patient per year.[362] However, it is likely this value depends on the total number of patients, PDNSs and nurse activity. Furthermore, PDNS care versus standard care and nurse activity may not be consistent between services. Therefore, cost-effectiveness results may not be generalisable. Due to the difficulty in disentangling PDNS care and consultant care in different practices and the limited measurable benefits, a more general net cost approach, based on completely substituted care with equivalent effectiveness and average nurse activity, was performed.

Conclusion

Increasing the cost of salary per year and the additional costs of other health professionals' time discussing patients and reducing the cost savings of other health professionals' costs from assessing patients by 10% resulted in additional costs. Therefore, the cost effectiveness of PDNS care requires further evidence. This highlights the need for further studies to measure the benefits of PDNS care to adequately assess the cost effectiveness. Due to the interactions of care and data limitations, benefits have been simplified in the form of cost savings from standard unit costs. The cost-saving estimates are subject to the assumptions and therefore the results should be interpreted correspondingly.

Appendix H: Glossary

H.1 Guide to assessment scales

Activities of daily living (ADL)	Measures the impact of PD on 14 categories; each category is scored on a 0–4 scale, with higher scores reflecting greater disability and the need for assistance. The overall score ranges from 0 to 56.
Alzheimer's disease assessment scale – cognitive subscore (ADAS-cog)	A test for measuring cognitive function in people suffering from dementia. The scale can range from 0 to 70, with higher scores indicating more severe impairment and lower scores indicating improvement.
Alzheimer's disease cooperative study – activities of daily living (ADCS-ADL)	A test for measuring quality of life in people suffering from dementia. Scores range from 0 to 78, with higher scores indicating better function.
Alzheimer's disease cooperative study – clinician's global impression of change (ADCS-CGIC)	A test for assessing a change in condition (ie improvement, worsening or no change) of a person suffering from dementia as judged by the clinician. Scores can range from 1 to 7, with a score of 1 indicating marked improvement to a score of 7 indicating marked worsening.
Attitudes to self scale	Measures 'feelings and attitudes towards our bodies/selves'. Consisted of 15 semantic paired opposites (eg tense/relaxed). Positive score was 0 and negative score was 6 (range of total scores 0–90).
Barthel index	Measures the impact of PD on 10 categories of 'activities of daily living'. The range of scores is 0–100 with higher scores indicating better functionality.
Beck depression inventory (BDI)	A test used to measure manifestations and severity of depression. The BDI is a 21-item self-rating scale depression. Each item comprises 4 statements (rated 0–4) describing increasing severity of the abnormality concerned.
Brief psychiatric rating scale (BPRS)	An 18-item scale measuring psychiatric symptoms. Some items can be rated simply on observation; other items involve an element of self-reporting. There are 24 symptom constructs; each rated on a 7-point scale of severity ranging from 'not present' (1) to 'extremely severe' (7).
Clinical global impression (CGI) scale	A participant's illness is compared with change over time, and rated on a scale of very much improved to very much worse. A three-item scale (severity of illness; global improvement; and efficacy index) is used to assess treatment response in participants.

Core assessment program for intracerebral transplantations (CAPIT) dyskinesia rating scale	A pre-operative neurological evaluation. People are evaluated in the 'on' and 'off' phases according to CAPIT protocol. The protocol incorporates UPDRS, a dyskinesia rating scale and timed motor tests to demonstrate efficacy of surgical interventions.
Delis-Kaplan executive function system (D-KEFS) verbal fluency test	Assesses key areas of cognitive function (problem solving, thinking flexibility, fluency, planning, deductive reasoning) in both spatial awareness and verbal communication. Higher scores indicate better performance.
Dementia rating scale (DRS) total score	A test to assess cognitive function in older adults with neurological impairment. The test provides a measurement of attention, initiation, construction, conceptualization, and memory.
Epworth sleepiness scale (ESS)	A subjective scale in which participants rate the likelihood that they will fall asleep or doze in daily sedentary settings (eg watching TV). Each question receives a score of 0 to 3, making the maximum score 24.
EuroQol EQ-5D (VAS)	A questionnaire that provides a simple descriptive profile and a single index value for health status. The questionnaire also includes a visual analogue scale (VAS) to allow the patient to indicate their general health status. On this scale, choosing 100 indicates the best possible health status.
Frenchay dysarthria assessment	A tool developed to diagnose dysarthria by quantitatively evaluating speech across a range of parameters including orofacial muscle movements and a measurement of intelligibility.
Hamilton Rating Scale for Depression (HRSD/HAM-D)	A 17–21 item observer-rated scale to assess the presence and severity of depressive states. A score of 11 is generally regarded as indicative of a diagnosis of depression.
Hoehn and Yahr staging	To establish the severity of PD, stages of disease are classified from I to V where: • I indicates unilateral disease • II indicates bilateral without postural instability • III indicates postural instability • IV indicates considerable disability but ability to walk independently • V indicates wheelchair-bound or walking only with assistance.
Health related quality of life (HRQL)	A combination of a person's physical, mental and social well-being; not merely the absence of disease.

Maintenance of wakefulness test (MWT)	An evaluation of the person's ability to maintain wakefulness for 20-minute periods in a quiet, darkened room with the participant in a reclined position. This test evaluates the person's degree of alertness and his/her tendency to fall asleep at inappropriate times.
Mini-mental state examination (MMSE)	Assessment scale of global cognitive function, with scores ranging from 0 to 30. Higher scores indicate better mental function; <23 is usually indicative of cognitive impairment.
Modified Columbia rating scale (MCRS)	22-item scale (maximum possible score 240) that evaluates parkinsonian and dyskinesia severity, where global disability is rated as 0 (absent) to 4 (severe).
Modified Hoehn and Yahr scale	A modified eight-point version of the original scale.
Montgomery-Asberg depression rating scale	A depression rating scale used to monitor a participant's depressive state over time. Scores range from 0 to 60, with higher scores indicating a greater degree of depression.
Neuropsychiatric inventory 10-item (NPI-10)	A test that evaluates dementia-related behaviours. Scores range from 1 to120, with higher scores indicating more severe or more frequent behavioural problems.
New York University Parkinson's disease scale (NYUPDS)	Determines clinical efficacy by rating participants on 5 symptoms using a 5-point scale ranging from 0 (normal functioning) to 4 (marked impairment).
Northwestern University disability scale (NUDS)	Assessed impairments in activities of daily living on 6 categories, with a scale ranging from 0 (normal functioning) to 10 (marked disability).
Nottingham Health Profile	Generic health-related quality of life measure. The instrument is used to evaluate perceived distress across various populations. There are 38 items with 6 domains. Scores range from 0 to100 where higher scores indicate a greater health problem.
Parkinson's Disease Quality of Life Questionnaire (PDQL)	A questionnaire comprising 37 items addressing four health domains (parkinsonian symptoms, systemic symptoms, social function, and emotional function).
Parkinson's Disease Quality of Life Questionnaire (PDQUALIF)	A questionnaire consisting of 32 questions addressing seven health domains (eg social role, self-image/ sexuality, sleep). The total score ranges from 0 to 128, with lower scores signifying better quality of life.
Parkinson's Disease Questionnaire 39 (PDQ 39)	A self-administered questionnaire, which comprises 39 items addressing eight domains of health, which participants consider to be adversely affected by the disease. Scores range from 0 to 100, where lower scores indicate a better-perceived health status. The results are presented as eight discrete domain scores and not as a total score.

Patient's Global Impression (PGI) scale	A participant rates the change in their illness over time on a scale of '1' very much improved to '7' very much worse.
Positive and Negative Symptoms Scale (PANSS)	A psychotic rating scale of 30 items, each assessed on a seven-point scale from absent to extreme. It is divided into sub-scales covering both positive (PANSS-P) and negative symptoms (N).
Scale for the Assessment of Positive Symptoms (SAPS)	Assesses the severity of psychotic symptoms.
Schwab and England scale ADL (SEADL)	The scale reflects the participant's ability to perform daily activities in terms of speed and independence, and is comprised of 20 points.
Self-assessment Parkinson's Disease Disability Scale (SPDDS)	Participants rate how easy or difficult it was to perform 25 separate actions at their best and at their worst times on a 5-point scale (range of total scores 25 to 125). Higher scores indicate increased difficulty.
Short Form 36 (SF 36)	The SF-36 assesses functioning and well-being in any participant group with chronic disease. Thirty-six items in eight domains are included, which cover functional status, well-being, and overall evaluation of health. Scored range from 0 to 100, where a higher score indicates a better-perceived health status.
Sickness Impact Profile (SIP)	SIP is a general quality of life scale. It consists of 136 items, which measure 12 distinct domains of quality of life. Participants identify those statements, which describe their experience. Higher scores represent greater dysfunction.
Ten-point Clock Drawing Test	A test in which the participant is asked to draw a clock face marking the hours and then draw the hands to indicate a particular time.
Timed-tapping scores	The number of times the participant hits with a finger two spots some 40 cm apart in a 20-second interval.
Trail Making Test	The test consists of two parts. In Part A participants connect, in order, numbers 1–25 in as little time as possible. Part B requires the participant to connect numbers and letters in an alternating pattern (ie 1–A–2–B) in as little time as possible.
Unified Parkinson's Disease Rating Scale (UPDRS)	A scale used to measure severity of Parkinson's disease. It has six parts, and a higher score denotes greater disability.
UPDRS I	Mentation, behaviour, and mood (4 items).
UPDRS II	Activities of daily living (13 items).
UPDRS III	Motor examination (14 items).
UPDRS IV	Complications of treatment (11 items).

UPDRS Total score	Sum total of subscores.
UPDRS V	Modified Hoehn and Yahr staging (8 items).
UPDRS VI	Schwab and England activities of daily living score (20 items).
UPSIT	University of Pennsylvania Smell Identification Test. There are 40 microencapsulated scented pads in a booklet. Each individual scented pad is scratched with a pencil and sniffed one at a time. From a list of 4 choices for each pad, a correct answer must be chosen or a guess made.
Webster Rating Scale	Changes in the scale over time can reflect changes due to disease progression or therapeutic interventions. The scores range from 0 to 30; higher scores indicate greater disease severity.

H.2 Glossary of terms

Adverse events	A harmful, and usually relatively rare, event arising from treatment.
Akinesia	Absence or reduced functionality of movements.
Algorithm (in guidelines)	A flowchart of the clinical decision pathway described in the guideline.
Allied health professional (AHP)	Allied health professionals are involved in the delivery of health services pertaining to the identification, evaluation and prevention of diseases and disorders.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT, and potential bias that may result.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	The effect that the results of a study are not an accurate reflection of any trends in the wider population. This may result from flaws in the design of a study or in the analysis of results.
Blinding (masking)	A feature of study design to keep the participants, researchers and outcome assessors unaware of the interventions that have been allocated.
Bradykinesia	Slowness of movement.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition, such as a relative or spouse.
Clinical audit	A systematic process for setting and monitoring standards of clinical care.

Cochrane Review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration.
Cohort	A group of participants.
Confidence interval (CI)	A range of values, which contains the true value for the population with a stated 'confidence' (conventionally 95%).
Control	A person in the comparison group who receives a placebo, no intervention, usual care or another form of care.
Cost-effectiveness analysis (CEA)	An analytic tool in which costs and effects of a programme and at least one alternative are calculated and presented in a ratio of incremental cost to incremental effect. Effects are health outcomes, such as cases of a disease prevented, years of life gained, or quality-adjusted life-years, rather than monetary measures as in cost-benefit analysis.
Cost-minimisation analysis (CMA)	An analytic tool used to compare the net costs of programmes that achieve the same outcome.
Crossover trials	Type of trial comparing two or more interventions in which participants, upon completion of the course of one treatment, are switched to another.
DBS	Deep brain stimulation
Diagnostic study	Any research study aimed at evaluating the utility of a diagnostic procedure.
Differential diagnosis	An attempt to distinguish between two or more diseases with similar symptoms.
Direct costs	The value of all goods, services and other resources that are consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it.
Discount rate	The interest rate used to compute present value or the interest rate used in discounting future values.
Discounting	The process of converting future values and future health outcomes to their present value.
Disease-modifying therapy	Refers to any treatment that beneficially affects the underlying pathophysiology of PD (also known as 'neuroprotection').
Dysarthria	Slurred or otherwise impaired speech.
Dysarthria profile	A description of the dysarthric person's problems, to supply the speech therapist with indications of where to begin in treatment.

Dyskinesia	The impairment of the power of voluntary movement, resulting in fragmentary or incomplete movements.
Dysphagia	Difficulty in swallowing.
Dystonia	Disordered tonicity of muscle.
Evidence-based healthcare	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
Ergot	This is a fungus: *Claviceps purpurea*. Ergot derivatives are nowadays mostly used for their potential to enhance the neurotransmitter, dopamine.
Expert	A qualified medical specialist (see specialist).
False positive	A positive diagnostic test result in a person who does not possess the attribute for which the test is conducted.
FEES	Fibreoptic endoscopic examination of swallow safety.
Follow-up	An attempt to measure the outcomes of an intervention after the intervention has ended.
Generalisability	The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in the NHS in England and Wales.
Gold standard	See 'Reference standard'.
Good practice points	Recommended good practice based on the clinical experience of the Guideline Development Group.
Guideline development group (GDG)	An independent group set up by NICE to develop a guideline. They include healthcare professionals and patient/carer representatives.
Hazard ratio (HR)	A statistic to describe the relative risk of complications due to treatment, based on a comparison of event rates.
Heterogeneity	In systematic reviews, heterogeneity refers to variability or differences between studies in estimates of effect.
Homogeneity	In a systematic review, homogeneity means there are no or minor variations in the results between individual studies included in a systematic review.
Hypersomnolence	Excessive sleepiness.
Hypokinesia	Decreased muscular activity, bradykinesia, reduced or slowed movement.
Inclusion criteria	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental cost	The cost of one alternative less the cost of another.
Incremental cost effectiveness ratio (ICER)	The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.

Intention-to-treat analysis (ITT analysis)	An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.
LD	Levodopa.
Lee Silverman Voice Treatment (LSVT)	A treatment for voice and speech disorders associated with Parkinson's disease to improve loudness, voice quality, and articulation.
MAOB inhibitor	Monoamine oxidase type B inhibitor.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result.[1]
Mortality	The number of deaths in a given population and during a given time.
Motor fluctuations	Periods of the day with poor or absent motor response to medication alternating with periods of improved motor function.
MSA	Multiple system atrophy.
National Collaborating Centres (NCC)	Professionally led groups established by NICE to harness the expertise of the Royal Medical Colleges, specialist societies and person/carer organisations when developing clinical guidelines.
NCC-CC	National Collaborating Centre for Chronic Conditions.
Negative predictive value	The proportion of people with a negative test result who do not have the disease.
Neuroleptic malignant syndrome	A rare idiosyncratic reaction to neuroleptic medication. The syndrome is characterised by fever, muscular rigidity, altered mental status, and autonomic dysfunction.
NICE	National Institute for Health and Clinical Excellence.
NSF	National service framework.
Odds ratio (OR)	The odds of an event happening in the treatment group, divided by the odds of it happening in the control group.
Off time	The duration of time when anti-parkinsonian medication is not controlling the person's symptoms or is 'wearing-off'.
On time	The duration of time when anti-parkinsonian medication is controlling PD symptoms.

Open label trial design	A clinical trial in which the investigator and participant are aware which intervention is being used for which person. These trials may or may not be randomised.
p values	The probability that an observed difference could have occurred by chance. A p value of less than 0.05 is conventionally considered to be 'statistically significant'.
PD	Parkinson's disease.
PDNS	Parkinson's disease nurse specialist.
PDS	Parkinson's Disease Society.
Phenomenological study	A qualitative study design, the goal of which is to describe a 'lived experience'.
Placebo	An inactive and physically indistinguishable substitute for a medication or procedure, used as a comparator in controlled clinical trials.
Positive predictive value (PPV)	The proportion of people with a positive test result who actually have the disease.
Present value	The value which healthcare professionals and people with PD would attribute at present to an outcome (or avoidance of an outcome) in the future.
PSP	Progressive supranuclear palsy.
Quality of life	Refers to the patient's ability to enjoy normal life activities, sometimes used as an outcome measure in a clinical trial.
Quality-adjusted life-year (QALY)	A measure of health outcome which assigns to each period of time a weighting, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.
Randomisation	Allocation of participants in a study into two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
Reference standard (or gold standard)	The most specific and sensitive test to diagnose a disease or agreed desirable standard treatment and against which other tests or treatments can be compared. An ideal 'gold standard' test would have 100% sensitivity and specificity.

Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another.
Rigidity	Abnormal stiffness or inflexibility.
Sample size	The number of participants included in a trial or intervention group.
Sensitivity (of a test)	The proportion of people classified as positive by the gold standard who are correctly identified by the study test.
Sensitivity analysis	A measure of the extent to which small changes in parameters and variables affect a result calculated from them. In this guideline, sensitivity analysis is used in health economic modelling.
Sialorrhoea	Increased saliva or drooling.
Single blind study	A study where the investigator is aware of the treatment or intervention the participant is being given, but the participant is unaware.
Somnolence	Sleepiness or unnatural drowsiness.
Specialist	A clinician whose practice is limited to a particular branch of medicine or surgery, especially one who is certified by a higher medical educational organisation.
Specificity (of a test)	The proportion of people classified as negative by the gold standard who are correctly identified by the study test.
Stakeholder	Any national organisation, including patient and carers' groups, healthcare professionals and commercial companies with an interest in the guideline under development.
Statistical power	In clinical trials, the probability of correctly detecting an effect due to the intervention or treatment under consideration. Power is determined by the study design, and in particular, the sample size. Larger sample sizes increase the chance of small effects being detected correctly.
Statistical significance	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Stereotactic surgery	A precise method of locating deep brain structures by using three-dimensional coordinates. The surgical technique may either involve stimulation or lesioning of the located site.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and

	report their findings. It may or may not use statistical meta-analysis.
Time horizon	The period of time for which costs and effects are measured in a cost-effectiveness analysis.
Uptake	The absorption of a substance (often a radionucleotide such as Fluoro-dopa) into the brain tissue, which can then be visualised through imaging techniques.
Videofluoroscopy	Videofluoroscopy is a test for assessing the integrity of the oral and pharyngeal stages of the swallowing process. Involves videotaping fluoroscopic images as the patient swallows a bolus of barium.
Washout period	The stage in a crossover trial when one treatment is withdrawn before the second treatment is given.
Withdrawal	When a trial participant discontinues the assigned intervention before completion of the study.

Appendix I: List of registered stakeholders

Addenbrooke's NHS Trust
Age Concern Cymru
Age Concern England
Airedale General Hospital
Alliance Pharmaceuticals Ltd
Amersham Health
Anglesey Local Health Board
Ashfield and Mansfield District PCTs
Association for Continence Advice (ACA)
Association of British Health-Care Industries
Association of British Neurologists
Association of Professional Music Therapists
Association of the British Pharmaceuticals Industry (ABPI)
Barts and the London NHS Trust
Bayer PLC
Birmingham Clinical Trials Unit
Birmingham Heartlands & Solihull NHS Trust
Boehringer Ingelheim Ltd
Bolton, Salford & Trafford Mental Health
Bradford South & West Primary Care Trust
Brain and Spine Foundation
Bristol-Myers Squibb Pharmaceuticals Ltd
Britannia Pharmaceuticals Ltd
British Association for Counselling and Psychotherapy
British Association for Psychopharmacology
British Dietetic Association
British Geriatrics Society
British National Formulary (BNF)
British Neuropsychiatry Association
British Nuclear Medicine Society
British Psychological Society, The
British Society of Neuroradiologists
British Society of Rehabilitation Medicine
BUPA
Cephalon UK Ltd
Chartered Society of Physiotherapy
Cheltenham & Tewkesbury PCT
Cochrane Movement Disorders Group
College of Occupational Therapists
Community District Nurses Association
Community Psychiatric Nurses' Association
Continence Foundation
Co-operative Pharmacy Association
Cyberonics SA/NV
Department of Health
Derbyshire Mental Health Services NHS Trust
Dudley Beacon & Castle Primary Care Trust
Eisai Limited
Elan Pharmaceuticals Ltd
Eli Lilly and Company Ltd
Faculty of Public Health
Gateshead Health NHS Trust
GE Health Care
Gedling Primary Care Trust
GlaxoSmithKline UK
Greater Peterborough Primary Care Partnership-North PCT
Guys & St Thomas NHS Trust
Hammersmith Hospitals NHS Trust
Hampshire Partnership NHS Trust
Healthcare Commission
Help the Aged

Help the Hospices
Hereford Hospital NHS Trust
Herefordshire Primary Care Trust
Hertfordshire Partnership NHS Trust
Independent Healthcare Forum
Institute of Rehabilitation
Institute of Sport and Recreation Management
James Parkinson Centre
Kyowa Hakko UK Ltd
Long Term Medical Conditions Alliance
Lundbeck Limited
Mansfield District PCT
Medeus Pharma Limited
Medicines and Healthcare Products Regulatory Agency (MHRA)
Medtronic Limited
Merck Pharmaceuticals
Mid Staffordshire General Hospitals NHS Trust
National Council for Disabled People, Black, Minority and Ethnic community (Equalities)
National Mental Health Partnership
National Patient Safety Agency
National Public Health Service – Wales
National Schizophrenia Fellowship (Rethink)
National Tremor Foundation
Neurological Alliance
Newcastle, North Tyneside and Northumberland MH Trust
NHS Direct
NHS Health and Social Care Information Centre
NHS Modernisation Agency, The
NHS Quality Improvement Scotland
North Essex Mental Health Partnership Trust
North Staffordshire Combined Healthcare NHS Trust
Novartis Pharmaceuticals UK Ltd
Orion Pharma (UK) Ltd
Orphan Europe UK Ltd
Parkinson's Disease Nurse Specialist Association (PDNSA)
Parkinson's Disease Society
Pfizer Limited
Plymouth Primary Care Trust
Primary Care Neurology Society
Princess Alexandra Hospital NHS Trust
PromoCon (Disabled Living)
Relatives and Residents Association
Roche Products Limited
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners Wales
Royal College of Nursing (RCN)
Royal College of Physicians of London
Royal College of Psychiatrists
Royal College of Speech and Language Therapists
Royal Pharmaceutical Society of Great Britain
Sanofi-Synthelabo
Schwarz Pharma
Scottish Intercollegiate Guidelines Network (SIGN)
Selby & York PCT
Sheffield Teaching Hospitals NHS Trust
Sherwood Forest Hospitals NHS Trust
Social Care Institute for Excellence (SCIE)
Society of British Neurological Surgeons
Solvay Healthcare Limited
South Birmingham Primary Care Trust
Sue Ryder Care
Teva Pharmaceuticals Ltd
The Medway NHS Trust
The Progressive Supranuclear Palsy [PSP Europe] Association

The Royal Society of Medicine

The Royal West Sussex Trust

Trafford Primary Care Trusts

UK Clinical Pharmacy Association

University College London Hospitals NHS Trust

Valeant Pharmaceuticals

Walton Centre for Neurology and Neurosurgery NHS Trust

Welsh Assembly Government (formerly National Assembly for Wales)

West Cornwall PCT

Wirral Hospital NHS Trust

References

1 National Institute for Health and Clinical Excellence. *Guideline development methods: information for national collaborating centres and guideline developers.* London: National Institute for Health and Clinical Excellence, 2004. Ref ID: 20114

2 Parkinson's Disease Society. *Parkinson's disease: the personal view.* London: Parkinson's Disease Society, 1993. Ref ID: 19909

3 *Dateline* interview: Michael J Fox. New York: NBC News, 2003. Ref ID: 19911

4 Parkinson's Disease Society. *One in twenty: an information pack for younger people with Parkinson's.* London: Parkinson's Disease Society, 2002. Ref ID: 19910

5 Parkinson J. *Essay on the shaking palsy.* London: Sherwood, Neely, and Jones, 1817. Ref ID: 19927

6 Burch B, Sheerin F. Parkinson's disease. *Lancet.* 2005; 365:622-627. Ref ID: 19928

7 Goetz CG. Excerpts from nine case presentations on general neurology delivered at the Salpetriere Hospital in 1887-8. In: Charcot JM (ed), *The Tuesday lessons*, New York: Raven Press, 1987. Ref ID: 19929

8 Dodel RC, Eggert KM, Singer MS et al. Costs of drug treatment in Parkinson's disease. *Movement Disorders.* 1998; 13(2):249-254. Ref ID: 19653

9 Ben-Shlomo Y. The epidemiology of Parkinson's disease. In: Quinn NP (ed), *Parkinsonism.* London: Bailliere-Tindall, 1997: 55-68. Ref ID: 20125

10 Findley L, Aujla M, Bain PG et al. Direct economic impact of Parkinson's disease: A research survey in the United Kingdom. *Movement Disorders.* 2003; 18(10):1139–1145. Ref ID: 40

11 Dodel RC, Berger K, Oertel WH. Health-related quality of life and healthcare utilisation in patients with Parkinson's disease: impact of motor fluctuations and dyskinesias. *Pharmacoeconomics.* 2001; 19(10): 1013–1038. Ref ID: 19691

12 Wood BH, Bilclough JA, Walker RW. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. *Journal of Neurology, Neurosurgery & Psychiatry.* 2002; 72:721–725. Ref ID: 19857

13 National Institute for Health and Clinical Excellence. *Guideline development methods: an overview for stakeholders, the public and the NHS.* London: National Institute for Health and Clinical Excellence, 2004. Ref ID: 20115

14 Department of Health. *The national service framework for long-term (neurological) conditions.* London: HMSO, 2005. Ref ID: 19904

15 Department of Health. *The national service framework for older people.* London: HMSO, 2001. Ref ID: 19942

16 National Institute for Health and Clinical Excellence. *Falls: The assessment and prevention of falls in older people.* (Clinical Guideline 21). London: National Institute for Health and Clinical Excellence, 2004. Ref ID: 19925

17 National Institute for Health and Clinical Excellence and Social Care Institute for Excellence. *Dementia: management of dementia, including use of antipsychotic medication in older people (In progress).* London: National Institute for Health and Clinical Excellence, 2007. Ref ID: 19926

18 National Institute for Clinical Excellence. *Depression: management of depression in primary and secondary care.* (Clinical Guideline 23). London: National Institute for Clinical Excellence, 2004. Ref ID: 19852

19 National Institute for Clinical Excellence. *The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care.* (Clinical Guideline 20). London: National Institute for Clinical Excellence, 2004. Ref ID: 20031

20 National Institute for Clinical Excellence. *Guidance on the use of donepezil, rivastigmine and galantamine for the treatment of Alzheimer's disease.* (Technology Appraisal Guidance 19). London: National Institute for Clinical Excellence, 2001. Ref ID: 19943

21 National Institute for Clinical Excellence. *Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care.* (Clinical Guideline 22). London: National Institute for Clinical Excellence, 2004. Ref ID: 19941

22 National Institute for Clinical and Public Health Excellence. *Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition.* (Clinical Guideline 32). London: National Institute for Clinical and Public Health Excellence, 2006. Ref ID: 20124

23 National Institute for Clinical Excellence. *Deep brain stimulation for Parkinson's disease.* (IPG019). London: NICE, 2003. Ref ID: 95

24 National Collaborating Centre for Chronic Conditions. *Methodology pack.* London: NCC-CC, 2006. Available from: www.rcplondon.ac.uk/college/NCC-CC. Ref ID: 20117

25 Department of Health. *The expert patient: a new approach to chronic disease management for the 21st century.* London: Department of Health, 2001. Ref ID: 19595

26 Montgomery EB, Lieberman A, Singh G et al. Patient education and health promotion can be effective in Parkinson's disease: a randomized controlled trial. PROPATH Advisory Board. *American Journal of Medicine.* 1994; 97(5):429–435. Ref ID: 737

27 Mercer BS. A randomized study of the efficacy of the PROPATH program for patients with Parkinson disease. *Archives of Neurology.* 1996; 53:881–884. Ref ID: 739

28 Findley L, Eichhorn T, Janca A et al. Factors impacting on quality of life in Parkinson's disease: results from an international survey. *Movement Disorders.* 2002; 17(1):60–67. Ref ID: 742

29 Habermann B. Day-to-day demands of Parkinson's disease. *Western Journal of Nursing Research.* 1996; 18(4):397–413. Ref ID: 65

30 Pentland B, Pitkairn TK, Gray TK. The effects of reduced expression in Parkinson's disease in impression formation by health professionals. *Clinical Rehabilitation.* 1987; 1:307–313. Ref ID: 2766

31 Yarrow, S. *Survey of members of the Parkinson's Disease Society.* London: Parkinson's Disease Society of the United Kingdom and Policy Studies Institute, 1999. Ref ID: 786

32 Shimbo T, Goto M, Morimoto T et al. Association between patient education and health-related quality of life in patients with Parkinson's disease. *Quality of Life Research.* 2004; 13(1):81–89. Ref ID: 19841

33 Meadowcroft RS, Scott S, and Woodford C. *Communicating with people with Parkinson's and their carers.* London: Parkinson's Disease Society, 2005. Ref ID: 19903

34 Bennett DA, Beckett AM, Shannon KM et al. Prevalence of parkinsonian signs and associated mortality in a community population of older people. *New England Journal of Medicine.* 1996; 334(24):71–76. Ref ID: 2772

35 Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 1988; 51(6):745–752. Ref ID: 2773

36 Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in Parkinsonism - A prospective study. *Canadian Journal of Neurological Sciences.* 1991; 18(3):275–278. Ref ID: 111

37 Hughes AJ, Daniel SE, Kilford L et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery & Psychiatry.* 1992; 55(3): 181–184. Ref ID: 99

38 Hughes AJ, Daniel SE, Ben Shlomo Y et al. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain.* 2002; 125(Pt:4):4–70. Ref ID: 96

39 Schrag A, Ben Shlomo Y, Quinn N. How valid is the clinical diagnosis of Parkinson's disease in the community? *Journal of Neurology, Neurosurgery & Psychiatry.* 2002; 73(5):529–534. Ref ID: 142

40 Meara J, Bhowmick BK, Hobson P. Accuracy of diagnosis in patients with presumed Parkinson's disease. *Age & Ageing.* 1999; 28(2):99–102. Ref ID: 108

41 Jankovic J, Rajput AH, McDermott MP et al. The evolution of diagnosis in early Parkinson disease. *Archives of Neurology.* 2000; 57(3):369–372. Ref ID: 81

42 Lees AJ, Katzenschlager R, Head J et al. Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial. *Neurology.* 2001; 57(9):1687–1694. Ref ID: 2309

43 Benamer HT, Oertel WH, Patterson J et al. Prospective study of presynaptic dopaminergic imaging in patients with mild parkinsonism and tremor disorders: part 1. Baseline and 3-month observations. *Movement Disorders.* 2003; 18(9):977–984. Ref ID: 425

44 Popperl G, Radau P, Linke R et al. Diagnostic performance of a 3-D automated quantification method of dopamine D2 receptor SPECT studies in the differential diagnosis of parkinsonism. *Nuclear Medicine Communications.* 2005; 26(1):39–43. Ref ID: 19822

45 Benamer TS, Patterson J, Grosset DG et al. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group. *Movement Disorders.* 2000; 15(3):503–510. Ref ID: 484

46 Booij J, Speelman JD, Horstink MW et al. The clinical benefit of imaging striatal dopamine transporters with [123I]FP-CIT SPET in differentiating patients with presynaptic parkinsonism from those with other forms of parkinsonism. *European Journal of Nuclear Medicine.* 2001; 28(3):266–272. Ref ID: 467

47 Lokkegaard A, Werdelin LM, Friberg L. Clinical impact of diagnostic SPET investigations with a dopamine re-uptake ligand. *European Journal of Nuclear Medicine & Molecular Imaging.* 2002; 29(12):1623–1629. Ref ID: 439

48 Prunier C, Tranquart F, Cottier JP et al. Quantitative analysis of striatal dopamine D2 receptors with 123 I-iodolisuride SPECT in degenerative extrapyramidal diseases. *Nuclear Medicine Communications.* 2001; 22(11):1207–1214. Ref ID: 459

49 Parkinson Study Group. A multicenter assessment of dopamine transporter imaging with DOPASCAN/SPECT in parkinsonism. *Neurology.* 2000; 55(10):1540–1547. Ref ID: 475

50 Van Laere K, De Ceuninck L, Dom R et al. Dopamine transporter SPECT using fast kinetic ligands: 123I-FP- beta-CIT versus 99mTc-TRODAT-1. *European Journal of Nuclear Medicine & Molecular Imaging.* 2004; 31(8):1119–1127. Ref ID: 19824

51 Chou KL, Hurtig HI, Stern MB et al. Diagnostic accuracy of [99mTc]TRODAT-1 SPECT imaging in early Parkinson's disease. *Parkinsonism & Related Disorders.* 2004; 10(6):375–379. Ref ID: 19817

52 Asenbaum S, Pirker W, Angelberger P et al. [123I]beta-CIT and SPECT in essential tremor and Parkinson's disease. *Journal of Neural Transmission.* 1998; 105(10-12):1213–1228. Ref ID: 507

53 Acton PD, Mozley PD, Kung HF. Logistic discriminant parametric mapping: a novel method for the pixel-based differential diagnosis of Parkinson's disease. *European Journal of Nuclear Medicine.* 1999; 26(11): 1413–1423. Ref ID: 196

54 Varrone A, Marek KL, Jennings D et al. [123I]beta-CIT SPECT imaging demonstrates reduced density of striatal dopamine transporters in Parkinson's disease and multiple system atrophy. *Movement Disorders.* 2001; 16(6):1023–1032. Ref ID: 453

55 Huang WS, Lee MS, Lin JC et al. Usefulness of brain 99mTc-TRODAT-1 SPET for the evaluation of Parkinson's disease. *European Journal of Nuclear Medicine & Molecular Imaging.* 2004; 31(2):155–161. Ref ID: 19820

56 Catafau AM, Tolosa E, Laloux P et al. Impact of dopamine transporter SPECT using 123I-Ioflupane on diagnosis and management of patients with clinically uncertain parkinsonian syndromes. *Movement Disorders.* 2004; 19(10):1175–1182. Ref ID: 19823

57 Weng YH, Yen TC, Chen MC et al. Sensitivity and specificity of 99mTc-TRODAT-1 SPECT imaging in differentiating patients with idiopathic Parkinson's disease from healthy subjects. *Journal of Nuclear Medicine.* 2004; 45(3):393–401. Ref ID: 19821

58 Jennings DL, Seibyl JP, Oakes D et al. [123I]beta-CIT and single-photon emission computed tomographic imaging vs clinical evaluation in Parkinsonian syndrome: unmasking an early diagnosis. *Archives of Neurology.* 2004; 61(8):1224–1229. Ref ID: 19818

59 Dodel RC, Hoffken H, Moller JC et al. Dopamine transporter imaging and SPECT in diagnostic work-up of Parkinson's disease: a decision-analytic approach. *Movement Disorders.* 2003; 18(Suppl 7):S52–S62. Ref ID: 19666

60 Holloway R, Shoulson I, Kieburtz K et al. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. *Journal of the American Medical Association.* 2000; 284(15): 1931–1938. Ref ID: 1477

61 Whone AL, Watts RL, Stoessl AJ et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. *Annals of Neurology.* 2003; 54(1):93–101. Ref ID: 808

62 Fahn S, Oakes D, Shoulson I et al. Levodopa and the progression of Parkinson's disease. *New England Journal of Medicine.* 2004; 351(24):2498–2508. Ref ID: 19725

63 Burn DJ, Sawle GV, Brooks DJ. Differential diagnosis of Parkinson's disease, multiple system atrophy, and Steele-Richardson-Olszewski syndrome: discriminant analysis of striatal 18F-dopa PET data. *Journal of Neurology, Neurosurgery & Psychiatry.* 1994; 57(3):278–284. Ref ID: 329

64 Schocke MFH, Seppi K, Esterhammer R et al. Diffusion-weighted MRI differentiates the Parkinson variant of multiple system atrophy from PD. *Neurology.* 2002; 58(4):575–580. Ref ID: 130

65 Cercy SP, Bylsma FW. Lewy bodies and progressive dementia: A critical review and meta-analysis. *Journal of the International Neuropsychological Society.* 1997; 3(2):179–194. Ref ID: 29

66 Bhattacharya K, Saadia D, Eisenkraft B et al. Brain magnetic resonance imaging in multiple-system atrophy and Parkinson disease: A diagnostic algorithm. *Archives of Neurology.* 2002; 59(5):835-842. Ref ID: 13

67 Juh R, Kim J, Moon D et al. Different metabolic patterns analysis of Parkinsonism on the 18F-FDG PET. *European Journal of Radiology.* 2004; 51(3):223-233. Ref ID: 19839

68 Schreckenberger M, Hagele S, Siessmeier T et al. The dopamine D2 receptor ligand 18F-desmethoxy-fallypride: An appropriate fluorinated PET tracer for the differential diagnosis of parkinsonism. *European Journal of Nuclear Medicine & Molecular Imaging.* 2004; 31(8):1128–1135. Ref ID: 19838

69 Eidelberg D, Moeller JR, Ishikawa T et al. Early differential diagnosis of Parkinson's disease with 18F-fluorodeoxyglucose and positron emission tomography. *Neurology.* 1995; 45(11):1995–2004. Ref ID: 291

70 Sawle GV, Playford ED, Burn DJ et al. Separating Parkinson's disease from normality. Discriminant function analysis of fluorodopa F 18 positron emission tomography data. *Archives of Neurology.* 1994; 51(3):237–243. Ref ID: 213

71 Righini A, Antonini A, Ferrarini M et al. Thin section MR study of the basal ganglia in the differential diagnosis between striatonigral degeneration and Parkinson disease. *Journal of Computer Assisted Tomography.* 2002; 26(2):266–271. Ref ID: 129

72 Seppi K, Schocke MFH, Esterhammer R et al. Diffusion-weighted imaging discriminates progressive supranuclear palsy from PD, but not from the parkinson variant of multiple system atrophy. *Neurology.* 2003; 60(6):922–927. Ref ID: 133

73 Yekhlef F, Ballan G, Macia F et al. Routine MRI for the differential diagnosis of Parkinson's disease, MSA, PSP, and CBD. *Journal of Neural Transmission.* 2003; 110(2):151–169. Ref ID: 135

74 Price S, Paviour D, Scahill R et al. Voxel-based morphometry detects patterns of atrophy that help differentiate progressive supranuclear palsy and Parkinson's disease. *Neuroimage.* 2004; 23(2):663–669. Ref ID: 19826

75 Righini A, Antonini A, De Notaris R et al. MR imaging of the superior profile of the midbrain: Differential diagnosis between progressive supranuclear palsy and Parkinson disease. *American Journal of Neuroradiology.* 2004; 25(6):927–932. Ref ID: 19827

76 Paviour DC, Price SL, Stevens JM et al. Quantitative MRI measurement of superior cerebellar peduncle in progressive supranuclear palsy. *Neurology.* 2005; 64(4):675–679. Ref ID: 19831

77 Cordato NJ, Pantelis C, Halliday GM et al. Frontal atrophy correlates with behavioural changes in progressive supranuclear palsy. *Brain.* 2002; 125(4):789–800. Ref ID: 123

78 Clarke CE, Lowry M. Systematic review of proton magnetic resonance spectroscopy of the striatum in parkinsonian syndromes. *European Journal of Neurology.* 2001; 8(6):573–577. Ref ID: 17

79 Clarke CE, Davies P. Systematic review of acute levodopa and apomorphine challenge tests in the diagnosis of idiopathic Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 2000; 69(5):590–594. Ref ID: 21

80 Rossi P, Colosimo C, Moro E et al. Acute challenge with apomorphine and levodopa in Parkinsonism. *European Neurology.* 2000; 43(2):95–101. Ref ID: 719

81 Hughes AJ. Apomorphine test in the assessment of parkinsonian patients: a meta-analysis. *Advances in Neurology.* 1999; 80:363–368. Ref ID: 720

82 Hughes AJ, Lees AJ, Stern GM. Apomorphine test to predict dopaminergic responsiveness in parkinsonian syndromes. *Lancet.* 1990; 336(8706):32–34. Ref ID: 84

83 D'Costa DF, Abbott RJ, Pye IF et al. The apomorphine test in parkinsonian syndromes. *Journal of Neurology, Neurosurgery & Psychiatry.* 1991; 54(10):870–872. Ref ID: 79

84 Zappia M, Montesanti R, Colao R et al. Short-term levodopa test assessed by movement time accurately predicts dopaminergic responsiveness in Parkinson's disease. *Movement Disorders.* 1997; 12(1):103–106. Ref ID: 731

85 Double KL, Rowe DB, Hayes M et al. Identifying the pattern of olfactory deficits in Parkinson disease using the brief smell identification test. *Archives of Neurology.* 2003; 60(4):545–549. Ref ID: 699

86 Muller A, Mungersdorf M, Reichmann H et al. Olfactory function in Parkinsonian syndromes. *Journal of Clinical Neuroscience.* 2002; 9(5):521–524. Ref ID: 700

87 Wenning GK, Shephard B, Hawkes C et al. Olfactory function in atypical parkinsonian syndromes. *Acta Neurologica Scandinavica.* 1995; 91(4):247–250. Ref ID: 707

88 Antonini A, Benti R, De Notaris R et al. 123I-ioflupane/SPECT binding to striatal dopamine transporter (DAT) uptake in patients with Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Neurological Sciences.* 2003; 24(3):149–150. Ref ID: 789

89 Hawkes CH, Shephard BC, Daniel SE. Olfactory dysfunction in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 1997; 62(5):436–446. Ref ID: 703

90 Doty RL, Bromley SM, Stern MB. Olfactory testing as an aid in the diagnosis of Parkinson's disease: development of optimal discrimination criteria. *Neurodegeneration.* 1995; 4(1):93–97. Ref ID: 708

91 Katzenschlager R, Zijlmans J, Evans A et al. Olfactory function distinguishes vascular parkinsonism from Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 2004; 75(12):1749–1752. Ref ID: 19807

92 Mesholam RI, Moberg PJ, Mahr RN et al. Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. *Archives of Neurology.* 1998; 55(1):84–90. Ref ID: 702

93 Mitchell A, Lewis S, Foltynie T et al. Biomarkers and Parkinson's disease. *Brain.* 2004; 127:1693–1705. Ref ID: 19536

94 Clarke CE. A 'cure' for Parkinson's disease: can neuroprotection be proven with current trial designs? *Movement Disorders.* 2004; 19:491–499. Ref ID: 19538

95 Clarke CE. *Parkinson's disease in practice.* London: Royal Society of Medicine Press, 2001. Ref ID: 2

96 Schapira A. Disease modification in Parkinson's disease. *Lancet Neurology.* 2004; 3:362–368. Ref ID: 19537

97 Clarke CE, Guttman M. Dopamine agonist monotherapy in Parkinson's disease. *Lancet.* 2002; 360(9347):1767–1769. Ref ID: 16

98 Clarke CE. Neuroprotection and pharmacotherapy for motor symptoms in Parkinson's disease. *Lancet Neurology.* 2004; 3:466–475. Ref ID: 19540

99 Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Archives of Neurology.* 2004; 61(4):561–566. Ref ID: 2764

100 Ravina BM, Fagan SC, Hart RG. Neuroprotective agents for clinical trials in Parkinson's disease. *Neurology.* 2003; 60:1234–1240. Ref ID: 19541

101 Shults CW. Effect of selegiline (deprenyl) on the progression of disability in early Parkinson's disease. Parkinson Study Group. *Acta Neurologica Scandinavica Supplementum.* 1993; 146:36–42. Ref ID: 805

102 Kieburtz K, McDermott M, Como P et al. The effect of deprenyl and tocopherol on cognitive performance in early untreated Parkinson's disease. *Neurology.* 1994; 44(9):1756–1759. Ref ID: 281

103 Koller W, Olanow CW, Rodnitzky R et al. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *New England Journal of Medicine.* 1993; 328(3):176–183. Ref ID: 148

104 Shoulson I. Deprenyl and tocopherol antioxidative therapy of parkinsonism (DATATOP). *Acta Neurologica Scandinavica Supplementum.* 1989; 80(126):171–175. Ref ID: 363

105 Parker W, Boyson S, Parks J. Abnormalities of the electron transport chain in idiopathic Parkinson's disease. *Annals of Neurology.* 1989; 26:719–723. Ref ID: 19543

106 Schapira A, Mann V, Cooper J. Anatomic and disease specificity of NADH CoQ1 reductase (complex 1) deficiency in Parkinson's disease. *Journal of Neurochemistry.* 1990; 55:2142–2145. Ref ID: 19544

107 Shults C, Haas R, Passov D et al. Coenzyme Q10 levels correlate with the activities of the complex I and II/III mitochrondria from parkinsonian and non-parkinsonian subjects. *Annals of Neurology.* 1997; 42:261–264. Ref ID: 19545

108 Beal MF, Matthews R, Tieleman A et al. Coenzyme Q10 attenuates the MPTP induced loss of striatal dopamine and dopaminergic axons in aged mice. *Brain Research.* 1998; 783:109–114. Ref ID: 19546

109 Muller T, Buttner T, Gholipour AF et al. Coenzyme Q10 supplementation provides mild symptomatic benefit in patients with Parkinson's disease. *Neuroscience Letters.* 2003; 341(3):201–204. Ref ID: 799

110 Shults CW, Oakes D, Kieburtz K et al. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Archives of Neurology.* 2002; 59(10):1541–1550. Ref ID: 801

111 Lida M, Miyazaki I, Tanaka K et al. Dopamine D2 receptor-mediated antioxidant and neuroprotective effects of ropinirole, a dopamine agonist. *Brain Research.* 1999; 838:51–59. Ref ID: 19547

112 Schapira A, Olanow CW. Rationale for the use of dopamine agonists as neuroprotective agents in Parkinson's disease. *Annals of Neurology.* 2003; 53:S149–S157. Ref ID: 19549

113 Marek K. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *Journal of the American Medical Association.* 2002; 287(13):1653–1661. Ref ID: 809

114 Rakshi JS, Pavese N, Uema T et al. A comparison of the progression of early Parkinson's disease in patients started on ropinirole or L-dopa: an 18F-dopa PET study. *Journal of Neural Transmission.* 2002; 109(12):1433–1443. Ref ID: 2535

115 Przuntek H, Welzel D, Blumner E et al. Bromocriptine lessens the incidence of mortality in L-dopa-treated parkinsonian patients: prado-study discontinued. *European Journal of Clinical Pharmacology.* 1992; 43(4):357–363. Ref ID: 2518

116 Hely MA, Morris JG, Traficante R et al. The sydney multicentre study of Parkinson's disease: progression and mortality at 10 years. *Journal of Neurology, Neurosurgery & Psychiatry.* 1999; 67(3):300–307. Ref ID: 2184

117 Montastruc JL, Desboeuf K, Lapeyre-Mestre M et al. Long-term mortality results of the randomized controlled study comparing bromocriptine to which levodopa was later added with levodopa alone in previously untreated patients with Parkinson's disease. *Movement Disorders.* 2001; 16(3):511–514. Ref ID: 2414

118 Rinne UK, Bracco F, Chouza C et al. Early treatment of Parkinson's disease with Cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. *Drugs.* 1998; 55(Suppl 1):23–3TxCM 20. Ref ID: 19605

119 Hundemer HP, Lledo A, Van Laar T et al. The safety of pergolide monotherapy in early stage Parkinson's disease. One year interim analysis of a 3 year double blind randomised study of pergolide versus levodopa (abstract). *Movement Disorders.* 2000; 15(Supplement 3):115. Ref ID: 19598

120 Ives NJ, Stowe RL, Marro J et al. Monoamine oxidase type B inhibitors in early Parkinsons's disease: meta analysis of 17 randomised trials involving 3525 patients. *British Medical Journal.* 2004; 329(7466): 593–596. Ref ID: 2739

121 Macleod AD, Counsell CE, Ives N et al. Monoamine oxidase B inhibitors for early Parkinson's disease. *The Cochrane Database of Systematic Reviews.* 2005;(3):CD004898. Ref ID: 20026

122 Barone P, Bravi D, Bermejo-Pareja F et al. Pergolide monotherapy in the treatment of early PD: a randomized, controlled study. Pergolide Monotherapy Study Group. *Neurology.* 1999; 53(3):573–579. Ref ID: 1937

123 Kieburtz K. Safety and efficacy of pramipexole in early Parkinson disease: A randomized dose-ranging study. *Journal of the American Medical Association.* 1997; 278(2):125–130. Ref ID: 1501

124 Adler CH, Sethi KD, Hauser RA et al. Ropinirole for the treatment of early Parkinson's disease. *Neurology.* 1997; 49(2):393–399. Ref ID: 1902

125 Shannon KM, Bennett JPJ, Friedman JH. Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. *Neurology.* 1997; 49(3):724–728. Ref ID: 19764

126 Hubble JP, Koller WC, Cutler NR et al. Pramipexole in patients with early Parkinson's disease. *Clinical Neuropharmacology.* 1995; 18(4):338–347. Ref ID: 19643

127 Brooks DJ, Abbott RJ, Lees AJ et al. A placebo-controlled evaluation of ropinirole, a novel D2 agonist, as sole dopaminergic therapy in Parkinson's disease. *Clinical Neuropharmacology.* 1998; 21(2):101–107. Ref ID: 1977

128 Committee on Safety of Medicines. Fibrotic reactions with pergolide and other ergot-derived dopamine receptor agonists. *Current Problems in Pharmacovigilance.* 2002; 28(3) Ref ID: 19899

129 Baseman D, O'Suilleabhain P. Pergolide use in Parkinson's disease is associated with cardiac valve regurgitation. *Neurology.* 2004; 63:301–304. Ref ID: 19900

130 Van Camp G, Flamez A. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. *Lancet.* 2004; 363:1179–1183. Ref ID: 19901

131 Birkmayer W, Knoll J, Riederer P et al. Increased life expectancy resulting from addition of L-deprenyl to madopar treatment in Parkinson's disease: a long-term study. *Journal of Neural Transmission.* 1985; 64:113–127. Ref ID: 19677

132 Stern MB, Marek KL, Friedman J et al. Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. *Movement Disorders.* 2004; 19(8):916–923. Ref ID: 19854

133 Presthus J, Berstad J, Lien K. Selegiline (1-deprenyl) and low-dose levodopa treatment of Parkinson's disease. A double-blind crossover trial. *Acta Neurologica Scandinavica.* 1987; 76:200–203. Ref ID: 2761

134 Crosby NJ, Deane HO, Clarke CE. Beta-blocker therapy for tremor in Parkinson's disease.(Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2003;(1):CD003361. Ref ID: 80

135 Marsden CD, Parkes JD, Rees JE. Propanolol in Parkinson's disease. *Lancet.* 1974; 2(7877):410. Ref ID: 19533

136 Corbett JL. Beta blockers and the central nervous system. In: Kielkholz P (eds), *An International Symposium*, Bern: Huber, 1976: 200–217. Ref ID: 19534

137 Henderson JM, Yiannikas C, Morris JG et al. Postural tremor of Parkinson's disease. *Clinical Neuropharmacology.* 1994; 17(3):277–285. Ref ID: 755

138 Claveria L, Vakil S, George C et al. Oxprenolol in Parkinsonism. *The Journal of Clinical Pharmacology.* 1975; 15(1):66–68. Ref ID: 19532

139 Crosby N, Deane KHO, Clarke CE. Amantadine in Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2003;(1):CD003468. Ref ID: 51

140 Cox B, Danta G, Schnieden H et al. Interactions of L-dopa and amantadine in patients with Parkinsonism. *Journal of Neurology, Neurosurgery & Psychiatry.* 1973; 36(3):354–361. Ref ID: 19645

141 Savery F. Amantadine and a fixed combination of levodopa and carbidopa in the treatment of Parkinson's disease. *Diseases of the Nervous System.* 1977; 38(8):605–608. Ref ID: 19552

142 Walker JE, Albers JW, Tourtellotte WW et al. A qualitative and quantitative evaluation of amantadine in the treatment of Parkinson's disease. *Journal of Chronic Diseases.* 1972; 25:149–182. Ref ID: 19556

143 Katzenschlager R, Sampaio C, Costa J et al. Anticholinergics for symptomatic management of Parkinson´s disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2002;(3): CD003735. Ref ID: 92

144 Cooper JA, Sagar HJ, Doherty SM et al. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. *Brain.* 1992; 115(6):1701–1725. Ref ID: 19567

145 Parkes JD, Baxter RC, Marsden CD et al. Comparative trial of benzhexol, amantadine, and levodopa in the treatment of Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 1974; 37(4): 422–426. Ref ID: 19569

146 Hutton JT, Lynne DR, Bianchine JR. Controlled-release carbidopa/levodopa in the treatment of Parkinsonism. *Clinical Neuropharmacology.* 1984; 7(2):135–139. Ref ID: 783

147 Dupont E, Andersen A, Boas J et al. Sustained-release Madopar HBS compared with standard Madopar in the long-term treatment of de novo parkinsonian patients. *Acta Neurologica Scandinavica.* 1996; 93(1):14–20. Ref ID: 778

148 Kinnunen E, Asikaimen I, Jolma T et al. Three-year open comparison of standard and sustained-release levodopa/benserazide preparations in newly diagnosed Parkinsonian patients. *Focus on Parkinson's Disease.* 1997; 9(2):32–36. Ref ID: 304

149 Block G, Liss C, Reines S et al. Comparison of immediate-release and controlled release Carbidopa/Levodopa in Parkinson's disease. A multicenter 5-year study. *European Neurology.* 1997; 37(1):23–27. Ref ID: 257

150 Olanow CW, Hauser RA, Gauger L et al. The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Annals of Neurology.* 1995; 38:771–777. Ref ID: 2746

151 Weiner WJ, Factor SA, Sanchez-Ramos JR et al. Early combination therapy (bromocriptine and levodopa) does not prevent motor fluctuations in Parkinson's disease. *Neurology.* 1993; 43(1):21–27. Ref ID: 2718

152 Rascol O, Brooks DJ, Korczyn AD et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *New England Journal of Medicine.* 2000; 342(20):1484–1491. Ref ID: 2540

153 Hely MA, Morris JG, Reid WG et al. The Sydney Multicentre Study of Parkinson's disease: a randomised, prospective five year study comparing low dose bromocriptine with low dose levodopa-carbidopa. *Journal of Neurology, Neurosurgery & Psychiatry.* 1994; 57(8):903–910. Ref ID: 2185

154 Herskovits E, Yorio A, Leston J. Long term bromocriptine treatment in de novo parkinsonian patients. *Medicina.* 1988; 48(4):345–350. Ref ID: 2193

155 Riopelle RJ, Gawel MJ, Libman I et al. A double-blind study of bromocriptine and L-dopa in de novo Parkinson's disease. Short-term results. *European Neurology.* 1988; 28(SUPPL. 1):11–14. Ref ID: 1048

156 Caraceni T, Musicco M. Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomized multicenter study. *Parkinsonism & Related Disorders.* 2001; 7(2):107–114. Ref ID: 324

157 Kulisevsky J, Garcia-Sanchez C, Berthier ML et al. Chronic effects of dopaminergic replacement on cognitive function in Parkinson's disease: a two-year follow-up study of previously untreated patients. *Movement Disorders.* 2000; 15(4):613–626. Ref ID: 2287

158 Holloway RG, Shoulson I, Fahn S et al. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Archives of Neurology.* 2004; 61(7):1044–1053. Ref ID: 19842

159 Allain H, Destee A, Petit H et al. Five-year follow-up of early lisuride and levodopa combination therapy versus levodopa monotherapy in de novo Parkinson's disease. *European Neurology.* 2000; 44(1):22–30. Ref ID: 1914

160 Gimenez-Roldan S, Tolosa E, Burguera JA et al. Early combination of bromocriptine and levodopa in Parkinson's disease: a prospective randomized study of two parallel groups over a total follow-up period of 44 months including an initial 8-month double-blind stage. *Clinical Neuropharmacology.* 1997; 20(1):67–76. Ref ID: 2136

161 Alarcon F, Cevallos N, Lees AJ. Does combined levodopa and bromocriptine therapy in Parkinson's disease prevent late motor complications? *European Journal of Neurology.* 1998; 5(3):255–263. Ref ID: 1274

162 Przuntek H, Welzel D, Gerlach M et al. Early institution of bromocriptine in Parkinson's disease inhibits the emergence of levodopa-associated motor side effects. Long-term results of the PRADO study. *Journal of Neural Transmission.* 1996; 103(6):699–715. Ref ID: 2520

163 Ramaker C, Hilten JV. Bromocriptine/levodopa combined versus levodopa alone for early Parkinson's disease. (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2002;(2):CD003634. Ref ID: 42

164 Hoerger TJ, Bala MV, Rowland C et al. Cost effectiveness of pramipexole in Parkinson's disease in the US. *Pharmacoeconomics.* 1998; 14(5):541–557. Ref ID: 19750

165 Noyes K, Dick AW, Holloway RG. Pramipexole vs levodopa as initial treatment for Parkinson's disease: a randomized clinical-economic trial. *Med Decision Making.* 2004; 24(5):472–485. Ref ID: 19763

166 Iskedjian M, Einarson TR. Cost analysis of ropinirole versus levodopa in the treatment of Parkinson's disease. *Pharmacoeconomics.* 2003; 21(2):115–127. Ref ID: 19745

167 Smala AM, Spottke EA, Machat O et al. Cabergoline versus levodopa monotherapy: a decision analysis. *Movement Disorders.* 2003; 18(8):898–905. Ref ID: 19754

168 Lindgren P, Jonsson B, DuChane J. The cost-effectiveness of early cabergoline treatment compared to levodopa in Sweden. *European Journal of Health Economics.* 2003; 4(1):37–42. Ref ID: 19853

169 Noyes K, Dick AW, Holloway RG. Pramipexole and levodopa in early Parkinson's disease: dynamic changes in cost effectiveness. *Pharmacoeconomics.* 2005; 23(12):1257–1270. Ref ID: 20122

170 Cedarbaum JM, Hoey M, McDowell FH. A double-blind crossover comparison of Sinemet CR4 and standard Sinemet 25/100 in patients with Parkinson's disease and fluctuating motor performance. *Journal of Neurology, Neurosurgery & Psychiatry.* 1989; 52(2):207–212. Ref ID: 261

171 Hutton JT, Morris JL, Bush DF et al. Multicenter controlled study of Sinemet CR vs Sinemet (25/100) in advanced Parkinson's disease. *Neurology.* 1989; 39(11 SUPPL. 2):67–72. Ref ID: 293

172 Hutton JT, Morris JL, Roman GC et al. Treatment of chronic Parkinson's disease with controlled-release carbidopa/levodopa. *Archives of Neurology.* 1988; 45(8):861–864. Ref ID: 295

173 LeWitt PA, Nelson MV, Berchou RC et al. Controlled-release carbidopa/levodopa (Sinemet 50/200 CR4): Clinical and pharmacokinetic studies. *Neurology.* 1989; 39(11 SUPPL. 2):45–53. Ref ID: 310

174 Feldman RG, Mosbach PA, Kelly MR et al. Double-blind comparison of standard Sinemet and Sinemet CR in patients with mild-to-moderate Parkinson's disease. *Neurology.* 1989; 39(11 SUPPL. 2):96–101. Ref ID: 277

175 Lieberman A, Gopinathan G, Miller E et al. Randomized double-blind cross-over study of sinemet-controlled release (CR4 50/200) versus sinemet 25/100 in Parkinson's disease. *European Neurology.* 1990; 30(2):75–78. Ref ID: 157

176 Wolters EC, Horstink MW, Roos RA et al. Clinical efficacy of sinemet CR 50/200 versus sinemet 25/100 in patients with fluctuating Parkinson's disease. An open, and a double-blind, double-dummy, multicenter treatment evaluation. The Dutch Sinemet CR Study Group. *Clinical Neurology & Neurosurgery.* 1992; 94:205–211. Ref ID: 775

177 Wolters EC, Tesselaar HJ. International (NL-UK) double-blind study of Sinemet CR and standard Sinemet (25/100) in 170 patients with fluctuating Parkinson's disease. *Journal of Neurology.* 1996; 243(3):235–240. Ref ID: 19640

178 Sage JI, Mark MH. Comparison of controlled-release Sinemet (CR4) and standard Sinemet (25 mg/100 mg) in advanced Parkinson's disease: A double-blind, crossover study. *Clinical Neuropharmacology.* 1988; 11(2):174–179. Ref ID: 348

179 Juncos JL, Fabbrini G, Mouradian MM et al. Controlled release levodopa-carbidopa (CR-5) in the management of parkinsonian motor fluctuations. *Archives of Neurology.* 1987; 44(10):1010–1012. Ref ID: 109

180 Ahlskog JE, Muenter MD, McManis PG et al. Controlled-release Sinemet (CR-4): a double-blind crossover study in patients with fluctuating Parkinson's disease. *Mayo Clinic Proceedings.* 1988; 63(9):876–886. Ref ID: 248

181 Hammerstad JP, Carter J, Nutt JG. Buspirone in Parkinson's disease. *Clinical Neuropharmacology.* 1986; 9(6):556–560. Ref ID: 401

182 Van Hilten JJ, Ramaker C, van de Beek WJT et al. Bromocriptine for levodopa-induced motor complications in Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 1998;(3):CD001203. Ref ID: 47

183 Clarke CE, Deane KH. Cabergoline for levodopa-induced complications in Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2001;(1):CD001518. Ref ID: 52

184 Clarke CE, Speller JM. Lisuride for levodopa-induced complications in Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 1999;(1):CD001515. Ref ID: 54

185 Clarke CE, Speller JM. Pergolide for levodopa-induced complications in Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 1999;(2):CD000235. Ref ID: 56

186 Clarke CE, Speller JM, Clarke JA. Pramipexole for levodopa-induced complications in Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2000;(2):CD002261. Ref ID: 58

187 Clarke CE, Deane KHO. Ropinirole for levodopa-induced complications in Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2001;(1):CD001516. Ref ID: 60

188 Pogarell O, Gasser T, Van Hilten JJ et al. Pramipexole in patients with Parkinson's disease and marked drug resistant tremor: a randomised, double blind, placebo controlled multicentre study. *Journal of Neurology, Neurosurgery & Psychiatry.* 2002; 72(6):713–720. Ref ID: 2512

189 Wong KS, Lu C-S, Shan D-E et al. Efficacy, safety, and tolerability of pramipexole in untreated and levodopa-treated patients with Parkinson's disease. *Journal of the Neurological Sciences.* 2003; 216(1):81–87. Ref ID: 1823

190 Mizuno Y, Yanagisawa N, Kuno S et al. Randomized, double-blind study of pramipexole with placebo and bromocriptine in advanced Parkinson's disease. *Movement Disorders.* 2003; 18(10):1149–1156. Ref ID: 2405

191 Guttman M, The International Pramipexole-Bromocriptine Study Group. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. *Neurology.* 1997; 49(4):1060–1065. Ref ID: 19602

192 Bateman DN, Coxon A, Legg NJ et al. Treatment of the on-off syndrome in parkinsonism with low-dose bromocriptine in combination with levodopa. *Journal of Neurology, Neurosurgery & Psychiatry.* 1978; 41(12):1109–1113. Ref ID: 19614

193 Gron U. Bromocriptine versus placebo in levodopa treated patients with Parkinson's disease. *Acta Neurologica Scandinavica.* 1977; 56(3):269–273. Ref ID: 19615

194 Maier-Hoehn MM, Elton RL. Low dosages of bromocriptine added to levodopa in Parkinson's disease. *Neurology.* 1985; 35:199–206. Ref ID: 434

195 Jansen EN. Bromocrytine in levodopa response-losing parkinsonism. *European Neurology.* 1978; 17:92–99. Ref ID: 19617

196 Schneider E, Fischer PA. Bromocriptin in der Behandlung der fortgeschrittenen Stadien des Parkinson-syndroms [German]. *Deutsche Medizinische Wochenschrift.* 1982; 107:175–179. Ref ID: 19618

197 Temlett JA, Ming A, Saling M et al. Adjunctive therapy with bromocriptine in Parkinson's disease. *South African Medical Journal.* 1990; 78:680–685. Ref ID: 19620

198 Toyokura Y, Mizuno Y, Kase M et al. Effects of bromocriptine in parkinsonism: a nation-wide collaborative double-blind study. *Acta Neurologica Scandinavica.* 1985; 72:157–170. Ref ID: 19623

199 Miguel F, Obeso JA, Olive Plana JM et al. *Double-blind parallel group study of the efficacy and tolerability of the cabergoline vs placebo in Parkinson's patients with motor fluctuations.* (21336/722i). FCE report, 1993. Ref ID: 19609

200 Steiger MJ, El Debas T, Anderson T et al. Double-blind study of the activity and tolerablility of cabergoline versus placebo in parkinsonains with motor fluctuations. *Journal of Neurology.* 1996; 243:68–72. Ref ID: 19610

201 Hutton JT, Koller WC, Ahlskog JE et al. Multicentre, placebo-controlled trials of cabergoline taken once daily in the treatment of Parkinson's disease. *Neurology.* 1996; 46:1062–1065. Ref ID: 19608

202 Olanow CW, Fahn S, Muenter M et al. A multi-centre double-blind placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease. *Movement Disorders.* 1994; 9:40–47. Ref ID: 19607

203 Lieberman A, Ranhosky A, Korts D. Clinical Evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. *Neurology.* 1997; 49(1):162–168. Ref ID: 19603

204 Pinter MM, Pogarell O, Oertel WH. Efficacy, safety and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: a double-blind, placebo-controlled, randomised, multi-centre study. *Journal of Neurology, Neurosurgery & Psychiatry.* 1999; 66:436–441. Ref ID: 19604

205 Wermuth L. The Danish Pramipexole Study Group. A double-blind, placebo-controlled, randomised, multi-centre study of pramipexole in advanced Parkinson's disease. *European Journal of Neurology.* 1998; 5:235–242. Ref ID: 19606

206 Rascol O, Lees AJ, Senard JM et al. A placebo-controlled study of ropinirole, a new D2 agonist, in the treatment of motor fluctuations of L-DOPA-treated parkinsonian patients. *Advances in Neurology.* 1996; 69:531–534. Ref ID: 19601

207 Leiberman A, Olanow CW, Sethi K et al. A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. *Neurology.* 1998; 51:1057–1062. Ref ID: 19612

208 Korcyn AD. *Anti-Parkinson efficacy (L-dopa sparing effect) of ropinirole versus placebo as adjunct therapy in Parkinsonian patients not optimally controlled in L-dopa.* (MY-1002/SKF-101468/2/CPMS-034). SmithKline Beecham Pharmaceuticals, 1990. Unpublished data. Ref ID: 19611

209 Waters CH, Sethi KD, Hauser RA et al. Zydis selegiline reduces off time in Parkinson's disease patients with motor fluctuations: A 3-month, randomized, placebo-controlled study. *Movement Disorders.* 2004; 19(4):426–432. Ref ID: 428

210 Brodersen P, Philbert A, Gulliksen G et al. The effect of l-deprenyl on on-off phenomena in Parkinson's disease. *Acta Neurologica Scandinavica.* 1985; 71:494–497. Ref ID: 2762

211 Presthus J, Hajba A. Deprenyl (selegiline) combined with levodopa and a decarboxylase inhibitor in the treatment of Parkinson's disease. *Acta Neurologica Scandinavica Supplementum.* 1983; 95:127–133. Ref ID: 477

212 Golbe LI, Lieberman AN, Muenter MD et al. Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease. *Clinical Neuropharmacology.* 1988; 11(1):45–55. Ref ID: 510

213 Golbe LI, Duvoisin RC. Double-blind trial of R-deprenyl for the "on-off" effect complicating Parkinson's disease. *Journal of Neural Transmission Supplementum.* 1987; 25:123–129. Ref ID: 2760

214 Hubble JP, Koller WC, Waters C. Effects of selegiline dosing on motor fluctuations in Parkinson's disease. *Clinical Neuropharmacology.* 1993; 16:83–87. Ref ID: 2752

215 Sivertsen B, Dupont E, Mikkelsen B et al. Selegiline and levodopa in early or moderately advanced Parkinson's disease: A double-blind controlled short- and long-term study. *Acta Neurologica Scandinavica Supplementum.* 1989; 80(126):147–152. Ref ID: 193

216 Lieberman AN, Gopinathan G, Neophytides A et al. Deprenyl versus placebo in Parkinson disease: a double-blind study. *New York State Journal of Medicine.* 1987; 87:646–649. Ref ID: 88

217 Rascol O, Brooks DJ, Melamed E et al. Rasagiline as an adjunct to levodopa in Parkinson's disease patients with motor fluctuations (LARGO study): a randomised, double-blind, parallel-group trial. *Lancet.* 2005; 365:947–954. Ref ID: 19840

218 Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Archives of Neurology.* 2005; 62(2):241–248. Ref ID: 19833

219 Bonifati V, Meco G. New, selective catechol-O-methyltransferase inhibitors as therapeutic agents in Parkinson's disease. *Pharmacology and Therapeutics.* 1999; 81(1):1–36. Ref ID: 19766

220 Myllyla V, Haapaniemi TH, Kaakkola S et al. New triple combination levodopa/carbidopa/entacapone is a preferred treatment in patients in Parkinson's disease (abstract). *Neurology.* 2003; 60(suppl 1):A289. Ref ID: 20027

221 Deane KHO, Spieker S, Clarke CE. Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2004;(4):CD004554. Ref ID: 19624

222 Reichmann H, Boas J, Macmahon D et al. Efficacy of combining levodopa with entacapone on quality of life and activities of daily living in patients experiencing wearing-off type fluctuations. *Acta Neurologica Scandinavica.* 2005; 111(1):21–28. Ref ID: 19864

223 Olanow CW, Kieburtz K, Stern M et al. Double-blind, placebo-controlled study of entacapone in levodopa-treated patients with stable Parkinson disease. *Archives of Neurology.* 2004; 61(10):1563–1568. Ref ID: 104

224 Brooks DJ, Sagar HJ. Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease. A randomized, placebo-controlled, double-blind six month study. *Journal of Neurology, Neurosurgery & Psychiatry.* 2003; 74:1071–1079. Ref ID: 19670

225 Parkinson Study Group. Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. *Annals of Neurology.* 1997; 42(5):747–755. Ref ID: 19637

226 Poewe WH, Deuschl G, Gordin A et al. Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6 month randomised placebo-controlled double-blind study in Germany and Austria (Celomen Study). *Acta Neurologica Scandinavica.* 2004; 105:245–255. Ref ID: 19674

227 Rinne UK, Larsen JP, Siden A et al. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Nomecomt Study Group. *Neurology.* 1998; 51(5):1309–1314. Ref ID: 19638

228 Ruottinen HM, Rinne UK. Entacapone prolongs levodopa response in a one month double blind study in parkinsonian patients with levodopa related fluctuations. *Journal of Neurology, Neurosurgery & Psychiatry.* 1996; 60(1):36–40. Ref ID: 19636

229 Fenelon G, Bourdiex I, Pere J, Galiano L, Shadarack J. Entacapone provides additional symptomatic benefits in Parkinson's disease (PD) patients treated with L-DOPA and a dopamine agonist who are experiencing wearing-off motor fluctuations: results of a randomised, double-blind study. AAN conference, 2002. Ref ID: 19671

230 Im JH, Jeon BS, Lee MS et al. A multicentre, double-blind, placebo-controlled study to assess efficacy and safety of entacapone in Korean patients with Parkinson's disease experiencing end-of-dose deterioration. *Movement Disorders.* 2002; 17(5):S40. Ref ID: 19672

231 Myllyla VV, Kultalahti E-R, Haapaniemi H et al. Twelve-month safety of entacapone patients with Parkinson's disease. *European Journal of Neurology.* 2001; 8:53–60. Ref ID: 19673

232 Adler CH, Singer C, O'Brien C et al. Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson disease treated with levodopa-carbidopa. *Archives of Neurology.* 1998; 55(8):1089–1095. Ref ID: 19634

233 Baas H, Beiske A, Ghika J et al. Catechol-O-methyltransferase inhibition with tolcapone reduced the 'wearing-off' phenomenon and levodopa requirements in fluctuating Parkinsonian patients. *Journal of Neurology, Neurosurgery & Psychiatry.* 1997; 63(4):421–428. Ref ID: 19669

234 Dupont E, Burgunder JM, Findley LJ et al. Tolcapone added to levodopa in stable parkinsonian patients: a double-blind placebo-controlled study. *Movement Disorders.* 1997; 12(6):928–934. Ref ID: 19631

235 Kurth MC, Adler CH, Hilaire MS et al. Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. Tolcapone Fluctuator Study Group I. *Neurology.* 1997; 48(1):81–87. Ref ID: 19633

236 Myllyla VV, Jackson M, Larsen JP et al. Efficacy and safety of tolcapone in levodopa-treated Parkinson's disease patients with 'wearing-off' phenomenon: A multicentre, double-blind, randomized, placebo-controlled trial. *European Journal of Neurology.* 1997; 4(4):333–341. Ref ID: 19639

237 Rajput AH, Martin W, Saint-Hilaire MH et al. Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind, placebo-controlled, multicenter trial. *Neurology*. 1997; 49(4):1066–1071. Ref ID: 19632

238 Crosby NJ, Deane HO, Clarke CE. Amantadine for dyskinesia in Parkinson's disease. (Cochrane Review). *The Cochrane Database of Systematic Reviews*. 2003;(2):CD003467. Ref ID: 50

239 Thomas A, Iacono D, Luciano AL et al. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 2004; 75(1):141–143. Ref ID: 318

240 Luginger E, Wenning GK, Bosch S et al. Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. *Movement Disorders*. 2000; 15(5):873–878. Ref ID: 152

241 Snow BJ, Macdonald L, Mcauley D et al. The effect of amantadine on levodopa-induced dyskinesias in Parkinson's disease: A double-blind, placebo-controlled study. *Clinical Neuropharmacology*. 2000; 23(2):82–85. Ref ID: 311

242 Verhagen ML, Del Dotto P, van den Munckhof P et al. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology*. 1998; 50(5):1323–1326. Ref ID: 19594

243 Dewey RB, Hutton JT, LeWitt PA et al. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events. *Archives of Neurology*. 2001; 58(9):1385–1392. Ref ID: 19655

244 Ostergaard L, Werdelin L, Odin P et al. Pen injected apomorphine against off phenomena in late Parkinson's disease: a double blind, placebo controlled study. *Journal of Neurology, Neurosurgery & Psychiatry*. 1995; 58(6):681–687. Ref ID: 19628

245 Van Laar T, Jansen EN, Essink AW et al. A double-blind study of the efficacy of apomorphine and its assessment in 'off'-periods in Parkinson's disease. *Clinical Neurology & Neurosurgery*. 1993; 95(3):231–235. Ref ID: 19992

246 Poewe W, Kleedorfer B, Wagner M et al. Continuous subcutaneous apomorphine infusions for fluctuating Parkinson's disease. Long-term follow-up in 18 patients. *Advances in Neurology*. 1993; 60:656–659. Ref ID: 19651

247 Kanovsky P, Kubova D, Bares M et al. Levodopa-induced dyskinesias and continuous subcutaneous infusions of apomorphine: results of a two-year, prospective follow-up. *Movement Disorders*. 2002; 17(1):188–191. Ref ID: 19656

248 Frankel JP, Lees AJ, Kempster PA et al. Subcutaneous apomorphine in the treatment of Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 1990; 53(2):96–101. Ref ID: 19731

249 Stocchi F, Vacca L, De Pandis MF et al. Subcutaneous continuous apomorphine infusion in fluctuating patients with Parkinson's disease: long-term results. *Neurological Sciences*. 2001; 22(1):93–94. Ref ID: 19733

250 Pietz K, Hagell P, Odin P. Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up. *Journal of Neurology, Neurosurgery & Psychiatry*. 1998; 65(5):709–716. Ref ID: 19734

251 Hughes AJ, Bishop S, Kleedorfer B et al. Subcutaneous apomorphine in Parkinson's disease: response to chronic administration for up to five years. *Movement Disorders*. 1993; 8(2):165–170. Ref ID: 19735

252 Gancher ST, Nutt JG, Woodward WR. Apomorphine infusional therapy in Parkinson's disease: Clinical utility and lack of tolerance. *Movement Disorders*. 1995; 10(1):37–43. Ref ID: 19737

253 Manson AJ, Turner K, Lees AJ. Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: long-term follow-up study of 64 patients. *Movement Disorders*. 2002; 17(6):1235–1241. Ref ID: 19730

254 Colzi A, Turner K, Lees AJ. Continuous subcutaneous waking day apomorphine in the long term treatment of levodopa induced interdose dyskinesias in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 1998; 64(5):573–576. Ref ID: 19736

255 Katzenschlager R, Hughes A, Evans A et al. Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson's disease: a prospective study using single-dose challenges. *Movement Disorders*. 2005; 20(2):151–157. Ref ID: 19993

256 Deane KHO, Spieker S, Clarke CE. Catechol-O-methyltransferase inhibitors versus active comparators for levodopa-induced complications in Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2004;(4):CD004553. Ref ID: 19625

257 Koller W, Lees A, Doder M et al. Randomized trial of tolcapone versus pergolide as add-on to levodopa therapy in Parkinson's disease patients with motor fluctuations. *Movement Disorders.* 2001; 16(5):858–866. Ref ID: 307

258 Agid Y, Destee A, Durif F et al. Tolcapone, bromocriptine and Parkinson's disease. *Lancet.* 1997; 350:712–713. Ref ID: 217

259 Lenz FA, Tasker RR, Kwan HC et al. Selection of the optimal lesion site for the relief of parkinsonian tremor on the basis of spectral analysis of neuronal firing patterns. *Applied Neurophysiology.* 1987; 50(1–6):338–43. Ref ID: 19843

260 Cooper IS. Anterior chorodial artery ligation for involuntary movements. *Science.* 1953; 118(3059):193. Ref ID: 19844

261 Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *Journal of Neurosurgery.* 1992; 76:53–61. Ref ID: 19845

262 Huntington's Outreach Project for Education at Stanford. *Basal Ganglia.* Available from: www.stanford edu/group/hopes/ [accessed 20 April 2006]. Ref ID: 19939

263 Aziz TZ, Peggs D, Sambrook MA et al. Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. *Movement Disorders.* 1991; 6(4):288–292. Ref ID: 19846

264 Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science.* 1990; 249(4975):1436–1438. Ref ID: 19847

265 Limousin P, Pollak P, Benazzouz A et al. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet.* 1995; 345(8942):91–95. Ref ID: 19848

266 Spottke EA, Volkmann J, Lorenz D et al. Evaluation of healthcare utilization and health status of patients with Parkinson's disease treated with deep brain stimulation of the subthalamic nucleus. *Journal of Neurology.* 2002; 249(6):759–766. Ref ID: 19713

267 Tomaszewski KJ, Holloway RG. Deep brain stimulation in the treatment of Parkinson's disease: A cost-effectiveness analysis. *Neurology.* 2001; 57(4):663–671. Ref ID: 19714

268 McIntosh E, Gray A, Aziz T. Estimating the costs of surgical innovations: The case for subthalamic nucleus stimulation in the treatment of advanced Parkinson's disease. *Movement Disorders.* 2003; 18(9):993–999. Ref ID: 404

269 Charles PD, Padaliya BB, Newman WJ et al. Deep brain stimulation of the subthalamic nucleus reduces antiparkinsonian medication costs. *Parkinsonism & Related Disorders.* 2004; 10(8):475–479. Ref ID: 19708

270 Lagrange E, Krack P, Moro E et al. Bilateral subthalamic nucleus stimulation improves health-related quality of life in PD. *Neurology.* 2002; 59(12):1976–1978. Ref ID: 386

271 Welter ML, Houeto JL, Tezenas du MS et al. Clinical predictive factors of subthalamic stimulation in Parkinson's disease. *Brain.* 2002; 125(3):575–583. Ref ID: 19700

272 Herzog J, Volkmann J, Krack P et al. Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. *Movement Disorders.* 2003; 18(11):1332–1337. Ref ID: 19698

273 Funkiewiez A, Ardouin C, Caputo E et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 2004; 75(6):834–839. Ref ID: 19707

274 Tavella A, Bergamasco B, Bosticco E et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: Long-term follow-up. *Neurological Sciences.* 2002; 23(suppl 2):S111–S112. Ref ID: 389

275 Russmann H, Ghika J, Villemure JG et al. Subthalamic nucleus deep brain stimulation in Parkinson disease patients over age 70 years. *Neurology.* 2004; 63(10):1952–1954. Ref ID: 19727

276 Krack P, Batir A, Van Blercom N et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *New England Journal of Medicine.* 2003; 349(20):1925–1934. Ref ID: 19699

277 Limousin P, Speelman JD, Gielen F et al. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *Journal of Neurology, Neurosurgery & Psychiatry.* 1999; 66(3): 289–296. Ref ID: 19703

278 Vesper J, Klostermann F, Wille C et al. Long-term suppression of extrapyramidal motor symptoms with deep brain stimulation (DBS). *German Journal of Neurosurgery.* 2004; 65(3):117–122. Ref ID: 400

279 Obeso JA, Guridi J, Rodriguez-Oroz MC et al. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *New England Journal of Medicine.* 2001; 345(13):956–963. Ref ID: 417

280 Volkmann J, Allert N, Voges J et al. Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. *Neurology.* 2001; 56(4):548–551. Ref ID: 19701

281 Ardouin C, Pillon B, Peiffer E et al. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: A consecutive series of 62 patients. *Annals of Neurology.* 1999; 46(2):217–223. Ref ID: 19702

282 Minguez-Castellanos A, Escamilla-Sevilla F, Katati MJ et al. Different patterns of medication change after subthalamic or pallidal stimulation for Parkinson's disease: target related effect or selection bias? *Journal of Neurology, Neurosurgery & Psychiatry.* 2005; 76(1):34–39. Ref ID: 19885

283 Ondo W, Dat VK, Almaguer M et al. Thalamic deep brain stimulation: effects on the nontarget limbs. *Movement Disorders.* 2001; 16(6):1137–1142. Ref ID: 19704

284 Benabid AL, Pollak P, Seigneuret E et al. Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. *Acta Neurochirurgica Supplement (Wien).* 1993; 58:39–44. Ref ID: 19728

285 Krauss JK, Simpson RK, Jr., Ondo WG et al. Concepts and methods in chronic thalamic stimulation for treatment of tremor: technique and application. *Neurosurgery.* 2001; 48(3):535–541. Ref ID: 19705

286 Karlsen KH, Larsen JP, et al. Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 1999; 66(4):431–435. Ref ID: 19758

287 Hely MA, Morris JG, Reid J et al. Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Movement Disorders.* 2005; 20(2):190–199. Ref ID: 19892

288 Chaudhuri KR, Schapira A, Martinez-Martin P et al. The holisitic management of Parkinsons' disease using a novel non-motor symptom scale and questionnaire. *Advances in Clinical Neurosciences and Rehabilitation.* 2004; 4:20–24. Ref ID: 19893

289 Goetz CG, Koller WC, Poewe W et al. Treatment of depression in idiopathic Parkinson's disease. *Movement Disorders.* 2002; 17(suppl 4):S112–S119. Ref ID: 19760

290 Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? *Journal of Neurology, Neurosurgery & Psychiatry.* 2000; 69:308–312. Ref ID: 19887

291 Shabnam G, Chung TH, Deane KHO et al. Therapies for depression in Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2003;(2):CD003465. Ref ID: 78

292 Fregni F, Santos CM, Myczkowski ML et al. Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 2004; 75(8):1171–1174. Ref ID: 19761

293 Leentjens AF, Vreeling FW, Luijckx GJ et al. SSRIs in the treatment of depression in Parkinson's disease. *International Journal of Geriatric Psychiatry.* 2003; 18(6):552–554. Ref ID: 19762

294 Wermuth L, Sorensen PS, Timm S et al. Depression in idiopathic Parkinson's disease treated with citalopram. A placebo-controlled trial. *Nordic Journal of Psychiatry.* 1998; 52(2):163–169. Ref ID: 19772

295 Andersen J, Aabro E, Gulmann N et al. Anti-depressive treatment in Parkinson's disease. A controlled trial of the effect of nortriptyline in patients with Parkinson's disease treated with L-DOPA. *Acta Neurologica Scandinavica.* 1980; 62(4):210–219. Ref ID: 19771

296 Rabey J, Orlov E, Korczyn A. Comparison of fluvoamine versus amitriptyline for treatment of depression in Parkinson's disease. *Neurology.* (Abstract) 1996; 46:A374. Ref ID: 19788

297 Jiménez-Jiménez FJ, Tejeiro J, Martinez-Junquera G et al. Parkinsonism exacerbated by paroxetine. *Neurology.* 1994; 44(12):2406. Ref ID: 19895

298 Richard IH, Kurlan R, Tanner C et al. Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Parkinson Study Group. *Neurology.* 1997; 48(4):1070–1077. Ref ID: 20123

299 Fenelon G, Mahieux F, Huon R et al. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain.* 2000; 123:733–745. Ref ID: 19888

300 Graham JM, Grunewald RA, Sagar HJ. Hallucinosis in idiopathic Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 1997; 63:434–440. Ref ID: 19889

301 Friedman J, Lannon M, Cornelia C et al. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *New England Journal of Medicine.* 1999; 340(10):757–763. Ref ID: 19775

302 Ondo WG, Levy JK, Vuong KD et al. Olanzapine treatment for dopaminergic-induced hallucinations. *Movement Disorders.* 2002; 17(5):1031–1035. Ref ID: 19778

303 Breier A, Sutton VK, Feldman PD et al. Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease. *Biological Psychiatry.* 2002; 52(5):438–445. Ref ID: 19776

304 Pollak P, Tison F, Rascol O et al. Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. *Journal of Neurology, Neurosurgery & Psychiatry.* 2004; 75(5):689–695. Ref ID: 19779

305 Ondo W, Tintner R, Dat VK et al. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Movement Disorders.* 2005; 20(8):958–963. Ref ID: 19933

306 Goetz CG, Blasucci LM, Leurgans S et al. Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. *Neurology.* 2000; 55(6):789–794. Ref ID: 264

307 Morgante L, Epifanio A, Spina E et al. Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. *Clinical Neuropharmacology.* 2004; 27(4):153–156. Ref ID: 290

308 Ellis T, Cudkowicz ME, Sexton PM et al. Clozapine and risperidone treatment of psychosis in Parkinson's disease. *Journal of Neuropsychiatry & Clinical Neurosciences.* 2000; 12(3):364–369. Ref ID: 19781

309 Bain PG. The management of tremor. *Neurology in Practice.* 2002; 72(5 suppl 1):i3–i9. Ref ID: 2727

310 Message from Professor Gordon Duff, Chairman Committee on Safety of Medicines. *Atypical antipsychotic drugs and stroke.* Available from: www.mhra.gov.uk/home. Date of message: 3 September 2004. Ref ID: 19907

311 Aarsland D, Andersen K, Larsen JP et al. Prevalence and characteristics of dementia in Parkinson's disease: an 8 year prospective study. *Archives of Neurology.* 2003; 60:387–392. Ref ID: 19890

312 Aarsland D, Larsen JP, Karlsen KH et al. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. *International Journal of Geriatric Psychiatry.* 1999; 14:866–874. Ref ID: 19891

313 Emre M, Aarsland D, Albanese A et al. Rivastigmine for dementia associated with Parkinson's disease. *New England Journal of Medicine.* 2004; 351(24):2509–2518. Ref ID: 231

314 Leroi I, Brandt J, Reich S et al. Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. *International Journal of Geriatric Psychiatry.* 2004; 19(1):1–8. Ref ID: 243

315 Pakrasi S, Mukaetova-Ladinska EB, McKeith IG et al. Clinical predictors of response to Acetyl Cholinesterase Inhibitors: experience from routine clinical use in Newcastle. *International Journal of Geriatric Psychiatry.* 2003; 18(10):879–886. Ref ID: 19981

316 Ravina B, Putt M, Siderowf A et al. Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study. *Journal of Neurology, Neurosurgery & Psychiatry.* 2005; 76(7):934–939. Ref ID: 19948

317 Aarsland D, Laake K, Larsen JP et al. Donepezil for cognitive impairment in Parkinson's disease: A randomised controlled study. *Journal of Neurology, Neurosurgery & Psychiatry.* 2002; 72(6):708–712. Ref ID: 19965

318 Giladi N, Shabtai H, Gurevich T et al. Rivastigmine (Exelon) for dementia in patients with Parkinson's disease. *Acta Neurologica Scandinavica.* 2003; 108(5):368–373. Ref ID: 19967

319 Aarsland D, Hutchinson M, Larsen JP. Cognitive, psychiatric and motor response to galantamine in Parkinson's disease with dementia. *International Journal of Geriatric Psychiatry.* 2003; 18(10):937–941. Ref ID: 19958

320 Wild R, Pettit T, Burns A. Cholinesterase inhibitors for dementia with Lewy bodies (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2003;(3):CD003672. Ref ID: 19787

321 McKeith I, Del Ser T, Spano P et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet.* 2000; 356:2031–2036. Ref ID: 208

322 Barone P, Amboni M, Vitale C et al. Treatment of nocturnal disturbances and excessive daytime sleepiness in Parkinson's disease. *Neurology.* 2004; 63(8 (Suppl 3)):S35–S38. Ref ID: 19898

323 Chaudhuri KR, Forbes A, Grosset DG et al. Diagnosing restless legs syndrome (RLS) in primary care. *Current Medical Research Opinion.* 2004; 20(11):1785–1795. Ref ID: 19902

324 Frucht S, Rogers JD, Greene PE et al. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology.* 1999; 52:1908–1910. Ref ID: 19896

325 Adler CH, Caviness JN, Hentz JG et al. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Movement Disorders.* 2003; 18(3):287–293. Ref ID: 2780

326 Hogl B, Saletu M, Brandauer E et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. *Sleep.* 2002; 25(8):905–909. Ref ID: 2781

327 Ondo WG, Fayle R, Atassi F et al. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. *Journal of Neurology, Neurosurgery & Psychiatry.* 2005; 76(12): 1636–1639. Ref ID: 20116

328 The UK Madopar CR Study Group. A comparison of Madopar CR and standard Madopar in the treatment of nocturnal and early-morning disability in Parkinson's disease. *Clinical Neuropharmacology.* 1989; 12(6):498–505. Ref ID: 19641

329 Ashburn A, Stack E, Pickering RM et al. A community-dwelling sample of people with Parkinson's disease: characteristics of fallers and non-fallers. *Age & Ageing.* 2001; 30:47–52. Ref ID: 19858

330 Schrag A, Ben Shlomo Y, Quinn N. How common are the complications of Parkinson's disease? *Journal of Neurology.* 2002; 294(4):419–423. Ref ID: 19859

331 Wenning GK, Ebersbach G, Verny M et al. Progression of falls in post-mortem-confirmed Parkinsonian disorders. *Movement Disorders.* 2001; 14(6):947–950. Ref ID: 19860

332 Schaafsma JD, Giladi N, Balash Y et al. Gait dynamics in Parkinson's disease:relationship to parkinsonian features, falls and response to levodopa. *Journal of Neurological Sciences.* 2003; 212:47–53. Ref ID: 19861

333 Bloem BR, Grimbergen YA, Cramer M et al. Prospective assessment of falls in Parkinson's disease. *Journal of Neurology.* 2001; 248(11):950–958. Ref ID: 19862

334 Wielinski CL, Erickson-Davis C, Wichmann R et al. Falls and injuries resulting from falls among patients with Parkinson's disease and other Parkinsonian syndromes. Early view published online in advance of print. *Movement Disorders.* 2004;(Dec 3) Ref ID: 19863

335 National Institute for Health and Clinical Excellence. *Falls: The assessment and prevention of falls in older people. Quick reference guide.* (Clinical Guideline 21). London: National Institute for Health and Clinical Excellence, 2004. Ref ID: 20126

336 Abbott R, Cox M, Markus HS et al. Diet, body size and micronutrient status in Parkinson's disease. *European Journal of Clinical Nutrition.* 1992; 46:879–884. Ref ID: 19791

337 Kempster PA, Wahlqvist ML. Dietary factors in the management of Parkinson's disease. *Nutrition Reviews.* 1994; 52:51–58. Ref ID: 19801

338 Gazewood JD, Mehr R. Diagnosis and Management of weight loss in the elderly. *Journal of Family Practice.* 1998; 47(1):19–25. Ref ID: 19934

339 Nilsson H, Ekberg O, Olsson R et al. Quantitative assessment of oral and pharyngeal function in Parkinson's Disease. *Dysphagia.* 1996; 11(2):144–150. Ref ID: 19923

340 Logemann JA, Blonsky ER, Boshe SE. Dysphagia in parkisonism. *Journal of the American Medical Association.* 1975; 231(1):69–70. Ref ID: 19924

341 Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. *Neurology.* 1967; 17:427–442. Ref ID: 19930

342 Hunter PC, Crameri J, Austin S et al. Response of parkinsonian swallowing dysfunction to dopaminergic stimulation. *Journal of Neurology, Neurosurgery & Psychiatry.* 1997; 63:579–583. Ref ID: 19799

343 Sonies BC. Patterns of care for dysphagic patients with degenerative neurological diseases. *Seminars in Speech and Language Therapy.* 2000; 21:4. Ref ID: 19932

344 Duranceau A. Cricopharyngeal myotomy in the management of neurogenic and muscular dysphagia. *Neuromuscular Disorders.* 1997;(Suppl 1):S85–S89. Ref ID: 19931

345 Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurology.* 2003; 2:107–116. Ref ID: 19802

346 Ashraf W, Pfeiffer R, Park F et al. Constipation in Parkinson's disease: objective assessment and response to psyllium. *Movement Disorders.* 1997; 12:946–951. Ref ID: 19793

347 Gruss HJ, Ulm G. Efficacy and tolerability of PEG 3350 plus electrolytes (Movicol) in chronic constipation associated with Parkinson's disease. *European Journal of Geriatrics.* 2004; 6:143–150. Ref ID: 19798

348 Stocchi F, Carbone A, Inghilleri M et al. Urodynamic and neurophysiological evaluation in Parkinson's disease and multiple system atrophy. *Journal of Neurology, Neurosurgery & Psychiatry.* 1997; 62:507–511. Ref ID: 19805

349 Bronner G, Royter V, Korczyn A et al. Sexual dysfunction in Parkinson's disease. *Journal of Sex and Marital Therapy.* 2004; 30:95–105. Ref ID: 19794

350 Singer C, Weiner WJ, Sanchez-Ramos J. Autonomic dysfunction in men with Parkinson's disease. *European Neurology.* 1992; 32:134–140. Ref ID: 19804

351 Allcock LM, Ullyart K, Kenny R et al. Frequency of orthostatic hypotension in a community acquired cohort of patients with Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 2003; 75:1470–1471. Ref ID: 19792

352 Senard JM, Rai S, Lapeyre-Mestre M et al. Prevalence of orthostatic hypotension in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 1997; 63:584–589. Ref ID: 19803

353 Kaufmann H. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. *Clinical Autonomic Research.* 1996; 6:125–126. Ref ID: 19800

354 Edwards LL, Pfeiffer R, Quigley E et al. Gastrointestinal symptoms in Parkinson's disease. *Movement Disorders.* 1991; 6:151–156. Ref ID: 19796

355 Boyce HW, Bakheet MR. Sialorrhea: a review of a vexing, often unrecognized sign of oropharyngeal and esophageal disease. *Journal of Clinical Gastroenterology.* 2005; 39(2):89–97. Ref ID: 19936

356 Marks L, Turner K, O'Sullivan J et al. Drooling in Parkinson's disease: A novel speech and language therapy Intervention. *International Journal of Language and Communication Disorders.* 2001; 36(Suppl):282–287. Ref ID: 19922

357 Hyson HC, Johnson AM, Jog MS. Sublingual atropine for sialorrhea secondary to parkinsonism: a pilot study. *Movement Disorders.* 2002; 17(6):1318. Ref ID: 19935

358 Sullivan JD, Bhatia KP, Lees AJ. Botulinum toxin A as a treatment for drooling saliva in PD. *Neurology.* 2000; 55:606–607. Ref ID: 19806

359 Ford B. Pain in Parkinson's disease. *Clinical Neuroscience.* 1998; 5:63–72. Ref ID: 19897

360 Parkinson's Disease Society. *Competencies: an integrated career and competency framework for nurses working in PD management.* London: Parkinson's Disease Society, 2005. Ref ID: 19937

361 Bell L. *Changing roles: the impact of Parkinson's disease nurse specialists.* London: Parkinson's Disease Society, 2004. Ref ID: 787

362 Jarman B, Hurwitz B, Cook A. Effects of community based nurses specialising in Parkinson's disease on health outcome and costs: randomised controlled trial. *British Medical Journal.* 2002; 324(7345): 1072–1075. Ref ID: 223

363 Jahanshahi M, Brown RG, Whitehouse C et al. Contact with a nurse practitioner: A short-term evaluation study in Parkinson's disease and dystonia. *Behavioural Neurology.* 1994; 7(3–4):189–196. Ref ID: 200

364 Reynolds H, Wilson-Barnett J, Richardson G. Evaluation of the role of the Parkinson's disease nurse specialist. *International Journal of Nursing Studies.* 2000; 37(4):337–349. Ref ID: 744

365 Hobson P, Roberts S, Meara J. The economic value of a Parkinson's disease nurse specialist service. *Health and Ageing.* (3); ii–iii. 2003. Ref ID: 19668

366 The Chartered Society of Physiotherapy. *The Curriculum Framework for qualifying programmes in physiotherapy.* London: The Chartered Society of Physiotherapy, The Council for Professions Supplementary to Medicine, 1996. Ref ID: 19660

367 *Physical therapy management of Parkinson's disease (clinics in physical therapy).* New York: Churchill Livingston; 1992. Ref ID: 19678

368 Deane KHO, Jones D, Playford ED et al. Physiotherapy versus placebo or no intervention in Parkinson's disease.(Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2001;(3):CD002817. Ref ID: 90

369 Bergen JL, Toole T, Elliott RG, III et al. Aerobic exercise intervention improves aerobic capacity and movement initiation in Parkinson's disease patients. *NeuroRehabilitation.* 2002; 17(2):161–168. Ref ID: 2778

370 Stallibrass C, Sissons P, Chalmers C. Randomized controlled trial of the Alexander technique for idiopathic Parkinson's disease. *Clinical Rehabilitation.* 2002; 16(7):695–708. Ref ID: 2779

371 Schenkman M, Cutson TM, Kuchibhatla M et al. Exercise to improve spinal flexibility and function for people with Parkinson's disease: a randomized, controlled trial. *Journal of the American Geriatrics Society.* 1998; 46(10):1207–1216. Ref ID: 498

372 Thaut MH, McIntosh GC, Rice RR et al. Rhythmic auditory stimulation in gait training for Parkinson's disease patients. *Movement Disorders.* 1996; 11(2):193–200. Ref ID: 19573

373 Hurwitz A. The benefit of a home exercise regimen for ambulatory Parkinson's disease patients. *Journal of Neuroscience Nursing.* 1989; 21(3):180–184. Ref ID: 415

374 Patti F, Reggio A, Nicoletti F et al. Effects of rehabilitation therapy on Parkinson's disability and functional independence. *Journal of Neurologic Rehabilitation.* 1996; 10(4):223–231. Ref ID: 19572

375 World Federation of Occupational Therapists. *World federation of Occupational therapists definition 2004.* Available from: www wfot com/ [accessed 20 April 2006]. Ref ID: 19869

376 Birleson A. Occupational therapy in Parkinson's disease. *Geriatric Medicine.* 1998; 28(1) Ref ID: 19866

377 Deane HO, Ellis-Hill C, Dekker K et al. A survey of current OT practice for Parkinson's Disease in the UK. *British Journal of Occupational Therapy.* 2003; 66(5):193–200. Ref ID: 19867

378 Aragon A. Physical therapies keep your independence with the help of Occupational therapy. *The Parkinson.* 2004;19–20. Ref ID: 19865

379 Deane KHO, Ellis-Hill C, Playford ED et al. Occupational therapy for Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2001;(2):CD002813. Ref ID: 72

380 Gauthier L, Dalziel S, Gauthier S. The benefits of group occupational therapy for patients with Parkinson's disease. *The American Journal of Occupational Therapy.* 1987; 41(6):360–365. Ref ID: 19739

381 Fiorani CF, Mari F, Bartolini M et al. Occupational therapy increases ADL score and quality of life in Parkinson's disease. *Movement Disorders.* 1997; 121:135. Ref ID: 19738

382 Erb E. Improving speech in Parkinson's disease. *American Journal of Nursing.* 1973; 73:1910–1911. Ref ID: 19877

383 Scott S, Caird FI. Speech Therapy for Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 1983; 47:140–144. Ref ID: 19881

384 Robertson SJ, Thomson F. Speech therapy in Parkinson's disease: a study of the efficacy and long term effects of intensive treatment. *British Journal of Disorders of Communication.* 1984; 19:213–224. Ref ID: 19769

385 Hanson W, Metter E. DAF speech rate modification in Parkinson's disease; a report of two cases. In Berry W (ed), *Clinical disarthria.* Austin, TX: ProEd, 1983:231–254. Ref ID: 19878

386 Rubow R, Swift E. A micro-computer based wearable biofeedback device to improve transfer of treatment in parkinsonian Dysarthria. *Journal of Speech and Hearing Disorders.* 1985; 50:166–178. Ref ID: 19880

387 Deane KHO, Whurr R, Playford ED et al. Speech and language therapy versus placebo or no intervention for dysarthria in Parkinson's disease (Cochrane Review). *The Cochrane Database of Systematic Reviews.* 2001;(2):CD002812. Ref ID: 77

388 Johnson JA, Pring TR. Speech Therapy and Parkinson's disease: A review and further data. *British Journal of Disorders of Communication.* 1990; 25:183–194. Ref ID: 19767

389 Ramig LO, Sapir S, Fox C et al. Changes in vocal loudness following intensive voice treatment (LSVT) in individuals with Parkinson's disease: a comparison with untreated patients and normal age-matched controls. *Movement Disorders.* 2001; 16(1):79–83. Ref ID: 19768

390 Ramig LO, Sapir S, Countryman S et al. Intensive voice treatment (LSVT) for patients with Parkinson's disease: a 2 year follow up. *Journal of Neurology, Neurosurgery & Psychiatry.* 2001; 71(4):493–498. Ref ID: 19770

391 Baumgartner CA, Sapir S, Ramig TO. Voice quality changes following phonatory-respiratory effort treatment (LSVT) versus respiratory effort treatment for individuals with Parkinson disease. *Journal of Voice.* 2001; 15(1):105–114. Ref ID: 20028

392 Sapir S, Ramig LO, Hoyt P et al. Speech loudness and quality 12 months after intensive voice treatment (LSVT) for Parkinson's disease: a comparison with an alternative speech treatment. *Folia Phoniatrica et Logopaedica* 2002; 54(6):296–303. Ref ID: 20029

393 Deane KH, Whurr R, Playford ED et al. Speech and language therapy for dysarthria in Parkinson's disease. *The Cochrane Database of Systematic Reviews.* 2001;(2):CD002814. Ref ID: 20030

394 World Health Organisation. *WHO definition of palliative care.* Available from: www who int/cancer/palliative/definition/en/ [accessed 27 March 2006]. Ref ID: 20127

395 O'Brien T, Welsh J, Dunn FG. ABC of palliative care. Non-malignant conditions. *British Medical Journal.* 1998; 316(7127):286–289. Ref ID: 19938

396 Scott S ,Meadowcroft RS. *Just invisible: a summary.* London: Parkinsons Disease Society, 2005. Ref ID: 19944

397 MacMahon DG, Thomas S. Practical approach to quality of life in Parkinson's disease: the nurse's role. *Journal of Neurology.* 1998; 245(Suppl1):S19–S22. Ref ID: 748

398 MacMahon DG, Thomas S, Campbell S. Validation of pathways paradigm for the management of PD. *Parkinsonism & Related Disorders.* 1999; 5(S53) Ref ID: 19912

399 Parkinson's Disease Society. *Carers' assessment.* (FS46). London: Parkinson's Disease Society, 2003. Ref ID: 19945

400 Buchanan S,Willis E. *Carers' guide.* London: Parkinson's Disease Society, 2004. Ref ID: 19946

401 Goetz CG, Stebbins GT. Risk factors for nursing home placement in advanced Parkinson's disease. *Neurology.* 1993; 43:2227–2229. Ref ID: 19914

402 Goetz CG, Stebbins GT. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. *Neurology.* 1995; 45:669–671. Ref ID: 19913

403 Mitchell SL, Kiely DK, Kiel DP et al. The epidemiology, clinical characteristics, and natural history of older nursing home residents with a diagnosis of Parkinson's disease. *Journal of the American Geriatrics Society.* 1996; 44(4):394–399. Ref ID: 19915

404 Thomas S, Macmahon D. Parkinson's disease, palliative care and older people: Part 2. *Nursing Older People*. 2004; 16(2):22–26. Ref ID: 19692

405 Thomas S, Macmahon D. Parkinson's disease, palliative care and older people: Part 1. *Nursing Older People*. 2004; 16(1):22–26. Ref ID: 19693

406 Thomas S, Macmahon D. Managing Parkinson's disease in long-term care. *Nursing Older People*. 2002; 14(9):23–30. Ref ID: 20128

407 National Institute for Health and Clinical Excellence. *Pressure relieving devices*. London: National Institute for Health and Clinical Excellence, 2003. Ref ID: 19917

408 National Institute for Health and Clinical Excellence. *Pressure ulcer risk management and prevention (Guideline B)*. London: National Institute for Health and Clinical Excellence, 2003. Ref ID: 19916

409 Royal College of Nursing. *Pressure ulcer risk assessment and prevention: implementation guide and audit protocol*. Oxford: Royal College of Nursing, 2003. Ref ID: 19918

410 Howards A, Pemberton C, and Storey L. *The preferred place of care plan (PPC)*. Lancashire: Lancashire and South Cumbria Cancer Network, 2004. Ref ID: 19919

411 Macmillan Cancer Relief. *Gold standards framework*. London: Macmillan Cancer Relief, 2005. Ref ID: 19920

412 Liverpool Care Pathway. *Liverpool care pathway for the dying patient*. Liverpool: Liverpool Care Pathway, 2005. Ref ID: 19921

413 Northumbria University, Katholieke Universiteit, Vrije Universiteit. *The rescue project*. Available from: www rescueproject org/overview/welcome/html [accessed on 2 March 2006]. Ref ID: 20121

414 Moher D, Schulz K, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*. 2001; 357:1191–1194. Ref ID: 19448

415 Thomas S, Macmahon D, Maguire J. *Moving and shaping: a guide to commissioning integrated services for people with Parkinson's disease*, 2nd edn. London: Parkinson's Disease Society, 2006. Ref ID: 41

416 Nicholson T, Milne R. *Pallidotomy, thalamotomy and deep brain stimulation for severe Parkinson's disease*. Southampton: Wessex Institute for Health Research and Development, 1999. Ref ID: 43

417 Bhatia K, Brooks DJ, Burn DJ et al. Updated guidelines for the management of Parkinson's disease. *Hospital Medicine (London)*. 2001; 62(8):456–470. Ref ID: 9

418 Curtis L, Netten A. *Unit costs of health and social care data 2004*. Personal Social Services Research Unit, University of Kent. Canterbury: 2004. Available from: www.pssru.ac.uk/uc/uc2004.htm

PARKINSONS DISEASE EVIDENCE TABLES

COMM1 – section 4

Evidence Table **COMM 1** What approach to patient engagement best aids patient understanding of the diagnosis of Parkinson's disease?	
Bibliographic reference	Habermann, B. 1996, "Day-to-day demands of Parkinson's disease", *Western Journal of Nursing Research*, vol. 18, no. 4, pp. 397-413.
Study type	Qualitative study: interpretative phenomenology
Evidence level	3
Number of patients	N=16 Location: San Francisco, USA
Patient characteristics	➢ 9 men; 7 women ➢ Recruitment: various neurology practices and Parkinson support groups in the greater San Francisco Bay area ➢ Age range: 42 to 59 years (mean=48 years) ➢ Majority were Caucasian (94%) ➢ Time since diagnosis: 11/16 less than 5 years; 4/16 less than 10 years, 1/16 diagnosed 16 years ➢ Level of disease severity: ranged from stage I-III on the Hoehn and Yahr scale ➢ Majority had bilateral disease (75%) (Stages II- III)
Intervention	Interviews: ''participants interviewed on 3 occasions during a 3-month period by the investigator. Interviews on average lasted 1 hour to 1½ hour. Interviews were tape recorded and transcribed verbatim''.
Comparison	N/A

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Length of follow-up	3 month
Outcome measures	Day-to-day demands experienced by the Parkinson's disease patient (included gaining formal knowledge)
Results	➢ ''Once diagnosed, patients identified a need to know more about Parkinson's disease. Information provided at diagnosis was difficult to process by most participants. By their own descriptions, they were in 'shock' and did not recall the dialogue between themselves and the diagnosing physicians. There were a few exceptions to this; some clearly recalled being given a diagnosis but very little additional information''. ➢ ''The human significance was passed over and objectified by what is known about the disease and treatment. Self-care and day-to-day coping with the illness were ignored''. ➢ ''….the first months to a year after diagnosis often were spent reading 'whatever I could get my hands on' participants confronted the limits of formal knowledge. They began to acknowledge that their experiences mattered and that they knew what was best for themselves''. ➢ ''Participants came to see the limits of such 'book knowledge' and began to develop experimental or practical knowledge''.
Source of Funding	National Research Service Award from the National Institute of Nursing
Additional comments	➢ **Aim**: ''to explore the demands experienced by middle-aged persons with Parkinson's disease' ➢ Interviews were semi-structured using an interview guide to ensure that all areas were discussed ➢ Three interrelated interpretative strategies (thematic analysis, analysis of exemplars, and search for paradigm cases) were used to recognize meanings and patterns in the text of the interview ➢ Interpretations were presented to several Parkinson's disease support groups who provided feedback indicating that they could identify with the interpretations ➢ Several paradigm cases were also shared with the individuals for validation ➢ 8 themes of 'demands' for the day-to-day PD patient were described- one of which was question-specific (Gaining formal Knowledge) and the results were listed above in the 'results section' ➢ validation of interpretations
Citation	
NCC CC ID (Ref Man)	65

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Evidence Table
COMM1
What approach to patient engagement best aids patient understanding of the diagnosis of Parkinson's disease?

Bibliographic reference	Montgomery, E. B., Jr., Lieberman, A., Singh, G., & Fries, J. F. 1994, "Patient education and health promotion can be effective in Parkinson's disease: a randomized controlled trial. PROPATH Advisory Board.", *American Journal of Medicine*, vol. 97, no. 5, pp. 429-435.
Study type	RCT: questionnaire format
Evidence level	1+
Number of patients	N=155 experimental PROPATH group N=167 controls Location: USA
Patient characteristics	➢ Patients had self-reported Parkinson's disease independently confirmed by their physicians ➢ No statistically significant differences between groups at baseline for age, disease duration, disease severity, side effects, and summary variables (they exercised similarly, experiences similar problems with disease, and disease state was progressing at similar rates)
Intervention The PROPATH program:	➢ One page, patient questionnaires completed at 0, 2, 4 & 6 months ➢ Educational materials including pamphlets were provided to intervention group (no specified detail) ➢ Computer-generated individualized recommendation letters and a report summarizing progress was provided to intervention patients ➢ Reports included recommendations such as exercise as appropriate for age, disease severity, co-morbidity, present exercise level, diet, compliance, side effect control, and information about specific reported problems ➢ In each 2 month cycle physicians were provided a report of suggestions made to the patient and additional suggestions to be considered by the physician ➢ At 6 months, a quality-of-life test battery was administered to each group
Comparison	Standard medical care
Length of follow-up	6 months
Outcome measures	See effect size table for list of reported clinical and quality-of-life outcomes
Effect size	Difference in clinical outcomes at baseline and final 6 month observation (NS= not significant):

Clinical Outcomes	**Intervention (Mean)**	**Control (Mean)**	**P value**

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	Parkinson's on-score	22.1	24.6	NS
	Parkinson's off-score	**30.6**	**35.2**	**0.04**
	Percent off	39.2	38.6	NS
	Patient global assessment	40.8	43.3	NS
	Summary score	28.9	31.9	NS
	End of dose (%)	48.1	51.4	NS
	On/off problem (%)	32.1	30.5	NS
	Rate of progression during program	**0.07**	**3.48**	**0.03**
	Exercise %	**76.4**	**61.3**	**0.006**
	Exercise (sessions/week)	8.7	7.7	NS
	Levodopa (%/dose)	88/502.2	89/561.6	NS
	Bromocriptine (%/dose)	24/11.2	25/13.4	NS
	Selegiline (%/dose)	59/9.0	53/9.2	NS
	Side effects index	22.2	24.3	NS
	Doctor visits (per 6 months)	**2.5**	**3.1**	**0.06**
	Hospital days (per 6 months)	0.5	1.0	NS
	Sick days (per 6 months)	4.6	5.9	NS

Differences in Quality-of-life assessment in final observation

Quality-of-Life Outcomes	Intervention	Control	P value
Patient global assessment	41.0	43.5	NS
Self-efficacy (controlling symptoms)	297.0	256.0	P<0.05
Self-efficacy (improved timed function of daily activities)	267.0	237.0	P<0.05
Self-efficacy (management of disease problems)	340.0	302.0	P<0.05
Total self-efficacy (sum of above 3 categories)	904.0	795.0	P<0.01
Spousal stress (n =100,102)	35.0	38.2	NS
Spousal assessment (n= 100, 102)	12.1	11.3	NS

- Patient global assessment favoured the intervention group but was not statistically significant

Source of Funding	Supported by a grant from Sandoz Pharmaceuticals
Additional comments	➢ **Aim**: ''to evaluate the effectiveness a patient education and health promotion program in the

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	treatment of Parkinson's disease''. ➢ Investigators are members of the PROPATH Advisory Board (bias the interpretation of results?) ➢ Investigators do not report blinding to patient group allocation in data analysis ➢ 75% of patients were seen by neurologists ➢ Diagnoses not confirmed by investigators ➢ Physician feedback on value of PROPATH not stated ➢ 400 consecutive enrolment cards from the ongoing PROPATH program were selected for randomisation ➢ Patients already enrolled in the PROPATH program? (Controls apparently received the full program after the study? But they were already enrolled with PROPATH??) ➢ Differences in the length of time enrolled not specified? ➢ 140/155 experimental group patients and 150/167 controls completed the 6 mo study ➢ Low cost, mail delivered, patient education and health promotion program ➢ The author's state: ''the program reduced progression as measured by a Parkinson's Summary Score compared with controls, improved the frequency of exercise, improved health confidence, reduced medication requirements, and decreased physician visitation''. ➢ Author's suggest some of improvements seen in the intervention group may be due to better patient-physician discussions due to PROPATH summary reports ➢ America-based program…generalizability to UK questionable? ➢ PROPATH enrolment 1-800 number provided in methods section? ➢ Patients who are currently receiving two specific drugs (one a Sandoz drug) are able to receive free continuation of the PROPATH program (normally offered for 9-months free to patients on any drug) ➢ Longer trial follow-up may improve the outcomes of this intervention?
Citation	
NCC CC ID (Ref Man)	737

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Evidence Table
COMM1
What approach to patient engagement best aids patient understanding of the diagnosis of Parkinson's disease?

Bibliographic reference	Findley, L., Eichhorn, T., Janca, A., Kazenwadel, J., Baker, M., Currie-Gnjesda, D., Koller, W., Liebermann, A., Mizuno, Y., Rajput, A., Roy, S., Stocchi, F., & Tolosa, E. 2002, "Factors impacting on quality of life in Parkinson's disease: Results from an international survey", *Movement Disorders*, vol. 17, no. 1, pp. 60-67.
Study type	Qualitative: cross-sectional, randomised selection, multi-national survey of clinicians, patients with PD and their caregivers
Evidence level	3
Number of patients	

Country	No. Clinicians	No. Patients	No. Caregivers
UK	41	201	176
Italy	41	205	133
Spain	40	200	106
USA	38	185	110
Canada	23	128	99
Japan	20	101	63
Total	203	1020	687

Patient characteristics

- Subjects randomly selected from the patient lists of specialists were invited to participate in a randomised manner until 5 patients had been recruited from each specialist clinician

Entry criteria:

- Patients who had a mini-mental state examination (MMSE) $\leq$ 23
- Patients included in the analysis has a mean MMSE of 28.4 $\pm$ 1.7
- Or exhibited extreme response set on Parkinson's disease Questionnaire (PDQ)-39

- Patients included in the analysis had a mean PDQ-39 score of 32.2 $\pm$ 19.7
- Median Hoehn and Yahr score was 2.5 $\pm$ 1.0
- Majority of patients were male (60%); ages 60-74 years (mean 67.8 $\pm$ 9.8%)
- 77% had access to a caregiver; which was usually their partner 72.8%
- Range of concomitant conditions: arthritis (14%), heart disease (13%), depression (1%)
- Mean duration since diagnosis of PD was 7.4 $\pm$ 5.8 years
- Majority of patients were taking levodopa (either in mono- or combined therapy) (89.3%)

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	➢ Hoehn and Yahr scores: 45.1% of patients scored ≥ 3.0, and 16.9% scored 4.0 and 5.0 (median score 2.5 ± 1.0) ➢ Average MMSE was 27.2 ± 3.6; mean BDI score was 12.4 ± 9.2 (50% of patients had a score above 10% and were therefore considered at least mildly depressed)
Intervention	Questionnaire based on factors affecting HRQL, grouped into 6 domains: 1. Process of communicating the clinical diagnosis 2. Specialist clinicians' use of information and holistic therapies 3. The ability of patients to gain the information and contact they require 4. Patients' use of holistic therapies 5. Patients' emotional state (including depression) 6. Patients' access to and use of a patient support group Each domain consisted of one or more factors which were assessed and evaluated independently
Comparison	N/A
Length of follow-up	N/A
Outcome measures	Health-related quality of life scores (HRQL)
Effect size	➢ Hoehn and Yahr (H&Y) (disease severity) was a significant predictor of HRQL (p<0.05) ➢ Only levodopa (either in mono or combination therapy) was a significant predictor of HRQL score than H&Y alone (p<0.05) ➢ 17.3% of the variability in HRQL scores across the cohort of patients can be explained if H&Y stage and medication are known ***Other factors that significantly contribute to variability in HRQL scores*** ➢ Depression as measured by BDI had an large impact on HRQL p<0.001 ➢ ''Satisfaction with explanation of condition at diagnosis'' small but significant effect p<0.05 ➢ ''Current feelings of optimism'' p<0.05 ➢ These three factors can explain 59.7% of variability in HRQL between patients
Source of Funding	F.Hoffman-La Roche Ltd
Additional comments	➢ **Aim**: to assess the health-related quality of life of people with PD, and to systematically identify and evaluate those factors (other than disease severity and medication) which could impact ➢ Data from 902 patients were included in the analysis (115 with MMSE ≤ 23 and 3 patients with an extreme response sets were excluded from the analysis) ➢ Author's state: ''satisfaction with the explanation of the condition at diagnosis is retrospective and may be influenced by events that have happened subsequently. However it can be speculated that

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	the relationship between this and HRQL reflects the importance of the diagnostic process as a first step in therapy as well as the first step in the coping process''. ➢ Author's suggest: ''further investigation is required to establish whether, prospectively, a strategy for imparting clear information about the disease at the time of diagnosis can be combined with the maintenance of optimism and enhancement of HRQL.
Citation	
NCC CC ID (Ref Man)	742

Evidence Table
COMM1
What approach to patient engagement best aids patient understanding of the diagnosis of Parkinson's disease?

Bibliographic reference	Mercer, B. S. 1996, "A randomized study of the efficacy of the PROPATH Program for patients with Parkinson disease." *Archives of Neurology*, vol. 53, pp. 881-884.
Study type	RCT: questionnaire format
Evidence level	1+
Number of patients	N= 50 PROPATH Group N= 23 usual treatment group Location: Boston, USA
Patient characteristics	Patients with diagnosed Parkinson's disease (PD) Exclusion criteria: ➢ Non-English speaking ➢ Hoehn and Yahr stage V No statistically significant differences in the analysis of patient characteristics which included:

Characteristics	**PROPATH**	**Controls**	***P***
Mean age (years)	66.7	65.0	0.14
Sex (male: female)	18:7	12:9	0.29

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	Hoehn and Yahr stage (I, II, III, IV)	2,12,8,3	2,10,8,1	0.67
	Race (white, black, Hispanic, missing)	23,2,0,0	18,0,1,2	0.60
	Martial status (married, widowed or divorced, never married, missing)	18,5,2,0	13,4,2,2	0.57
Intervention	PROPATH programme: health management program designed for patients with PD to be used in addition to standard medical care. Includes: an introductory videocassette, a series of educational pamphlets, and a periodic report mailed to patients and their physicians based on the patient completing regularly scheduled questionnaires. The questionnaire is scored on a system based on the UPDRS and a report is generated based on an algorithm developed by movement disorder experts. 3 questionnaires sent out: ➢ (1) Both groups completed a patient questionnaire (at 0, 3, 6, & 12 months) examining: patient-perceived health and psychological well-being, satisfaction with care, and demographics ➢ (2) The patient's physician were sent a questionnaire examining: physician's rating of the patient's health at onset and then 6 &12 months after the initiation of the PROPATH program ➢ (3) Physicians with patients participating in the PROPATH program (at 12 months after onset) completed another questionnaire to examine: physician's global assessment of the program.			
Comparison	Standard medical treatment			
Length of follow-up	12 months			
Outcome measures	Perception of general health and psychological well-being, satisfaction with care, health care utilization, and physician's rating of patient's health status and physician's global assessment (all measured for significance using p values)			
Effect size	➢ Patient **perception of general health and psychological well-being** improved over the 12 month period in the PROPATH group and declined in the standard care group (this reached statistical significance **p =0.04**) ➢ The specific factors addressed in the questionnaire under this topic (including: general health, disability days, fatigue, and a decrease in psychological distress) all slightly improved but did not reach statistical significance ➢ Patient satisfaction with care showed an increase from baseline in both groups, but there was no statistically significant difference ➢ Physician's rating of patient's health status declined over time in both groups (decline in control group is larger but not statistically significant p =0.26)			

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	➢ Health care utilization was measured by medical record review at the end of the study and this data did not show a significant difference between the two groups ➢ Physicians caring for patients enrolled in the PROPATH program rated the program as 'fair' or 'poor' for 80% of their patients ➢ In 88% of the cases the physicians thought the PROPATH programme should not be recommended for all patients with Parkinson's disease
Source of Funding	Sandoz Pharmaceuticals Inc (The PROPATH program is a product of this company)
Additional comments	➢ **Aim**: to assess the effects of the PROPATH program on patient-perceived general health and psychological well-being, satisfaction with medical care, utilization of health care resources ➢ The physician's impressions of the PROPATH Program were also assessed ➢ Although perception of general health and psychological well-being significantly improved in the PROPATH group, the author's state ''this appears to be a cumulative effect'' ➢ The improvements in this area the author's state ''are obtained in the absence of any benefit of the program or improvement in patient health as perceived by the treating neurologist'' ➢ Study was conducted from June 1992 to June 1993 ➢ Patients were recruited from a staff model health maintenance organization ➢ Patients were recruited from a total population of 300 000 members ➢ Patients were randomised by Hoehn and Yahr stage to the group receiving PROPATH program and the group receiving usual treatment ➢ Not possible to determine if patient sample, and therefore patient perceptions, are representative of general PD population ➢ America-based program…generalizability to UK questionable? ➢ Small population of patients which could affect the statistical power of the results ➢ Investigators do not report blinding to patient group allocation in data analysis ➢ Each patient's medical records were reviewed to confirm clinical diagnosis and assign Hoehn and Yahr stage ➢ Compliance with the program was not measured in this study ➢ Intention to treat analysis ➢ Explanations given for 4 patients not completing the program questionnaires (these patients not included in the data analysis)
Citation	
NCC CC ID (Ref Man)	739

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Evidence Table
COMM 1
What approach to patient engagement best aids patient understanding of the diagnosis of Parkinson's disease?

Bibliographic reference	Yarrow, S. 1999, *Survey of Members of the Parkinson's Disease Society*, Parkinson's Disease Society of the United Kingdom and Policy Studies Institute.
Study type	Survey
Evidence level	3
Number of patients	N=2,500 Location: UK
Patient characteristics	About 2/3 of respondents have Parkinson's disease; 12% were carers; 10% were formers carers of a person with the condition; 3% were professionals (almost all health care related); 9% belonged to PDS (mostly because they were friends or family of person with PD) 830 male respondents; 859 female respondents
Intervention	A self-completion questionnaire was sent to 2,500 members selected at random
Comparison	N/A
Length of follow-up	N/A
Outcome measures	% of respondents who answered in a particular category per question
Effect size	➢ 1802 completed questionnaires were received (72% response rate) ➢ The number of questionnaires received that were usable included 1,693

Whether the person had Parkinson's explained to them on diagnosis	
	% (N=1127)
Very clearly explained	20
Fairly clearly explained	24
Neither clearly nor unclear explained	9
Not very clearly explained	17
Not at all clearly explained	9
No explanation given	15

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Unsure/don't remember	3
Not answered	5

Whether people with Parkinson's disease were given an opportunity to ask questions on diagnosis	
	% (N=1127)
Adequate opportunity	28
Fairly adequate opportunity	22
No opportunity at all	15
Did not want/feel able to ask question at the time	22
Unsure/ don't remember	7
Not answered	7

Important points:

- 44% of respondents thought they had a clear explanation of the condition and what treatment was available when they were first diagnosed
- 15% said they were given no explanation at all
- 1 in 3 said they were given an opportunity to ask questions on diagnosis
- 22% thought they had adequate opportunity to do so
- 15% said they were given no opportunity
- There was little to no difference between men and women and whether they felt they were given a clear explanation or able to ask questions
- Nor were there any differences found in the above categories between regions
- People in manual occupations were more likely to say they had an unclear explanation (53%) than non-manual workers (27%)

How useful people find resources of information about Parkinson's				
	Very useful	Not very useful	Not used/not available	Did not answer

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				(N=1693)	
Hospital doctor/ consultant	56	19	14	12
PDS- local branch	40	7	36	17
GP	39	37	13	11
PDS-national office	36	9	36	19
People who have Parkinson's or care for someone with Parkinson's	36	7	36	21
Newspapers or magazines	32	24	26	19
Pharmacist	25	11	45	19
PD nurse specialist	24	3	56	17
Physiotherapist	23	9	50	18
Occupational therapist	19	7	56	19
Television/radio	19	29	32	20
Social services department	18	12	51	18
Speech therapist	16	7	58	19
PDS-field staff (e.g. area officer)	15	6	57	21
Public library	11	10	58	22
YAPP & Rs	4	1	70	24
SPRING	2	2	72	24
Other	8	1	29	61

Important points:

- Hospital doctors and consultants were most frequently regarded as useful (56%)
- They were also the most widely available resource
- Newspapers and magazines were regarded as more useful than radio or TV
- Almost half of the respondents who had used GPs as a source of information found them 'not very useful'
- PD nurse specialists were strongly regarded as useful by those who had used them, but a large proportion said they were not used or not available

- There is a recognized need for information on Parkinson's disease and how to cope with it. 56% of respondents agreed that they needed more information, while 26% disagreed. Respondents

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were also asked on which subjects that needed information nowadays.

Table 7.2 Subjects on which people need information nowadays	
	Percentages (n=945)
New treatments that may be available in future	90
What drugs are available and/or their side effects	84
Specific health problems related to Parkinson's disease	81
How the disease is likely to affect me or the person I care for in the future	75
Aids and equipment and how to get them	49
How Parkinson's disease can affect personal relationships	44
How to get health or social services assistance	41
How to get welfare benefits and financial help	39
How to deal with difficulties in getting services for people with Parkinson's from insurance companies, banks, etc	30
How to find a suitable holiday	29
How to find suitable respite care	26
Other subjects	4
Not answered	1

Table 7.3 Methods of getting information about Parkinson's which members would find helpful	
	Percentages (n=945)
The Parkinson magazine	80
Leaflets or booklets	76
A face-to-face chat	36
Videos	35
Telephone helpline	24
Audio cassettes	15
Large print material	13
The internet	6
Leaflets or booklets translated into community languages	2
Other	2
Not answered	6

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	Other comments ➢ The respondents were invited to add any extra comments to the questionnaire ➢ These comments showed a strong desire for more information, especially on medical subjects ➢ The main topic, above all, was the progress of research into Parkinson's ➢ Other topics of information included: new treatments such as surgery, an explanation of drugs, complementary therapies, and related conditions such as Lewy Body Disease and Multiple System Atrophy ➢ The respondents also perceived a particular need for patients to receive information at the time of first diagnosis
Source of Funding	Parkinson's Disease Society UK
Additional comments	➢ ''To obtain an accurate picture of the membership of the PDS, its needs and priorities, in order to facilitate future planning about service provision and allocation of resources'' ➢ Survey carried out by the Policy Studies Institute an independent research organization ➢ The questionnaire was pre-tested in a small number of face-to-face interviews and then mailed to a pilot sample of 100 people, changes were made according to this feedback ➢ Explanations given for the unable or non-completed questionnaires
Citation	
NCC CC ID (Ref Man)	786

Evidence Table **COMM 1** What approach to patient engagement best aids patient understanding of the diagnosis of Parkinson's disease?	
Bibliographic reference	Pentland B, Pitkairn TK, Gray TK. The effects of reduced expresssion in Parkinson's disease in impression formation by health professionals. *Clinical Rehabilitation* 1987;**1**:307-13.
Study type	Questionnaire
Evidence level	3
Number of patients	N=4 idiopathic Parkinson's disease patients N=4 ischaemic heart disease patients (controls)

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	Location: UK sites:
Patient characteristics	Parkinsonian patients: Male individuals, mean age 53 (range 37-59 years) Mild to moderate features of the disease Time since diagnosis mean 3.25 (range 1–7) years Without dyskinesias, independent in daily living activities 2 were on stage 2 and 2 were on stage 3 of Hoehn and Yahr scale Ischaemic heart disease: All had suffered myocardial infarctions 3 had coronary artery bypass grafting although none had any neurological abnormality Mean age 54.5 (range 43-71) Mean time since diagnosis 3 (range 1-5) years
Intervention	Parkinsonian patients: Video recordings of interviews conducted by 2 doctors each of whom conversed with 2 patients from each group using a semi-structured script covering non-medical aspects of the patient's personal histories. Approximately 1-1.5 minute segments of each interview were taken from the same stage of each interview and edited into a single tape. The order of the segments was such that Parkinson patients were shown first, fourth, seventh, and eighth. The recordings were shown to subjects without soundtrack who were informed the study was nonverbal communication in patients with neurological disorders and that the aim was to gauge their initial impressions of the patients seen. Physiotherapists and occupational therapists were recruited as subjects- both first year students and experienced therapists working in general hospitals. Videorecordings were shown in 4 separate occasions to the following groups: Student physiotherapists (34), physiotherapists (16), student occupational therapists (28), occupational therapists (13).
Comparison	Same as above but for cardiac patients
Length of follow-up	N/A
Outcome measures	Mood, personality traits and intelligence of both groups were assessed clinically and by standardised psychosocial tests
Results	➢ Therapists subjects were asked to record their impressions on a questionnaire with 15 10cm visual analogue scales ➢ 6 questions were directed at mood, 5 at personality and intellect, 3 at conversation itself, and one at overall estimate of likeability of patient

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	➢ Comparisons of the responses to the parkinsonian and to the cardiac patients were significantly different for all 15 variables ➢ Parkinsonian patients were rated more: ➢ Anxious/worried/apprehensive; angry/irritable/hostile; suspicious/unforthcoming; morose/sad/down; bored/detached; tense/ill at ease (all were statistically significant at p<0.001) ➢ The parkinsonian patients appeared more: ➢ Introverted/shy; anxious/dissatisfied; sensitive/emotional; passive/dependent; less intelligent (all factors were p<0.001) ➢ With respect to the conversation itself the parkinsonian patients seemed to be enjoying the conversation less well (p<0.001); relating less well to the interviewer (p<0.001) and holding up their own end of the conversation less well (p<0.001) ➢ The question of how likeable the patient appeared to the subjects, the parkinsonian patients appeared less likeable p<0.001
Source of Funding	None stated
Additional comments	➢ Authors comments: worth emphasising that the parkinsonian patients had mild to moderate symptoms and were leading active lives. They did not have advanced disease with resultant social isolation.
Citation	
NCC CC ID (Ref Man)	2766

Evidence Table **COMM 1** What approach to patient engagement best aids patient understanding of the diagnosis of Parkinson's disease?	
Bibliographic reference	Shimbo T, Goto M, Morimoto T, Hira K, Takemura M, Matsui K *et al*. Association between patient education and health-related quality of life in patients with Parkinson's disease. *Quality of Life Research* 2004;**13**:81-9.
Study type	Cross-sectional questionnaire study
Evidence level	3
Study objective	To determine whether educating patients with Parkinson's disease (PD) is related to better health-related quality of life (HRQOL).
Number of patients	N=1200 patients with PD

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<table>
<tr><td></td><td>Location: Japan sites: not stated</td></tr>
<tr><td>Patient characteristics</td><td>Members of the Japan Association of Patients with Parkinson's disease were randomly selected. Among approximately 3700 members, 1200 patients were selected and mailed the questionnaire package. 762 (63.5%) replied with analysable data.
<table>
<tr><th>Patient characteristics</th><th></th></tr>
<tr><td>Age in years (± SD)</td><td>67.1 ± 8.7</td></tr>
<tr><td>Male ratio (%)</td><td>51.1</td></tr>
<tr><td>Disease duration in years (±SD)</td><td>9.5 ± 6.7</td></tr>
<tr><td>Hoehn and Yahr staging (%)</td><td></td></tr>
<tr><td>Stage 0</td><td>9.1</td></tr>
<tr><td>Stage 1</td><td>14.7</td></tr>
<tr><td>Stage 2</td><td>8.6</td></tr>
<tr><td>Stage 3</td><td>27.6</td></tr>
<tr><td>Stage 4</td><td>27.3</td></tr>
<tr><td>Stage 5</td><td>12.7</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Education information (types of educational activity and who provided it was not assessed)
Patient satisfaction with the medical information they received was measured on a 5-point scale from 1 (not at all satisfied) to 5 (very satisfied). Evaluated information included: 1) disease condition and pathophysiology, 2) drug effectiveness, 3) adverse drug reactions, 4) publicly available financial and social resources, and 5) rehabilitation and daily life activities.</td></tr>
<tr><td>Comparison</td><td>Not applicable</td></tr>
<tr><td>Length of follow-up</td><td>Not applicable</td></tr>
<tr><td>Outcome measures</td><td>SF-36 used to measure HRQOL</td></tr>
<tr><td>Effect size</td><td>➢ The study did not assess the amount of information provided- but asked patients about their satisfaction with the information they had received

Relationship of patient education with SF-36 (regression coefficients of patient education score)
<table>
<tr><th></th><th>PF</th><th>RP</th><th>BP</th><th>GH</th><th>VT</th><th>SF</th><th>RE</th><th>MH</th></tr>
<tr><td>All patients</td><td>-0.76</td><td>3.74*</td><td>2.01</td><td>2.10*</td><td>3.32*</td><td>3.04*</td><td>4.18*</td><td>2.83*</td></tr>
<tr><td>Excluding Hoehn & Yahr (4,5)</td><td>-0.47</td><td>5.23*</td><td>0.06</td><td>1.99</td><td>3.66*</td><td>4.40*</td><td>4.91</td><td>4.10*</td></tr>
</table>
Adjusted for age, sex, number of co morbidities, and activities of daily living score, and complications of therapy. The patient education score was 1 for 'not at all satisfied' and 5 for 'very satisfied' with information given. Therefore the difference in subscale</td></tr>
</table>

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	score of SF-36 between two extremes was fourfold the number in the table. PF= physical functioning; RP= role physical; BP= bodily pain; GH=general health; VT=vitality; SF=social functioning; RE= role emotional; MH= mental health. *P<0.05 ➢ The average patient education score was 2.96 ± 0.88 (mean ± SD) indicating that participants were neither particularly satisfied nor dissatisfied with the information they received ➢ There was no relation between this score and sex, age or Hoehn and Yahr stage ➢ When the analysis included all patients, a higher patient education score was associated with higher HRQOL scores in all subscales of the SF-36 except for physical function and bodily pain ➢ Most satisfied patients were in regards to role emotional and least satisfied were in regards to general health ➢ After excluding patients with advanced disease (Hoehn and Yahr 4-5) the regression coefficient increased in several subscales ➢ Scores in all subscales of SF-36 were generally lower in patients with more advanced disease, demonstrating that the disease stage is associated with a decline in HRQOL involving all aspect of daily living ➢ Complications of therapy had a substantial effect on each subscale of SF-36
Source of funding	Government and pharmaceutical
Additional comments	➢ Non-randomised, non-controlled, unblinded analysis of results
Citation	
NCC CC ID (Ref Man)	19841

DIAG1 – section 5.3

Evidence Table **DIAG1** How effective is clinical expert diagnosis (using UK brain bank criteria) versus non-expert diagnosis in diagnosing patients with Parkinson's disease?	
Author / title / reference / yr	Schrag, A., Ben Shlomo, Y., & Quinn, N. 2002, "How valid is the clinical diagnosis of Parkinson's disease in the community?", *Journal of Neurology, Neurosurgery & Psychiatry.*,

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	vol. 73, no. 5, pp. 529-534.
N=	N= 126 pre-existing clinical diagnosis of probable and possible Parkinson's disease Location= London Sites= 15 general practices (14 in London, 1 in Kent)
Research design	A community based diagnostic study with a one-year follow-up period.
Aim	To assess the diagnostic accuracy of a specialist vs non-specialist diagnosis of Parkinsonism.
Population	15 general practices in the area of London were screened for patients- computerised records were screened. Patients with a pre-existing clinical diagnosis of probable and possible Parkinson's disease- patients identified through an initial diagnosis of parkinsonism, a record of tremor with onset after age 50, or identified through previous prescription of anti-parkinsonian drugs, excluding those who were referred for diagnosis. **Parkinsonism** was diagnosed if bradykinesia and at least one other cardinal sign (resting tremor, rigidity, or postural instability) were present. **Parkinson's disease** was diagnosed according to the UK Parkinson's disease society brain bank criteria, with the exception that an isolated positive Babinski sign, for instance in an elderly patient with otherwise typical Parkinson's disease, was not considered to invalidate the diagnosis. **Possible Parkinson's disease** was diagnosed in patients with isolated classical resting tremor only. **Vascular Parkinsonism** was diagnosed when there was the presence of at least two of the following: a history of previous strokes, abrupt onset with the stepwise progression, hypertension, a wide based gait with small steps, cognitive decline, and pseudobulbar or pyramidal signs. **Drug induced Parkinsonism** was diagnosed if the onset of parkinsonian symptoms was within six months of at least six months treatment with dopamine receptor blocking drugs, and still present on prevalence day. Patients were excluded if: (1) they had used antiparkinsonian drugs for other indications; (2) if they

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<table>
<tr><td></td><td>had another known cause of tremor; (3) if they were miscoded; (4) patients whose onset of parkinsonian symptoms was within six months of treatment with dopamine receptor blocking drugs and patients who had developed dementia before the onset of parkinsonism.</td></tr>
<tr><td>Intervention</td><td>Clinical diagnosis sub grouped for specialist and non-specialist clinician:
➢ Diagnosis was completed by one investigator
➢ A video recording of the neurological signs was made
➢ The diagnosis was made according to published criteria after review and discussion of each subject and examination of their videotape
➢ All patients in whom a diagnosis of parkinsonism was made received a questionnaire on atypical features and symptoms of progression every three months for a period of one year
➢ The general practitioners were asked about any new, atypical features in the eligible patients at the end of the study
➢ Patients who had atypical features at the first visit, or developed them during follow-up, and those in whom a probable diagnosis could not be made at the first visit, were reviewed after 1 year.</td></tr>
<tr><td>Comparison</td><td>Existing diagnosis from records</td></tr>
<tr><td>Outcome</td><td>➢ Sensitivity- specialist vs. existing diagnosis- sub-grouped into specialist vs. non-specialist
➢ Specificity- same as above
➢ Positive predictive value- same as above
➢ Positive predictive value- same as above</td></tr>
<tr><td>Characteristics</td><td>Patients with an initial diagnosis of Parkinson’s disease (N=131)

<table>
<tr><th>Final diagnosis</th><th>N</th><th>Mean age</th><th>Seen by specialist (%)</th></tr>
<tr><td>Probable PD</td><td>109</td><td>71.6</td><td>85 (78%)</td></tr>
<tr><td>Possible PD</td><td>2</td><td>81.5</td><td>1 (50%)</td></tr>
<tr><td>Multiple System Atrophy</td><td>3</td><td>78.3</td><td>1 (33%)</td></tr>
<tr><td>Progressive Supranuclear Palsy</td><td>4</td><td>71.8</td><td>2 (50%)</td></tr>
<tr><td>Vascular parkinsonism</td><td>6</td><td>82.5</td><td>5 (83%)</td></tr>
<tr><td>Non-parkinsonian tremor</td><td>4</td><td>65.5</td><td>3 (75%)</td></tr>
<tr><td>Other</td><td>3</td><td>84.7</td><td>0</td></tr>
</table></td></tr>
</table>

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Patients with a final diagnosis of probable Parkinson's disease (N=124)

Initial diagnosis	N	Mean age	Seen by specialist (%)
Parkinson's disease	109	72	85 (78%)
Atypical parkinsonism	1	55	1 (100%)
Vascular parkinsonism	1	69	1 (100%)
Non-parkinsonian tremor	9	74	3 (33%)
On antiparkinsonian drugs	2	84.5	0
Referred for diagnosis	2	82.5	2 (100%)

Results

Of 126 patients with a pre-existing clinical diagnosis of probable and possible Parkinson's disease in the overall sample, 111 were confirmed Parkinson's disease, resulting in:
Sensitivity: 88.1% (95% confidence interval, 81.1% to 93.2%) (111 of 126 patients)
Specificity: 73.0% (61.3% to 82.6%) (54 of 74 patients)
Positive predictive value: 84.7% (77.4% to 90.4%) (111 of 131 patients)
Negative predictive value: 78.3% (66.7% to 87.3%) (54 of 69 patients)

When this was broken down by a specialist vs other doctor diagnosis, the diagnostic validity was as follows:

Neurologists and geriatricians

Sensitivity: 93.5% (86.3% to 97.6%) (86 of 92 patients)
Specificity: 64.5% (45.4% to 80.8%) (20 of 31patients)
Positive predictive value: 88.7% (80.6% to 94.2%)
Negative predictive value: 76.9% (56.4 to 91.0%)
Non-specialists:
Sensitivity: 73.5% (55.6% to 87.1%) (25 of 34 patients)
Specificity: 79.1% (64.0% to 90.0%) (34 of 43 patients)
Positive predictive value: 73.5% (55.6% to 87.1%)
Negative predictive value: 79.1 (64.0% to 90.0%)
The positive predictive values were greater for specialists than for non-specialists but the negative predictive values were equivalent.

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SIGN quality rating	+
Evidence hierarchy grading	DSII
Comments	➢ Comparison of existing diagnosis may be inaccurate- do not know whether this was made by a specialist or non-specialist. ➢ Community study-London- the study may not be completely transferable to other communities. ➢ No information regarding duration of illness or severity of illness. ➢ The diagnostic accuracy of a specialist vs non-specialist diagnosis of Parkinson's disease was a secondary outcome measure of the study. ➢ Questionable whether the method of diagnosis can be generalised- very comprehensive and specific to the study. ➢ "Only practices with computerised records were-included – mainly inner city practices- and the age range was relatively young, representative of the London population. It is thus possible that a similar study in a different population and health care system might have yielded somewhat different results". ➢ "Our figures for sensitivity and specificity for both groups of clinicians are slightly unfair as referral to a specialist in itself may reflect the general practitioners uncertainty about the diagnosis, and as we had the benefit of making the diagnosis after some time had elapsed. In this way we may have been able to detect additional features that were atypical but not present when the initial diagnosis was made".
NCC CC ID	142

Evidence Table **DIAG1** How effective is clinical expert diagnosis (using UK brain bank criteria) versus non-expert diagnosis in diagnosing patients with Parkinson's disease?	
Author / title / reference / yr	Meara, J., Bhowmick, B. K., Hobson, P. (1999). Accuracy of diagnosis in patients with presumed Parkinson's disease. *Age and Ageing,* 28, 99-102
N=	N=502 Location= N Wales Sites= 74 general practices

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Research design	Epidemiological prevalence study
Aim	To assess the diagnostic accuracy of a specialist vs non-specialist diagnosis of Parkinsonism.
Population	A computerised list of patients receiving anti-Parkinson's medication from 74 GP practices. Cases of drug induced parkinsonism were excluded
Intervention	402 of 502 cases found from GP registers were assessed using UKPDBB criteria at a home or clinic visit where a history was taken and a neurological examination performed
Comparison	Existing diagnosis from records
Outcome	Confirmed or ruled out diagnosis of IPD
Characteristics	Mean onset of symptoms at 67yrs 80% of population 60 yrs+ at time of study
Results	299 cases were confirmed as having parkinsonism symptoms from original 402 records Definite IPD diagnosis made on 213 (53%) of all cases (47% error rate) 21% of cases were classified as possible IPD or parkinsonism clearly due to other causes Cause of Parkinsonism in the 299 confirmed cases was probable IPD in 71% of cases. No dates specified for sampling, study reported in 1999.
SIGN quality rating	+
Evidence hierarchy grading	DSII
Comments	No clear definition of blinding All patients in trial on existing PD medication does not allow for extrapolation to de novo cases No assumed non-PD cases included in study as part of reference standard No accuracy analysis performed (sensitivity or specificity) No comparison was made of cases who refused to participate in the study (9%) these may have been more difficult cases to establish a diagnosis using UKPDBB criteria.
NCC CC ID	108

Evidence Table **DIAG1** How effective is clinical expert diagnosis (using UK brain bank criteria) versus non-expert diagnosis in diagnosing patients with Parkinson's disease?	
Author / title / reference / yr	Jankovic, J., Rajput, A. H., McDermott, M. P., & Perl, D. P. 2000, "The evolution of diagnosis in early

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	Parkinson disease", *Archives of Neurology.*, vol. 57, no. 3, pp. 369
N=	N=800 patients with mild parkinsonian symptoms Location: US and Canada sites: multiple
Research design	Diagnostic study
Aim	To determine the evolution of clinical diagnosis in patients with early PD made initially by experts in PD.
Population	Parkinsonian patients selected for DATATOP study Received diagnosis of PD less than 5 years before beginning of study
Intervention	Expert clinical diagnosis from ~2000
Comparison	Expert clinical diagnosis from DATATOP study in 1987-1996
Outcome	% Of patients with changed diagnosis during 7.6 year follow-up
Characteristics	528 (66%) men, 272 (34%) women Between the ages of 30 and 79 (mean age at randomisation was 61.1 years) Mean duration of symptoms was 2.1 years Mean Hoehn and Yahr stage 1.6 (404 at stage 1 and 396 at stage 2) Mean follow-up was 6 years Not undergoing symptomatic anti-parkinsonian therapy Exclusion criteria: patients with dementia (22 on Mini Mental State Examination), depression (16 on the Hamilton Psychiatric Rating Scale), or resting tremor ($\geq$ 3 on UPDRS), and patients with clinical evidence of secondary parkinsonism, or those who had parkinsonism due to other causes than idiopathic PD
Results	➢ **65/800 (8.15%) patients had a changed diagnosis according to study criteria** ➢ **92% of patients still considered to have same diagnosis as initial diagnosis after 6 years** ➢ In 43 cases little or no response to levodopa suggested that the PD diagnosis was in error ➢ The other major feature indicative of non-PD was an atypical neuroimaging result ➢ In 5 cases the diagnosis was not confirmed at autopsy ➢ The 65 patients who did not have PD according to study criteria had higher mean scores for the following: ➢ Bradykinesia (p=0.03) ➢ Postural instability and gait difficulty score (p=0.01)

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	➢ Hoehn and Yahr stage (p=0.006) ➢ Lower mean tremor score (p=0.03) ➢ The two groups were not significantly different for: duration of symptoms, age at symptom onset, rigidity score, and likelihood for reporting rigidity and bradykinesia as initial symptoms
SIGN quality rating	+
Evidence hierarchy grading	DSII
Comments	➢ Aim: to determine the evolution of clinical diagnosis in patients with early PD made initially by experts in PD ➢ Follow-up of patients for 7.6 years ➢ 34 investigators (major interest in movement disorders and experience in treating PD) ➢ Diagnostic criteria for initial diagnosis not specified ➢ Initial diagnosis by 'experts' and final diagnosis by 'experts' ➢ Definitions of 'expert' not listed ➢ Does not state whether investigators are blind to initial diagnosis
NCC CC ID	81

Evidence Table **TxNP2** Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Lees, A. J., Katzenschlager, R., Head, J., & Ben Shlomo, Y. 2001, "Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial.[see comment]", *Neurology*, vol. 57, no. 9, pp. 1687-1694.
Study type	Randomised open trial
Evidence level	1+
Study Objective	To report the results of a ten-year follow-up of bromocriptine, L-dopa and L-dopa/selegiline treated PD patients
Number of patients	N=782 de novo PD patients N=249 levodopa alone group N=271 levodopa/selegiline N=262 bromocriptine

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<table>
<tr><td></td><td>Location: United Kingdom Sites: 93</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
All patients fulfilled the criteria for a clinical diagnosis of PD
Untreated patients required dopaminergic treatment were included
Patients with co morbid conditions could be included
Patients on anticholinergics and amantadine were included
Exclusion criteria:
Patients who were known to have failed to respond to dopaminergic drugs
Patients with incapacitating cognitive impairment
Characteristics:
Baseline characteristics of three treatment groups were similar in age, sex, duration of PD, disability scores</td></tr>
<tr><td>Intervention</td><td>Bromocriptine alone (arm 3)</td></tr>
<tr><td>Comparison</td><td>Levodopa and decarboxylase inhibitor (arm 1); Levodopa/decarboxylase inhibitor & selegiline (arm 2)</td></tr>
<tr><td>Length of follow-up</td><td>10 years</td></tr>
<tr><td>Outcome measures</td><td>Mortality and disability</td></tr>
<tr><td>Effect size</td><td>➢ 49 patients (16 arm1, 16 arm2, 17 arm3) had diagnosis revised during course of trial
Mortality
➢ Average follow-up 9.2 years
➢ Standardized mortality ratio (SMR) for patients in the study compared to the general population of United Kingdom was 1.78 (95%CI, 1.62 to 1.96)
➢ Statistical significance of difference among 3 arms in first 5 years of study; p=0.27
➢ Hazard ratio of bromocriptine versus levodopa was 1.15 (95%CI, 0.90 to 1.47)
➢ After adjustment for age, sex, duration of disease before randomisation, hazard ratio 1.12
➢ Hazard ratio for arms 2 vs. 3: 1.06 (95%CI, 0.84 to 1.34)
➢ Hazard ratio for arms 2 vs. 1: 1.22 (95%CI, 0.95 to 1.55)
➢ Hazard ratio (mortality attributed to PD arm 3 vs. arm 1) was 1.63 (95%CI, 1.0 to 2.7)

Disability
Table: difference (95%CI) in mean Webster disability scores
<table>
<tr><td>Time in trials</td><td>Arm 3 vs. 1</td><td>Arm 3 vs. 2</td><td>Arm 1 vs. 2</td></tr>
<tr><td>Year 1, n=670</td><td>0.9 (0.3 to 1.5)</td><td>1.3 (0.6 to 1.9)</td><td>0.3 (-0.3 to 1.0)</td></tr>
</table></td></tr>
</table>

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<table>
<tr><td></td><td>
<table>
<tr><td>Year 3, n=688</td><td>1.3 (0.4 to 2.2)</td><td>1.4 (0.6 to 2.3)</td><td>0.2 (-0.7 to 1.1)</td></tr>
<tr><td>Year 5, n=573</td><td>1.0 (-0.2 to 2.1)</td><td>1.4 (0.3 to 2.5)</td><td>0.4 (-0.7 to 1.6)</td></tr>
<tr><td>Year 9, n=270</td><td>0.2 (-1.5 to 1.5)</td><td>1.0 (0.6 to 2.5)</td><td>0.8 (-0.8 to 2.4)</td></tr>
</table>

Adjusted for baseline disability score. A positive difference indicates worse average disability in arm 1.
Difference in disability between arm 1 and 3 diminishes after 5th year of follow-up
The ‘final’ disability scores based on the average of the most recent two ratings before death or the end of 1999- adjusted difference of 0.8 (95%CI 0.3 to 1.9) between arm 1 and 3
Similar findings obtained from an analysis of Northwestern University disability scale
On average patients in bromocriptine arm returned to baseline disability after 3 years, 1 year before levodopa group (arm 1)
Significantly lower incidence of dyskinesia in the group initially randomised to bromocriptine than levodopa (arm 1) (rate ratio: 0.73 (95%CI 0.57 to 0.93)
Incidence rate for dystonia was slightly lower in the bromocriptine group (rate ratio: 0.84, 95%CI 0.65 to 1.09, p=0.17)
Slightly lower incidence of on/off fluctuations in the group initially randomised to bromocriptine (difference was not significant; 0.90 (95%CI 0.72 to 1.13)

</td></tr>
<tr><td>Source of Funding</td><td>Non-profit organization and pharmaceutical company</td></tr>
<tr><td>Additional comments</td><td>

Randomisation was carried out by independent coordinator methods listed
Intention-to-treat analysis
No blinding of investigators –possible bias in result interpretation
If patents did not improve they could be re-randomised to another group
Additional antiparkinsonian drugs were allowed during the trial
Comparability of results from different sites not stated
Trial took place between 1985 to 1990- where selegiline arm was terminated

</td></tr>
<tr><td>Citation</td><td></td></tr>
<tr><td>NCC CC ID (Ref Man)</td><td>2309</td></tr>
</table>

DIAG2 – section 5.2

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Evidence Table **DIAG2** How effective is clinical expert diagnosis (using brain bank criteria) versus the post-mortem gold standard in diagnosing patients with Parkinson's disease?	
Author / title / reference / yr	Rajput, A. H., Rozdilsky, B., & Rajput, A. 1991, "Accuracy of clinical diagnosis in Parkinsonism - A prospective study", *Canadian Journal of Neurological Sciences.*, vol. 18, no. 3, pp. 275-278.
N=	N=59 participants Location= Saskatchewan, Royal University Hospital Saskatoon Sites=1
Research design	Prospective clinico-pathological diagnostic study
Aim	To verify the accuracy of clinical diagnosis in Parkinsonism by autopsy
Population	Parkinsonian syndrome- clinical diagnosis
Intervention	***Diagnosis by autopsy N=59*** Where the substantia nigra neuronal loss was estimated at more than 50% and Lewy body inclusions were detected in some neurons the case was classified as Idiopathic Parkinson's disease (IPD). If rare Lewy body, without substantia nigra neuronal loss, was noted the Lewy body inclusion was regarded as incidental. The pathological diagnosis of other variants of Parkinsonism was made using the standard criteria for each entity.
Comparison	***Clinical diagnosis N=65*** The diagnosis of Parkinsonism was made when at least two of the three signs (bradykinesia, rigidity and resting tremor) were present. Those that had no identifiable cause and no clinical evidence of widespread central nervous system lesions were regarded as having Idiopathic Parkinson's disease. The three cardinal signs were measured using the criteria of Webster and Hoehn and Yahr scale measured the overall disability.
Outcome	Verification of Idiopathic Parkinson's disease by autopsy and accuracy of clinical diagnosis
Population characteristics	N=59 Male/female N=40/19 Average 11.7 yrs duration of illness No further details regarding population characteristics

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Results	➢ N= 43 with initial clinical diagnosis of IPD ➢ N= 28 (65%) with verified Lewy body pathology cases ➢ After a mean duration of 12 years the final clinical diagnosis was IPD in 41 cases, which was neuropathologically confirmed in 31 (76%)
SIGN quality rating	+
Evidence hierarchy grading	DS Ib
Comments	➢ Cases were seen between Dec 1st 1968 and Feb 28th 1990 ➢ Population characteristics restricted to male: female ratio, and average duration of illness ➢ The same neurologist made all clinical observations and most autopsies were done by the same neuropathologist- thus excluding inter-observer bias ➢ The pathological diagnosis was made independently of the clinical observations ➢ The study strictly retained the initial diagnosis made by a neurologist as well as the final clinical diagnosis. ➢ The study states that it "includes cases that were diagnosed in the 1950's and 60's when several of the currently well known forms of Parkinson's syndrome were unknown, therefore the proportion of accurate diagnosis by contemporary standards would be lower".
NCC CC ID	111

Evidence Table **DIAG2** How effective is clinical expert diagnosis (using brain bank criteria) versus the post-mortem gold standard in diagnosing patients with Parkinson's disease?	
Author / title / reference / yr	Hughes, A. J., Daniel, S. E., Ben Shlomo, Y., & Lees, A. J. 2002, "The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service", *Brain.*, vol. 125, no. Pt:4, pp. 4-70.
N=	N= 143 participants N=73 Idiopathic Parkinson's Disease (IPD) patients N=70 other Parkinsonian disorder N=70 Location=London, UK Sites= Parkinson's Disease Society Brain Bank Research Centre

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Research design	Retrospective clinico-pathological diagnostic study
Aim	To assess the accuracy of clinical diagnosis of parkinsonian disorders based on diagnosis at autopsy
Population	Parkinsonian syndrome
Intervention	**Diagnosis by autopsy N=143** The diagnosis of IPD was based on finding a clear depletion of brainstem-pigmented neurons with Lewy bodies in some of the remaining nerve cells and a normal appearance in the striatum.
Comparison	**Clinical diagnosis N=143** ➢ One neurologist who was unblinded to the pathological diagnosis abstracted clinical features of the 143 cases identified ➢ Clinical records included: hospital, consultant and general practice case notes as well as UKPDSBRC annual assessment data ➢ When more than one possible clinical diagnosis was listed in the clinical files, an attempt was made to ascertain the clinical diagnosis thought most likely ➢ Only in cases where this was unclear, or where a definite 'unclassifiable' label had been used was a final clinical diagnosis of 'parkinsonism undetermined' recorded ➢ Cases clinically felt to have IPD and coexistent dementia at the time of death were classified as having a clinical diagnosis of IPD ➢ All cases satisfying the neuropathological criteria for IPD with or without cortical Lewy body deposition were classified neuropathologically as having IPD.
Outcome	➢ **Sensitivity:** The percentage of cases with a particular pathological diagnosis that had been clinically diagnosed correctly as having that diagnosis prior to death. ➢ **Specificity**: The percentage of cases without a particular pathological diagnosis that had been clinically diagnosed correctly as not having that diagnosis prior to death. ➢ **Positive predictive value:** The percentage of cases, which the clinicians had diagnosed correctly with a particular diagnosis, which was confirmed at post-mortem. ➢ **Negative predictive value:** The percentage of cases, which the clinicians correctly thought, did not have a particular diagnosis was confirmed to be correct at post-mortem.
Characteristics	N=143 cases (Idiopathic Parkinson's Disease N=73; Another Parkinsonian disorder N=70) All cases ➢ Mean age at disease onset=55.5 ➢ Mean disease duration=13

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	➢ Hoehn and Yahr stage at initial diagnosis =1.8 ➢ Hoehn and Yahr stage at death =4.7 ➢ Time from initial onset of symptoms to initial clinical diagnosis =1.6 ➢ Disease duration at time of final clinical diagnosis =2.9 ➢ Cases where clinical diagnosis was revised =44 ➢ Disease duration at time of final clinical diagnosis in those where the diagnosis was revised =5.3 Idiopathic Parkinson's Disease N=73 ➢ 47 male; 26 female ➢ Mean age at disease onset=57.1 yrs ➢ Mean disease duration= 16.2 yrs ➢ Hoehn and Yahr stage at initial diagnosis = 1.5 ➢ Hoehn and Yahr stage at death = 4.5 ➢ Time from initial onset of symptoms to initial clinical diagnosis = 1.3 yrs ➢ Disease duration at time of final clinical diagnosis = 1.4 yrs ➢ Cases where clinical diagnosis was revised = 2 ➢ Disease duration at time of final clinical diagnosis in those where the diagnosis was revised = 4.3
Results	➢ N =79 cases of confirmed IPD based on results from autopsy ➢ Seven cases of pathologically proven IPD had been misdiagnosed ➢ **Overall sensitivity** of clinical diagnosis of IPD = 91.1% (7 false-negative cases) ➢ **Specificity** of clinical diagnosis of IPD =98.4% ➢ **Positive predictive value** of clinical diagnosis of IPD =98.6% (72 out of 73) ➢ **Negative predictive value:** of clinical diagnosis of IPD = 90% The clinical diagnosis was made by 11 neurologists with 5 dedicated movement disorders specialists seeing 92%. The clinical diagnosis was later revised in 44 of 122 cases where full follow-up information was available after a mean of 3.4 (range 0.5-12) years. The mean duration of disease to final clinical diagnosis in these 44 cases was 5.3 years. "The diagnostic accuracy for IPD and parkinsonian syndromes (MSA, PSP) was higher than most previous prospective clinicopathological series and studies using the retrospective application of clinical diagnostic criteria. This study implies that neurologists with particular expertise in the field of

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	movement disorders may be using a method of pattern recognition for diagnosis which goes beyond that inherent in any formal set of diagnostic criteria".
SIGN quality rating	+
Evidence hierarchy grading	DS II
Comments	➢ Brains where collected between 1990 and the end of 1999. ➢ Clinical diagnoses were made by 11 neurologists associated with the movement disorders service at The National Hospital for Neurology and Neurosurgery in London, with five dedicated movement disorder specialists seeing 92%. ➢ IPD diagnosis by autopsy was based on finding a clear depletion of brainstem-pigmented neurons with Lewy bodies in some of the remaining nerve cells and a normal appearance in the striatum. ➢ Only one case diagnosed clinically as IPD was not confirmed pathologically. However, it is not specified what is meant by "clear" depletion. ➢ Positive and negative predictive values are highly sensitive to the prevalence of disease and the context within which patients are seen. ➢ One neurologist who was unblinded to the pathological diagnosis abstracted Clincial features of the 143 cases identified.
NCC CC ID	96

Evidence Table **DIAG2** How effective is clinical expert diagnosis (using brain bank criteria) versus the post-mortem gold standard in diagnosing patients with Parkinson's disease?	
Author / title / reference / yr	Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. 1992, "Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases", *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 55, no. 3, pp. 181-184.
N=	N= 100 participants Location=UK Sites=multiple
Research design	Prospective clinico-pathological diagnostic study

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Aim	To determine the accuracy of clinical diagnosis of idiopathic Parkinson's disease (IPD) through autopsy.
Population	Idiopathic Parkinson's disease as diagnosed through prospective clinical examination.
Intervention	Diagnosis by autopsy: ➢ A clear depletion of brain stem pigmented neurones with Lewy bodies in some of the remaining nerve cells.
Comparison	Prospective clinical diagnosis
Outcome	Verification of diagnosis of Parkinson's disease (PD)
Population characteristics	Mean age of disease onset=64.5yrs Mean duration of disease=11.9yrs Male/female ration=59/41
Results	➢ N=76 verified PD diagnosis at autopsy (fulfilled the pathological criteria for IPD) ➢ N=24 patients were misdiagnosed; ➢ No significant difference between the two groups for age at onset, age at death, or terminal disease severity; ➢ The principal findings in the 24 cases without Lewy bodies were progressive supranuclear palsy (N=6); multiple system atrophy (N=5); Alzheimer's disease (N=3); Alzheimer-type pathology (N=3); vascular atrophy with no Lewy bodies (N=2), and postencephalitic parkinsonism (N=1) ➢ In one case there were no abnormal pathological findings and review of the clinical details raised the possibility of benign essential tremor.
SIGN quality rating	+
Evidence hierarchy grading	DS II
Comments	➢ Brains where collected between June 1987 and Aug 1990 ➢ Not clear whether investigators at autopsy were blind to PD clinical diagnosis ➢ Various neurologists associated with the Parkinson's Disease Society Brain Bank, consultant neurologists and geriatricians were involved in the clinical diagnosis of Parkinson's disease ➢ Not clear how many clinicians were involved in diagnosis by autopsy ➢ Inter-observer bias or variability is questionable-unknown effects
NCC CC ID	99

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Evidence Table **DIAG2** How effective is clinical expert diagnosis (using brain bank criteria) versus the post-mortem gold standard in diagnosing patients with Parkinson's disease?	
Author / title / reference / yr	Hughes, A. J., Daniel, S. E., & Lees, A. J. 2001, "Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease", *Neurology*, vol. 57, pp. 1497-1499.
N=	N= 100 participants Location=UK Sites=multiple
Research design	Prospective clinico-pathological diagnostic study (methodology identical to 1992 study)
Aim	To determine the accuracy of clinical diagnosis of idiopathic Parkinson's disease (IPD) through autopsy.
Population	Idiopathic Parkinson's disease as diagnosed through prospective clinical examination.
Intervention	Diagnosis by autopsy: ➢ A clear depletion of brain stem pigmented neurones with Lewy bodies in some of the remaining nerve cells.
Comparison	Prospective clinical diagnosis
Outcome	Verification of diagnosis of Parkinson's disease (PD)
Population characteristics	Mean age of disease onset=62.2yrs Mean duration of disease=15yrs Male/female ration=56/44
Results	➢ N=90 verified PD diagnosis at autopsy (fulfilled the pathological criteria for IPD) ➢ N=10 patients were misdiagnosed. ➢ The neuropathological diagnoses in the misdiagnosed cases were multiple system atrophy (6), progressive supranuclear palsy (2), neurofibrillary tangle pathology (1; probable postencephalitic parkinsonism) and extensive cerebrovascular disease with no other pathologic explanation for parkinsonism (1). ➢ This showed a significant improvement (14% 95%CI 3.8 to 24.2, p=0.008) in the clinical diagnostic accuracy of IPD over the last decade.
SIGN quality rating	+
Evidence hierarchy grading	DS II
Comments	➢ Brains were collected between 1996 and 1998

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	➢ Not clear whether investigators at autopsy were blind to PD clinical diagnosis ➢ Various neurologists associated with the Parkinson's Disease Society Brain Bank, consultant neurologists and geriatricians were involved in the clinical diagnosis of Parkinson's disease
NCC CC ID	20003

DIAG3 – section 5.10

Evidence Table **DIAG3** How effective is acute levodopa testing and apomorphine testing vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Bibliographic reference	Clarke, C. E. & Davies, P. 2000, "Systematic review of acute levodopa and apomorphine challenge tests in the diagnosis of idiopathic Parkinson's disease", *Journal of Neurology, Neurosurgery & Psychiatry.*, vol. 69, no. 5, pp. 590-594.
Study type	Meta-analysis
Evidence level	DSII
Number of patients	N= 645 (parkinsonian and non-parkinsonian patients) Location=multiple sites
Patient characteristics	Patient groups include: ➢ De novo idiopathic Parkinson's disease ➢ Longer-term idiopathic Parkinson's disease Non-parkinsonian conditions (Multiple System Atrophy and Progressive Supranuclear Palsy)
Intervention	APO and acute LD challenge tests for diagnosis of parkinsonian syndromes: Most challenge tests were performed on admission as a day case, following pre-treatment with domperidone. The actual dosages were 275mg of acute LD and between 0.7 and 10mg APO.
Comparison	Clinical diagnosis (including standard motor impairment rating scales, and timed tests)
Length of follow-up	Varied among studies between 1-6 months
Outcome measures	Sensitivity and specificity of APO and acute LD challenge tests for diagnosis of IPD

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<table>
<tr><td>Effect size</td><td>Meta-analysis results of the sensitivity and specificity for the diagnosis of idiopathic Parkinson's disease in the 13 studies included:

<table>
<tr><th></th><th>Sensitivity</th><th>Specificity</th></tr>
<tr><td>Acute Apomorphine challenge</td><td>0.86 (95% CI: 0.78 to 0.94)</td><td>0.85 (95% CI: 0.74, 0.96)</td></tr>
<tr><td>Acute Levodopa challenge</td><td>0.75 (95% CI: 0.64 to 0.85)</td><td>0.87 (95% CI: 0.77, 0.97)</td></tr>
<tr><td>Chronic levodopa therapy</td><td>0.91 (95% CI: 0.85 to 0.99)</td><td>0.77 (95% CI: 0.61, 0.93)</td></tr>
</table>
Neither heterogeneity tests in the meta-analysis, nor the logistic regression analysis comparing the diagnostic odds ratios of different studies, showed any signs of statistically significant variation between the studies in terms of the sensitivities and specificities.
➢ In two studies (Hughes et al., 1990 and d'Costa et al., 1991) it was possible to perform a conditional logistic regressive analysis which showed the odds ratio for misclassification between acute apomorphine test and chronic levodopa test was non-significant 3.0 (95%CI, 0.60 to 14.9)
➢ In two studies as well (Hughes et al., 1990 and Zappia et al., 1997) it was possible to perform a conditional logistic regressive analysis which showed the odds ratio for misclassification between acute levodopa test and chronic levodopa test was statistically significant 105 (95% CI, 2.5 to 44.8) in favour of chronic levodopa therapy (p<0.001)
➢ In de novo patients thought clinically to have idiopathic Parkinson's disease, the three tests did not show a statistically significant difference</td></tr>
<tr><td>Source of Funding</td><td>None stated</td></tr>
<tr><td>Additional comments</td><td>➢ Aim: To examine the diagnostic accuracy of acute challenge tests with levodopa (LD) and/or apomorphine (APO) in parkinsonian syndromes and to assess their value in the diagnosis of idiopathic Parkinson's disease.
➢ Only two databases searched (Medline, Cochrane)
➢ Inclusion criteria in relation to study design, reference standard, and outcomes were not given
➢ No details of review process
➢ No quality appraisal of primary papers
➢ No patient characteristics
➢ Author was contacted and verified quality-appraisal process for papers included</td></tr>
<tr><td>Citation</td><td></td></tr>
<tr><td>NCC CC ID (Ref Man)</td><td>21</td></tr>
</table>

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Evidence Table
DIAG3
How effective is acute levodopa testing and apomorphine testing vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?

Bibliographic reference	Rossi, P., Colosimo, C., Moro, E., Tonali, P., & Albanese, A. 2000, "Acute challenge with apomorphine and levodopa in Parkinsonism", *European Neurology*, vol. 43, no. 2, pp. 95-101.
Study type	Diagnostic
Evidence level	DS III
Number of patients	N=134 Parkinsonian patients ➢ N=83 idiopathic Parkinson's disease (IPD) ➢ N=51 non-PD (controls) N=28 multiple system atrophy (MSA) N=6 progressive supranuclear palsy (PSP) N=17 unclassified parkinsonian syndrome (non-classified (NC)) Location: Gemelli Hospital, Italy
Patient characteristics	56 women and 78 men All presented with akinesia and rigidity, often accompanied by other neurological symptoms All patients received chronic treatment with levodopa 13 PD, 2 MSA, 2 PSP patients were drug-naïve at time of acute challenge testing

	PD	**Non-PD**	MSA	PSP	NC
Number of patients (M: F)	**83 (51:32)**	**51 (27:24)**	28 (13:15)	6 (2:4)	17 (12:5)
Age at disease onset	**56.4**	**61.8**	58.3	67.3	63.3
Disease duration at test	**4.8**	**4.9**	4.7	3.0	5.6
Disease duration at evaluation	**7.1**	**6.7**	6.5	4.3	7.8

Intervention	Patients were tested early in the morning in a fasting state; received single standard oral dose of levodopa/carbidopa (250/25 mg) on the first day and apomorphine on the following days; apomorphine was given subcutaneously at a dose of 1.5, 3.0, 4.5 mg, with a delay of 90min between subsequent doses or on separate days. The dosage was increased until either side effects occurred or maximum dose was reached.

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Comparison	Clinical diagnosis: updated in regular follow-up at least twice a year (the most recent diagnosis or autopsy verification, if available, was considered in the retrospective evaluation)
Length of follow-up	6.9 years from onset of disease
Outcome measures	Sensitivity: ratio between number of patients classified as PD and total number in same group Specificity: ratio between number of patients classified as non-PD and total number in same group
Effect size	➢ For each test sensitivity and specificity were computed with 5% intervals from 0 to 50% and with 1% intervals (0.5% in the case of apomorphine 1.5 mg) for values encompassing 80% sensitivity and 80% specificity ➢ The point closest to 80% sensitivity/ specificity was defined as the best trade-off threshold for UPDRS motor score improvement ➢ **Chronic response to Levodopa therapy**: ➢ 78/83 PD patients were classified as chronic responders (the remaining being unclassified) ➢ 22/51 non-PD patients were classified as chronic responders and 26/51 as non-chronic responders (3 remained unclassified) ➢ Overall 100/134 (74.6%) benefited from chronic levodopa therapy, while 27/134 (20.1%) did not ➢ For practical reasons not all patients received all possible combinations of drugs ➢ Patients who had received a diagnosis of **PD compared to non-PD**: ➢ **Levodopa** diagnostic predictive value had a threshold improvement of 16% yielding a **sensitivity of 77.1% and specificity 71.7** ➢ **Apomorphine 1.5 mg**- threshold 13.5%- **sensitivity 70.5% and specificity 65.9%** ➢ **Apomorphine 3 mg**- threshold 13%- **sensitivity 76.5 and specificity 63.9%** ➢ **Apomorphine 4.5 mg**- threshold 16%- **sensitivity 76.5% and specificity 66.7%** ➢ Patients who received a diagnosis of **PD compared to MSA** ➢ Levodopa diagnostic predictive value- threshold 17%- sensitivity 74.3% and specificity 75% ➢ Apomorphine 1.5mg- threshold 13%- sensitivity 72.1% and specificity 64% ➢ Apomorphine 3 mg- threshold 15%- sensitivity 70.6% and specificity 66.7% ➢ Apomorphine 4.5 mg- threshold 18%- sensitivity 76.5% and specificity 66.7% ➢ Patients who were **chronic levodopa responders compared to non-responders** ➢ Levodopa- threshold 14.5%- sensitivity 69.4% and specificity 79.4% ➢ Apomorphine 1.5 mg- threshold 13 % –sensitivity 68.4% and specificity 79.2%

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	➢ Apomorphine 3 mg- threshold 14% - sensitivity 64.6% and specificity 76.5% ➢ Apomorphine 4.5 mg- threshold 14%- sensitivity 72.1% and specificity 78.6%
Source of Funding	None stated
Additional comments	➢ Aim: the motor improvement produced by each acute challenge was matched with the clinical diagnosis and with the response to chronic levodopa treatment. ➢ Author's conclusions: ''a patient improving at least 14.5% in all tests has a high probability of having a chronic response to therapy. A parkinsonian patient improving at least 16% in all tests has a high probability of having PD'' ➢ ''Levodopa challenge had the most convenient trade-off for the diagnosis of PD…, while apomorphine (3 and 4.5 mg) challenge had the best trade-off for the prediction of a chronic response''. ➢ Only 17/134 patients were drug-naïve- which probably reduced the number of false-negative results ➢ Patients consecutively selected in movement disorders clinic of the Gemelli Hospital ➢ Evaluation period 1992 to 1995 ➢ All received peripheral domperidone (20 mg t.i.d) 24 prior to assessment (for side effects) ➢ All anti-parkinsonian medication was withheld 12 h prior to testing ➢ Patients were considered to respond to chronic treatment when a sustained clinical improvement associated with levodopa-related motor fluctuations observed ➢ Clinical criteria for diagnoses provided ➢ Adverse reactions to apomorphine included drowsiness, nausea, vomiting, hypotension and sweating (they prevented dosage increase in some patients) ➢ Levodopa was better tolerated though nausea and vomiting occurred in occasion ➢ Blinding of investigators to clinical diagnosis not stated ➢ No age-matched control comparison- differential diagnosis ➢ Reference standard not gold standard
Citation	
NCC CC ID (Ref Man)	719

DIAG4a – section 5.7

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Evidence Table **DIAG4a** How effective is magnetic resonance imaging vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Author / title / reference / yr	Bhattacharya, K., Saadia, D., Eisenkraft, B., Yahr, M., Olanow, W., Drayer, B., & Kaufmann, H. 2002, "Brain magnetic resonance imaging in multiple-system atrophy and Parkinson disease: A diagnostic algorithm", *Archives of Neurology.*, vol. 59, no. 5, pp. 835-842.
N=	N=39 Total participants ➢ N=14 Multiple System Atrophy-Predominant Parkinsonism participants (MSA-P) ➢ N=4 Multiple System Atrophy-marked Cerebella ataxia (MSA-C) ➢ N=21 Parkinson's disease (PD) Location=Mount Sinai Medical Centre, New York Sites=1
Research design	Retrospective diagnostic study
Aim	To determine concordance between clinical and MR imaging-based diagnoses of MSA-P and PD.
Population	➢ Parkinson's disease as diagnosed according to the UK Brain Bank criteria. ➢ MSA (MSA-C/MSA-P) as diagnosed according to published criteria (Gilman et al., 1998)
Intervention	***MRI Protocol*** Sagittal T1-weighted images (repetition/time/echo time, 600/14 seconds; slice thickness, 5 mm), axial intermediate and T2-weighted sequences (repetition time /echo time, 2500/30-90 seconds; slice thickness, 5 mm), and inversion recovery axial T1 images (repetition time/echo time/inversion time, 2500/20/800 seconds; slice thickness, 4 mm). <u>Radiological diagnosis based on:</u> **MSA-P:** Moderate to severe putaminal abnormalities or mild putaminal change together with brainstem or cerebellar abnormality. **PD:** Near-normal MR images with few or no abnormalities, or the presence of only mild abnormality in the putamen, brainstem, or cerebellum. **MSA-C:** Cerebellar changes in the brainstem or cerebellum were moderate or severe regardless of putaminal change.

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<table>
<tr><td></td><td>➢ In addition, the neuroradiologists used their overall impression to assign a diagnosis.</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis of Multiple System Atrophy vs. Parkinson's disease</td></tr>
<tr><td>Outcome</td><td>Concordance between radiological and clinical diagnoses</td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><th>Groups</th><th>Male/female n</th><th>Mean age years</th><th>Mean disease duration years</th></tr>
<tr><td>MSA</td><td>13/5</td><td>59</td><td>5</td></tr>
<tr><td>MSA-P</td><td>9/5</td><td>59</td><td>5</td></tr>
<tr><td>MSA-C</td><td>All men</td><td>57</td><td>4</td></tr>
<tr><td>PD</td><td>15/6</td><td>64</td><td>7</td></tr>
</table>
➢ Patients in all groups had similar ages.
</td></tr>
<tr><td>Results</td><td>
Concordance between radiological and clinical diagnoses
➢ Neuroradiologists diagnosed 5 patient's with a clinical diagnoses of MSA-P as having PD (Patients with MSA-P wrongly diagnosed radiologically as having PD had significantly shorter disease duration (4 vs. 6 years; p=0.05) although they were of similar age. "Brain MR imaging may be of limited value in patients with MSA-P early in their disease, as it may show only mild abnormalities")
➢ Neuroradiologist diagnosed 2 patients with clinical diagnoses of PD as having MSA-P.
➢ Neuroradiologist diagnosed 1 patient with clinical diagnoses of MSA-C as having PD.
<table>
<tr><th>Brain MR imaging findings in patients with MSA-P with concordant radiological diagnosis of MSA-P and nonconcordant radiological diagnosis of PD</th><th>Diagnosis of MSA-P</th><th>Diagnosis of PD</th><th>P value</th></tr>
<tr><td>Mean age years</td><td>61</td><td>57</td><td>0.25</td></tr>
<tr><td>Mean disease duration</td><td>6</td><td>4</td><td>0.05</td></tr>
<tr><td>Putamen N (%)</td><td>7 (78)</td><td>4 (80)</td><td>> 0.99</td></tr>
<tr><td>Lateral slitlike hyperintensity</td><td>7 (78)</td><td>4 (80)</td><td>>0.99</td></tr>
<tr><td>Lateral slitlike hyperintensity >1</td><td>5 (71)</td><td>0</td><td>0.09</td></tr>
<tr><td>Low signal (body)</td><td>8 (89)</td><td>3 (60)</td><td>0.51</td></tr>
<tr><td>Low signal >1 (body)</td><td>6 (75)</td><td>0</td><td>0.03</td></tr>
<tr><td>Atrophy</td><td>5 (56)</td><td>1 (20)</td><td>0.30</td></tr>
</table>
</td></tr>
</table>

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	Atrophy>1	2 (40)	0	0.51
	Brainstem No (%) Brainstem atrophy	8 (89)	2 (40)	>0.99
	Cerebellum No % Cerebellar atrophy	5 (56)	2 (40)	>0.99

SIGN quality rating	+
Evidence hierarchy grading	DS II
Comments	➢ Matched age groups. ➢ Not known whether level of severity between the groups is matched. ➢ Two experienced neuroradiologists rated the MRI blind to the clinical diagnosis ➢ No inter-rater reliability ➢ Clinical diagnoses criteria specified ➢ Bases of radiological diagnoses specified ➢ No clinical diagnostic follow-up post MRI ➢ No sensitivity/specificity/predictive values data but concordance data available
NCC CC ID	13

Evidence Table **DIAG4a** How effective is magnetic resonance imaging vs long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Author / title / reference / yr	Schocke, M. F. H., Seppi, K., Esterhammer, R., Kremser, C., Jaschke, W., Poewe, W., & Wenning, G. K. 2002, "Diffusion-weighted MRI differentiates the Parkinson variant of multiple system atrophy from PD", *Neurology.*, vol. 58, no. 4, pp. 575-580.
N=	N=28 Total participants ➢ N=10 Multiple System Atrophy-striatonigral degeneration type (MSA-P) ➢ N=11 Parkinson's disease (PD) ➢ N=7 Healthy controls

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<table>
<tr><td></td><td>Location=Parkinson’s out-patient clinic, Austria Sites=1</td></tr>
<tr><td>Research design</td><td>Retrospective diagnostic study with a 1.5-year follow-up.</td></tr>
<tr><td>Aim</td><td>Can diffusion-weighted imaging discriminate between MSA-P and PD?</td></tr>
<tr><td>Population</td><td>MSA-P (probable) clinical diagnosis according to established criteria (Gilman et al. 1998)
PD (probable) clinical diagnosis according to established criteria (Hughes et al 1992)
A detailed clinical history and a careful neurologic examination were performed to exclude the presence of parkinsonian disorders.</td></tr>
<tr><td>Intervention</td><td>MRI Protocol
Conventional dual-echo fast spin-echo and DWI sequences were performed in all patients and healthy volunteers using a 1.5T whole-body MR scanner and a circular polarized head coil. The dual-echo spin-echo sequence had a repetition time of 3,500 ms, echo times of 22 and 90 ms, a slice thickness of 2mm, a matrix of 256X256 pixels, and a field of view of 200 ms. This sequence was performed twice providing 2 X 15 slices that were interleaved without any gap. DWI scans were acquired using a spin-echo type of echoplanar imaging (EPI) sequence with diffusion-sensitising gradients switched in slice direction and three different b-values (30, 300, and 1,100 s/mm²). Sequential sampling of k-space was used with an effective echo time of 123 ms, a bandwidth of 1250 Hz/pixel, and an acquisition matrix of 128 X128, which was interpolated to 256 X256 during image calculation. The DWI sequence provided 20 consecutive slices with a slice thickness of 3 mm and a field of view of 230 mm. The acquisition time of each DWI sequence was 5 seconds.

➢ Two blinded independent raters evaluated the conventional dual-echo fast spin scans for the presence or absence of putaminal atrophy and hyperintensity, those findings occurring significantly more often in patients with MSA than in controls and patients with PD.</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis of MSA-P vs. PD vs. healthy controls</td></tr>
<tr><td>Outcome</td><td>➢ Inter-rater reliability
➢ Subregional Apparent Diffusion Coefficient (ADC) on Diffusion Weighted Images (DWI) in early MSA-P compared with early PD.
➢ Sensitivity, specificity, positive predictive value, and interrater reliability of DWI abnormalities.
➢ MSA-P related structural changes on conventional MRI.</td></tr>
<tr><td>Characteristics</td><td><table><tr><th>Group (n)</th><th>Mean age at DWI</th><th>Mean disease duration at DWI</th></tr></table></td></tr>
</table>

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	<table><tr><td>PD (11)</td><td>64</td><td>2.8</td></tr><tr><td>MSA (10)</td><td>64</td><td>2.9</td></tr><tr><td>Controls (7)</td><td>59</td><td>-</td></tr></table> ➢ Patient age was not significantly different between groups at the time of MRI examination. ➢ There were no significant differences in disease duration of patients with PD and patients with MSA-P. ➢ Patients with MSA-P (median, 38) had significantly higher UPDRS OFF scores than patients with PD (median 26, p=0.001). ➢ The Hoehn and Yahr OFF stages of both patient groups were similar (p>0.1).
Results	***Inter-rater reliability*** ➢ DWI: inter-rater reliability of the segmentation procedure was 0.88 for the first measurement and 0.91 (pearson correlation coefficient) for the second. The inter-rater reliability was 0.94 for rater 1 and 0.90 for rater 2 (pearson correlation coefficient). ➢ MR: Putaminal atrophy k=0.81, putaminal hyperintense rim k=0.83 <u>Subregional ADC on DWI in early MSA-P compared with early PD.</u> ➢ Patients with MSA-P had higher putaminal rADC (median 0.791X 10^3 mm^2/s) than both patients with PD (median 0.698X10^3 mm^2/s, p<0.001) and healthy volunteers (median 0.727X10^3 mm^2/s, p<0.001) ➢ There were no significant differences in putaminal rADC between patients with PD and healthy volunteers ➢ None of the putaminal rADC values in the PD and control group surpassed the lowest value in the MSA-P group ➢ There was no significant group differences in the rADC values in other brain regions such as pons, substantia nigra, globus pallidus, caudate nucleus, thalamus, or grey and white matter. ➢ <u>Sensitivity, specificity, positive predictive value, and interrater reliability of DWI abnormalities.</u> Diffusion-weighted imaging and MRI differentiates the Parkinson variant of Multiple System Atrophy from PD and healthy controls (see table below). <table><tr><td>Validity Measures</td><td>Putamen rADC > 0.760 X 10^{-3} mm^2/s %</td><td>Putaminal hyperintense rim, %</td><td>Putaminal atrophy %</td></tr><tr><td>Sensitivity (MSA-P vs PD)</td><td>100</td><td>80</td><td>60</td></tr><tr><td>Specificity</td><td>100</td><td>91</td><td>100</td></tr></table>

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(MSA-P vs PD)				
Positive Predictive value (MSA-P vs PD)	100	89	100	
Sensitivity (MSA-P vs PD and controls)	100	80	60	
Specificity (MSA-P vs PD and controls)	100	94	100	
PPV (MSA-P vs PD and controls)	100	89	100	

MSA-P related structural changes on conventional MRI.

- Putaminal atrophy was seen exclusively in patients with MSA-P (60% of the patients with MSA-P)
- 80% of patients with MSA-P exhibited a putaminal hyperintense rim, which was seen in only one patient with a clinical diagnoses of PD (see table below)
- Follow-up examination 1.5 years after MRI examination revealed no atypical features or loss of levo-dopa response.

DWI and MRI data

Group (n)	Putamen rADC > 0.760 X 10 ³ mm²⁄s median range	Putaminal atrophy, n	Putaminal hyperintense rim, n
PD (11)	0.698 (0.585-0.759)	0	1
MSA (10)	0.791 (0.760-1.032)	6	8
Controls (7)	0.727 (0.635-0.754)	0	0

SIGN quality rating	+
Evidence hierarchy grading	DS II
Comments	➢ Patients matched for age and disease duration and Hoehn & Yahr OFF stage. ➢ Patients with MSA-P (median, 38) had significantly higher UPDRS OFF scores than patients with PD (median 26, p=0.001)-reflecting differences in the natural history of these disorders. ➢ Clinical diagnosis according to established criteria by a movement disorder specialist experienced in PD. ➢ Two blinded independent raters evaluated the MRI scans. ➢ Inter-rater reliability specified.

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	➢ No long term clinical diagnostic follow-up ➢ Homogeneity in scanning technique (images were acquired by the same scanner and protocol). ➢ Short disease duration (PD=2.8 years; MSA-P=2.9 years)
NCC CC ID	130

Evidence Table **DIAG4a** How effective is magnetic resonance imaging vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Author / title / reference / yr	Righini, A., Antonini, A., Ferrarini, M., De Notaris, R., Canesi, M., Triulzi, F., & Pezzoli, G. 2002, "Thin section MR study of the basal ganglia in the differential diagnosis between striatonigral degeneration and Parkinson disease", *Journal of Computer Assisted Tomography.*, vol. 26, no. 2, pp. 266-271.
N=	N=51 Total participants ➢ N= 27 Parkinson's disease (PD) ➢ N= 24 Multiple System Atrophy- striatonigral degeneration type (MSA-P) Location=Italy Sites= 1
Research design	Retrospective diagnostic study with 1.5 year clinical diagnoses follow-up post MRI
Aim	To evaluate the specificity and sensitivity of an acquisition protocol using thin section MRI to differentiate Multiple System Atrophy from Parkinson's disease.
Population	➢ PD & MSA-P ➢ Clinical diagnosis of probable MSA-P and PD was made based on published criteria (Gilman et al., 1999; Rajput et al., 1991). ➢ All those patients whose diagnoses had been confirmed clinically at least 1.5 years after the first neurologic examination, when the neuroimaging study had been performed.
Intervention	<u>MR Protocol Thick section:</u> Sagittal 5-mm-thick T1-weighted SE images were acquired first; axial 3-mm-thick contiguous double echo CSE images were then obtained centred on the mesencephalon and basal ganglia and orientated perpendicular to the main axis of the mesencephalon; axial 5-mm-thick T2-weighted FSE images were then acquired encompassing the

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<table>
<tr><td></td><td>whole brain and orientated according to the anteroposterior commissural line.
<u>MR Protocol Thin section:</u>
The following MR abnormalities in the thin section (3mm) protocol at the level of the putamen were takes into account:
➢ T2 hypointensity in the dorsolateral putamen equal to or lower than the intensity of the globus pallidus;
➢ A proton density signal in the lateral putamen higher then in the central thalamus.
The presence of at least one of the two following abnormalities was assessed:
➢ A putaminal T2 hypointensity equal to or lower than the intensity of the globus pallidus;
➢ A band of T2 hyperintensity within the putamen.</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis of MSA-P vs. PD</td></tr>
<tr><td>Outcome</td><td>Primary Outcomes:
➢ Sensitivity of CSE 3mm thin section protocol
➢ Specificity of CSE 3mm thin section protocol

Secondary Outcomes:
➢ Sensitivity of and specificity of FSE 5 mm thick section protocol</td></tr>
<tr><td>Characteristics</td><td>There were no statistically significant differences in the mean age and symptom duration at the time of MRI between the two groups.
Parkinson’s disease:
Mean age- 59.8 yrs
Mean symptom duration- 5.7 yrs
MSA-P:
Mean age- 62.0 yrs
Mean symptom duration- 5.9 yrs</td></tr>
<tr><td>Results</td><td>Dorsolateral putamen signal abnormalities:

<table><tr><th></th><th>CSE 3mm protocol
T2 hypointensity</th><th>CSE 3mm protocol
Proton density hyperintensity</th><th>FSE 5 mm protocol
T2 hypointensity or hyperintensity</th></tr><tr><td>PD</td><td>3/27 (88% specificity)</td><td>0/27 (100% specificity)</td><td>0/21 (100% specificity)</td></tr></table></td></tr>
</table>

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	MSA-P | 21/24 (87.5% sensitivity) | 20/24 (83.3% sensitivity) | 9/20 (45% sensitivity) CSE- conventional spin echo FSE- fast spin echo
SIGN quality rating	+
Evidence hierarchy grading	DS Ib
Comments	➢ Not known whether level of severity between the groups is matched ➢ Two senior neuroradiologists, blind to the clinical data, analysed the axial MR images independently. If there was a disagreement between the two raters, the scans were re-evaluated together until a consensus was reached ➢ No inter-rater reliability specified ➢ Homogeneity in scanning technique (images were acquired by the same scanner and protocol) ➢ "Since the study was retrospective, patients were followed clinically for at least 1.5 years after MR scanning, allowing a greater likelihood of clinical diagnoses" ➢ Sensitivity/specificity/predictive values data available
NCC CC ID	129

Evidence Table **DIAG4a** How effective is magnetic resonance imaging vs long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Author / title / reference / yr	Yekhlef, F., Ballan, G., Macia, F., Delmer, O., Sourgen, C., & Tison, F. 2003, "Routine MRI for the differential diagnosis of Parkinson's disease, MSA, PSP, and CBD", *Journal of Neural Transmission.*, vol. 110, no. 2, pp. 151-169.
N=	N=116 Total participants ➢ N=28 Multiple System Atrophy (MSA) (1 certain; 27 probable; 21 MSA-P; 7 MSA-C) ➢ N=30 Progressive Supranuclear Palsy (MSA) (1 certain; 23 probable; 6 possible)

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	➢ N=26 Corticobasal Degeneration (CD) ➢ N=32 Parkinson's disease (PD) Location=out-patients clinic, Austria Sites=1
Research design	Retrospective diagnostic study
Aim	The usefulness of routine MRI for the differential diagnosis of Parkinson's disease with atypical parkinsonian syndromes in everyday clinical practice based on a simple and practical scoring system using a limited number of easily recognisable and pertinent MRI abnormalities.
Population	➢ PD clinically diagnosed according to UKPDSBB criteria for PD (Hughes et al. 1992) ➢ MSA clinically diagnosed according to consensus criteria (Gilman et al., 1998) ➢ PSP clinically diagnosed according to consensus criteria (NINDS-SPSP) ➢ CBD clinically diagnosed according to provisional criteria (Litvan et al., 1997a) ➢ "The clinical diagnostic criteria were strictly applied without taking into account the MRI results" ➢ To increase the PD population the authors used the MRI's previously performed

Intervention	***MRI protocol***
	➢ Routine MRI's were used
	➢ MRI's were performed on 11 different machines with varying slice thickness
	➢ 26 MRI abnormalities were selected based on an exhaustive literature review including:
	  ➢ Atrophy- frontal, parietal, temporal, caudate nucleus, putamen, quadrigeminal plate, midbrain, middle cerebellar peduncle, pons, medulla, and vermis;
	  ➢ Dilatation: lateral ventricle, third ventricle, fourth ventricle, and aqueduct;
	  ➢ T2-hypointensities: putamen and thalamus;
	  ➢ T2-hyperintensities: putamen, pallidum, thalamus, periaqueductal, tegmentum, middle cerebellar peduncle, pons, inferior olivary nuclei, and dentate nuclei.
	
	➢ 11 MRI pointers, most frequently observed and easily recognisable, with the least inter-rater variability were selected
	➢ Four investigators blinded for the patient names and disease status, independently rated all the scans.

Comparison	MSA, PSP, CBD, and PD clinical retrospective diagnosis.
Outcome	➢ Frequency of MRI abnormalities in MSA, PSP, CBD, PD ➢ **Specificity, sensitivity, positive predictive value** of MRI vs. retrospective clinical diagnosis ➢ Inter-rater reliability

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<table>
<tr><td></td><td></td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><th>Group</th><th>Mean age years</th><th>Mean disease duration</th></tr>
<tr><td>MSA</td><td>65.2</td><td>3.4</td></tr>
<tr><td>PSP</td><td>67.7</td><td>2.7</td></tr>
<tr><td>CBD</td><td>67.8</td><td>3.1</td></tr>
<tr><td>PD</td><td>53.6</td><td>6.0</td></tr>
</table>

The mean age was significantly lower in the PD group than in other parkinsonian syndromes (p<0.05).
The mean disease duration was significantly shorter in the PSP patients than in the PD group (p<0.05).

</td></tr>
<tr><td>Results</td><td>

The median total score distinguished PD from other parkinsonian syndromes (p<0.05; MSA, PSP, CBD)
The total score detected ‘significantly’ more pronounced MRI abnormalities in “atypical” parkinsonism but did not distinguish between MSA, PSP, and CBD

<u>Sensitivity, specificity, positive predictive values</u>:

MSA, PSP and CBD groups were distinguished from PD using ROC curves, at threshold total score of 8:

<table>
<tr><th>Groups</th><th>Sensitivity</th><th>Specificity</th><th>Positive predictive value</th></tr>
<tr><td>MSA</td><td>71%</td><td>91%</td><td>87%</td></tr>
<tr><td>PSP</td><td>70%</td><td>91%</td><td>88%</td></tr>
<tr><td>CBD</td><td>90%</td><td>91%</td><td>89%</td></tr>
</table>
<u>Inter-rater reliability</u>
<table>
<tr><th></th><th>Inter-rater reliability k (kappa)</th></tr>
<tr><td>Frontal atrophy</td><td>0.84</td></tr>
</table>
</td></tr>
</table>

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	Lateral ventricle dilation	0.86
	Third ventricle dilation	0.85
	Fourth ventricle dilation	0.82
	Putaminal atrophy	0.66
	Putaminal hypointensities	0.62
	Putaminal hyperintensities	0.42
	Midbrain atrophy	0.59
	Cerebellar vermian atrophy	0.59
	Putaminal subscore	0.90
	Pontocerebellar score	0.90
	Total score	0.80
	Cortical score	0.70
	Midbrain score	0.50

SIGN quality rating	+
Evidence hierarchy grading	DS II
Comments	➢ Diagnostic criteria for groups specified. ➢ Mean age matched for different groups. ➢ The mean disease duration was significantly shorter in the PSP patients than in the PD group ($p<0.05$). ➢ Four investigators blinded for the patient names and disease status, independently rated all the scans. ➢ Heterogeneous use of MRI scanners, varying slice thickness, varying imaging centres/settings ➢ No clinical diagnostic follow-up post MRI
NCC CC ID	135

Evidence Table
DIAG4a
How effective is magnetic resonance imaging vs long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?

Author / title / reference / yr	Seppi, K., Schocke, M. F. H., Esterhammer, R., Kremser, C., Brenneis, C., Mueller, J., Boesch, S., Jaschke, W., Poewe, W., & Wenning, G. K. 2003, "Diffusion-weighted imaging discriminates progressive supranuclear

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	palsy from PD, but not from the parkinson variant of multiple system atrophy", *Neurology.*, vol. 60, no. 6, pp. 922-927.
N=	***N=35 Total participants*** ***N=12 Multiple System Atrophy-P (MSA-P) patients*** N=10 Progressive Supranuclear Palsy (PSP) patients ("Probable" N=10) N=13 Parkinson's disease (PD) patients Location=Parkinson's out-patient clinic, Austria Sites=1
Research design	Diagnostic study with 1 year clinical diagnoses follow-up post DWI
Aim	To examine the sensitivity of diffusion weighted MRI in discriminating Progressive Supranuclear Palsy from PD and MSA-P.
Population	➢ Clinical diagnoses of MSA-P, PSP, and PD was made according to established criteria (Gilman et al. 1998; Hughes et al., 1992) by movement disorder specialists experienced in parkinsonian disorders ➢ A detailed clinical history and a careful neurologic examination were performed ➢ Clinical diagnoses at 1 year follow-up following MRI.
Intervention	Diffusion weighted MRI <u>MRI Protocol:</u> Conventional dual-echo fast spin-echo and DWI sequences were performed in all patients using a 1.5-T whole-body MR scanner and a circular polarised head coil. The dual-echo spin-echo sequence had a repetition time of 3,500 ms, an echo time of 22 and 90 ms, a slice thickness of 2 mm, a matrix of 256X256 pixels, and a field of view of 200 ms. This sequence was performed twice, providing 2X15 slices that were interleaved without any gap. DWI scans were acquired using a spin-echo type of echoplanar imaging sequence with diffusion-sensitising gradients switched in slice direction and three different b-values (30, 300, and 1,100 s/mm2). Sequential sampling of k-space was used with an effective echo time of 123 ms, a bandwidth of 1,250 Hz/pixel, and an acquisition matrix of 128X128, which was interpolated to 256X256 during image calculation. The DWI sequence provided 20 consecutive slices with a slice thickness of 3 mm and a field of view of 230 mm. The acquisition time of each DWI sequence was 5 seconds.
Comparison	Clinical diagnoses of Progressive Supranuclear Palsy (PSP) patients, Parkinson's disease (PD) patients and

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<table>
<tr><td></td><td>Multiple System Atrophy-P (MSA-P) patients compared to DWI diagnoses</td></tr>
<tr><td>Outcome</td><td>

Sensitivity of the test for correctly assigning patients with clinical disease diagnosis
Specificity of the test for correctly assigning controls without the clinical disease diagnosis
Positive predictive value for a subject who tests positive (what is the probability that they have the condition?)
Negative predictive value for a subject who tests negative (what is the probability that they do not have the condition?)

</td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><th>Group (n)</th><th>M/F</th><th>Age at DWI (mean)</th><th>Disease duration at DWI (mean)</th><th>Hoehn & Yahr range</th><th>UPDRS mean (range)</th></tr>
<tr><td>PD (13)</td><td>7/6</td><td>62 (10.6)</td><td>3.0 (1.2)</td><td>I-III</td><td>26 (13-38)</td></tr>
<tr><td>MSA (12)</td><td>3/9</td><td>63 (6.6)</td><td>2.9 (1.1)</td><td>II-III</td><td>38 (29-53)</td></tr>
<tr><td>PSP (10)</td><td>5/5</td><td>68 (6.9)</td><td>2.7 (1.1)</td><td>II-III</td><td>35 (21-45)</td></tr>
</table>
UPDRS “off” state of Unified PD Rating Scale part III (motor section)

No significant differences between the groups on the above bar UPDRS “off” scores- patients with MSA-P and PSP had higher UPDRS “off” scores than patients with PD.
</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th>Group (n)</th><th>Putaminal rADC, X 10^{-3} mm^2/s, median (range)*</th><th>Caudate rADC, X 10^{-3} mm^2/s, median (range)</th><th>Pallidal rADC, X 10^{-3} mm^2/s, median (range)</th></tr>
<tr><td>PD (13)</td><td>0.728 (0.585; 0.759)</td><td>0.713 (0.645; 0.827)</td><td>0.655 (0.500; 0.776)</td></tr>
<tr><td>MSA (12)</td><td>0.806 (0.760; 1.046)</td><td>0.792 (0.710; 1.097)</td><td>0.731 (0.488; 0.879)</td></tr>
<tr><td>PSP (10)</td><td>0.814 (0.701; 0.970)</td><td>0.793 (0.711; 1.049)</td><td>0.742 (0.615; 0.822)</td></tr>
</table>

Increase in putaminal rADC values in MSA-P ($p<0.001$) and PSP ($p<0.001$) compared with PD;
None of the putaminal rADC values in the PD group surpassed the lowest value in the MSA-P group.
MSA-P ($p=0.007$) and PSP ($p=0.015$) both showed increased rADCs in the caudate nucleus compared with patients with PD.
An increase in pallidal rADCs in PSP ($p=0.005$) but not MSA-P compared with the PD group.
No significant group difference for any of the rADCs between patients with MSA-P and PSP.
RADC group differences of the other ROIs showed no significance.

</td></tr>
</table>

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	Sensitivity/specificity/positive predictive value/negative predictive value ➢ An rADC of > 0.760 X 10^{-3} mm^2/s is indicative of a diagnosis of atypical PD and a rADC<0.760X 10^{-3} mm^2/s is indicative of a diagnosis of PD. ➢ Sensitivity for the cut-off level of 0.760 X 10^{-3} mm^2/s was 96%, specificity 100%, the PPV 100%, and the NPV 93%. When using putaminal rADC of > 0.760 X 10^{-3} mm^2/s to distinguish MSA-P from PD: ➢ Sensitivity, specificity, positive predictive value, negative predictive value=100% When using putaminal rADC of > 0.760 X 10^{-3} mm^2/s to distinguish PSP from PD: ➢ Sensitivity = 90% ➢ Specificity=100% ➢ Positive predictive value=100% ➢ Negative predictive value=93% No patient with PD was classified as having APD and no patient with MSA-P was classified as having PD.
SIGN quality rating	+
Evidence hierarchy grading	DS II
Comments	➢ Patients matched for age, disease duration & Hoehn & Yahr "off" stage; ➢ Clinical diagnosis according to established criteria by a movement disorder specialist experienced in PD; ➢ Not enough information about investigators- number of investigators, inter-rater reliability etc. ➢ Blinding of investigators to clinical diagnosis not specified. ➢ Scanning homogeneity ➢ One-year follow-up after DWI examination of clinical diagnosis.
NCC CC ID	133

Evidence Table
DIAG 4c
How effective is magnetic resonance imaging vs. long-term clinical follow-up in determining an accurate diagnosis in patients with parkinsonian syndrome?

Bibliographic reference	Paviour DC, Price SL, Stevens JM, Lees AJ, Fox NC. Quantitative MRI measurement of superior cerebellar peduncle in progressive supranuclear palsy. *Neurology* 2005;**64**:675-9.

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<table>
<tr><td>Study type</td><td>Diagnostic</td></tr>
<tr><td>Evidence level</td><td>+ or II</td></tr>
<tr><td>Study objective</td><td>To determine whether MRI measurements of the superior cerebellar peduncle (SCP) may help in the diagnosis of progressive supranuclear palsy (PSP) during life.</td></tr>
<tr><td>Number of patients</td><td>N=19 PSP patients
N=10 multiple system atrophy (MSA) patients
N=12 Parkinson’s disease (PD) patients
N=12 healthy controls

Location: UK sites: single</td></tr>
<tr><td>Patient characteristics</td><td>Of the 19 patients with PSP, 12 were clinically definite and 7 clinically probable according to the National Institute of Neurologic Disorders and Stroke-SPSP diagnostic criteria. 10 patients with MSA were diagnosed according to the consensus clinical criteria, and the 12 patients with PD were diagnosed according to the Queen Square Brain Bank clinical diagnostic criteria.

<table>
<tr><th></th><th>PSP</th><th>MSA</th><th>PD</th><th>Controls</th><th>P value</th></tr>
<tr><td>N=</td><td>19</td><td>10</td><td>12</td><td>12</td><td>-</td></tr>
<tr><td>Mean age, y</td><td>64.7 ± 5.6</td><td>62.6 ± 7.0</td><td>65.2 ± 9.1</td><td>67.4 ± 4.6</td><td>-</td></tr>
<tr><td>Mean disease duration, y</td><td>4.6 ± 1.6</td><td>5.2 ± 1.7</td><td>13.25 ± 6.7</td><td>-</td><td>PSP v PD, MSA v PD P<0.001</td></tr>
<tr><td>UPDRS II</td><td>19.3 ± 6.5</td><td>25.4 ± 7.2</td><td>13.9 ± 5.1</td><td>-</td><td>MSA v PD, P<0.001</td></tr>
<tr><td>UPDRS III</td><td>20.0 ± 7.5</td><td>27.3 ± 10.1</td><td>16.7 ± 5.1</td><td>-</td><td>MSA v PD, P=0.007</td></tr>
<tr><td>Mean Hoehn and Yahr</td><td>3.5 ± 0.7</td><td>3.9 ± 0.9</td><td>2.6 ± 0.6</td><td>-</td><td>PSP v PD, MSA v PD P=0.004</td></tr>
<tr><td>Mean MMSE</td><td>26.2 ± 3.0</td><td>26.3 ± 3.4</td><td>27.7 ± 2.5</td><td>-</td><td>-</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>T1-weighted MRI, 1.5 mm thick slices (see paper for more details)</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis</td></tr>
<tr><td>Length of follow-up</td><td>None stated</td></tr>
<tr><td>Outcome measures</td><td>Sensitivity, specificity, positive and negative predictive values</td></tr>
<tr><td>Effect size</td><td>➢ The mean inter-rater variability in SCP measurements was 12.5% (range 0.2 to 36%)
➢ Mean total intracranial volumes (TIV) corrected SCP volumes differed between the groups (p<0.001)
➢ There was no difference between the TIV (p=0.9) or total brain volumes (p=0.3)</td></tr>
</table>

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	➢ Post-hoc analysis identified differences in mean TIV corrected SCP volumes between PSP and controls (p=<0.001), MSA (p=0.001) and PD (p=0.003) ➢ No significant differences in corrected SCP volume, TIV or total brain volumes were identified ➢ A negative correlation was found between Hoehn and Yahr score and corrected SCP volume (p=0.02) ➢ In PSP group alone this was not significant (p=0.08) ➢ The statistical; tests did not identify any correlation between age (p=0.3), disease duration (p=0.4), UPDRS II (p=0.3), UPDRS III (p=0.2) or MMSE (p=0.5) scores and the corrected SCP measurement in PSP group ➢ SCP atrophy on visual rating differentiated PSP from other conditions and controls with a sensitivity of 74% and a specificity of 94% ➢ 14/19 PSP cases were graded as having SCP atrophy while the SCP was rated as atrophic in only 2/34 non-PSP cases ➢ Both non-PSP cases of SCP atrophy had a clinical diagnosis of MSA (positive and negative predictive values of 88% and 86%) ➢ In quantitative volume measures, using receiver operating characteristics (ROC) curve analysis, the best sensitivity and specificity of the volumetric analysis was 74% and 77%
Source of funding	Non-profit
Additional comments	➢ Blinded rater unaware of clinical diagnosis ➢ Mean inter-rater reliability tested ➢ Small sample size ➢ No long-term clinical follow-up
Citation	
NCC CC ID (Ref Man)	19831

Evidence Table
DIAG 4a
How effective is magnetic resonance imaging vs. long-term clinical follow-up in determining an accurate diagnosis in patients with parkinsonian syndrome?

Bibliographic reference	Righini A, Antonini A, De Notaris R, Bianchini E, Meucci N, Sacilotto G *et al*. MR imaging of the superior profile of the midbrain: Differential diagnosis between progressive supranuclear palsy and Parkinson disease. *American Journal of Neuroradiology* 2004;**25**:927-32.

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<table>
<tr><td>Study type</td><td>Diagnostic study</td></tr>
<tr><td>Evidence level</td><td>++ or Ib</td></tr>
<tr><td>Study objective</td><td>To determine whether an abnormal superior midbrain profile (flat or concave aspect) is a more practical diagnostic parameter for PSP.</td></tr>
<tr><td>Number of patients</td><td>N=52 parkinsonian patients
N=27 with Parkinson’s disease
N=25 with progressive supranuclear palsy (PSP)

Location: Italy sites: single</td></tr>
<tr><td>Patient characteristics</td><td>25 consecutive patients with PSP were enrolled who had all presented with early onset postural instability, gaze palsy, axial rigidity, bradykinesia, and no notable response to dopaminergic drugs. They all fulfilled the clinical diagnostic criteria for probable PSP.
27 PD patients were selected who all fulfilled the UKPDS brain bank criteria.
All patients had to have been clinically followed-up for at least 1.5 years after the MRI study to increase confidence in clinical diagnosis, and the diagnosis had to be confirmed in all of them.
The two groups did not differ in mean age or symptom duration at the time of MR imaging, but mean Hoehn and Yahr stage was significantly higher (p<0.001) for PSP because of the severe and rapid course of this disease.
<table>
<tr><th></th><th>PD</th><th>PSP</th></tr>
<tr><td>Mean age, y</td><td>67.63 ± 3.66</td><td>68.88 ± 6.48</td></tr>
<tr><td>Symptom duration, y</td><td>5.25 ± 3.48</td><td>5.30 ± 3.28</td></tr>
<tr><td>Hoehn and Yahr stage</td><td>2.30 ± 0.72</td><td>2.78 ± 0.64</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>1.5T MRI imaging: first sagittal 5-mm thick T1-weighted spin-echo images were acquired. Then axial 3-mm thick contiguous double-echo conventional spin-echo imaged centred on the midbrain and basal ganglia and oriented perpendicular to the main axis of the midbrain, and axial 5 mm thick T2 weighted fast spin-echo (FSE) images were acquired to encompass the whole brain.</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis</td></tr>
<tr><td>Length of follow-up</td><td>1.5 years</td></tr>
<tr><td>Outcome measures</td><td>Sensitivity, specificity</td></tr>
<tr><td>Effect size</td><td>➢ The presence of abnormal superior profile of the midbrain had a 68% sensitivity and an 88.8% specificity
➢ The presence of global atrophy of the midbrain had 68% sensitivity and 77.7% specificity
➢ The presence of abnormal tegmental T2 hyperintensity had a sensitivity of 28% and a specificity of</td></tr>
</table>

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	100% ➢ Only 14.8% of PD patients and 24% of PSP patients had abnormal T2 hypointensity in the posterolateral putamen and none had abnormal putaminal proton density hyperintensity ➢ The PSP population had an average AP midbrain diameter smaller than that of the PD cohort (13.5 ± 1.4 mm vs. 15.5 ± 1.6 mm, $p<0.0001$) but here was an important overlap between the two populations ➢ The observed threshold value of 12mm distinguished only 7 of the 25 subjects with PSP ➢ Discordance between the two readers was lower for the superior profile of midbrain sign (8 of 52 cases), similar for the tegmental T2 hyperintensity (9 of 52 cases) and higher for global atrophy of midbrain (16 of 52 cases) ➢ There was no significant correlation between alteration in the superior profile of the midbrain and reduction in AP diameter (p=0.4) ➢ There was significant correlation between alteration in the superior midbrain profile and global atrophy of the midbrain (p-0.009)
Source of funding	Not stated
Additional comments	➢ Two senior neuroradiologists blinded to clinical data analysed the MR images independently and consecutively ➢ Do not know whether follow-up clinical examiners were blind to MRI data ➢ No positive or negative predictive values
Citation	
NCC CC ID (Ref Man)	19827

Evidence Table **DIAG 4a** How effective is magnetic resonance imaging vs. long-term clinical follow-up in determining an accurate diagnosis in patients with parkinsonian syndrome?	
Bibliographic reference	Price S, Paviour D, Scahill R, Stevens J, Rossor M, Lees A *et al*. Voxel-based morphometry detects patterns of atrophy that help differentiate progressive supranuclear palsy and Parkinson's disease. *Neuroimage* 2004;**23**:663-9.
Study type	Diagnostic
Evidence level	+ or II

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<table>
<tr><td>Study objective</td><td>To evaluate the clinical utility of voxel-based morphometry (VBM) in bradykinetic rigid syndromes and to apply these findings as a guide to a neuroradiological distinction between PSP, PD and controls.</td></tr>
<tr><td>Number of patients</td><td>N= 36 parkinsonian patients
N=12 PSP patients
N=12 PD patients
N=12 controls

Location: sites:</td></tr>
<tr><td>Patient characteristics</td><td>12 patients with PSP (8 clinically definite, 4 clinically probable) according to NINDS criteria and 12 patients with PD according to Queen Square Brain bank criteria were included as well as 12 controls with no history of neurological illness. The groups were age and sex matched.
<table>
<tr><th></th><th>PSP</th><th>PD</th><th>Controls</th></tr>
<tr><td>N (male)</td><td>12 (7)</td><td>12 (8)</td><td>12 (8)</td></tr>
<tr><td>Age at scan</td><td>65.3 ± 5.8</td><td>65.4 ± 9.2</td><td>67.4 ± 4.6</td></tr>
<tr><td>Disease duration</td><td>4.8 ± 1.7 *</td><td>13.3 ± 6.7</td><td>-</td></tr>
<tr><td>UPDRS II</td><td>19.2 ± 7.8</td><td>13.9 ± 5.1</td><td>-</td></tr>
<tr><td>UPDRS III</td><td>20.4 ± 8.7</td><td>16.7 ± 5.1</td><td>-</td></tr>
<tr><td>FAB</td><td>12.4 ± 3.1*</td><td>16.5 ± 1.4</td><td>-</td></tr>
<tr><td>MMSE</td><td>27 ± 3.3</td><td>28 ± 1.9</td><td>-</td></tr>
</table>
* Significant difference between PSP and PD patients (p<0.01)</td></tr>
<tr><td>Intervention</td><td>T-1 weighted volumetric MRI scans were acquired on a 1.5 GE Signa Unit using a spoiled gradient-echo technique. This yielded 124 contiguous 1.5 mm thick slices. For VBM analysis detail refer to paper.</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis</td></tr>
<tr><td>Length of follow-up</td><td>None stated</td></tr>
<tr><td>Outcome measures</td><td>Sensitivity, specificity</td></tr>
<tr><td>Effect size</td><td>➢ Subjects were allocated to either PSP or ‘non-PSP’ based on the presence or absence of atrophy on neuroradiological review of MR images
➢ The neuroradiologist was asked to rate the scans based on the subcortical region of tissue loss highlighted using VBM
➢ Controls and PD imaged were considered together as VBM detected no differences between these groups</td></tr>
</table>

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	➢ The VBM revealed that comparing this region on coronal imaged together with the axial and sagittal images as a guide to radiological diagnosis- there was a sensitivity of 83% and a specificity of 79% ➢ Of the two false negatives in the PSP group, one had a diagnosis of clinically probable PSP and one a clinically definite PSP ➢ Of the 5 false positives, two were non-diseased controls and 3 had a diagnosis of PD
Source of funding	
Additional comments	➢ An experienced neuroradiologist blinded to clinical diagnosis and clinical details ➢ No follow-up ➢ No positive or negative predictive values ➢ No inter-rater reliability ➢ Small sample sizes
Citation	Non-profit
NCC CC ID (Ref Man)	19826

DIAG 4b – section 5.8

Evidence Table **Q4b** How effective is magnetic resonance volumetry vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Author / title / reference / yr	Cordato, N. J., Pantelis, C., Halliday, G. M., Velakoulis, D., Wood, S. J., Stuart, G. W., Currie, J., Soo, M., Olivieri, G., Broe, G. A., & Morris, J. G. L. 2002, "Frontal atrophy correlates with behavioural changes in progressive supranuclear palsy", *Brain.*, vol. 125, no. 4, pp. 789-800.
N=	N=61 Total participants ➢ N=21 Progressive Supranuclear Palsy (PSP) ➢ N=17 Parkinson's disease (PD) ➢ N=23 Normal Controls Location= Movement Disorders Clinic at a large Teaching Hospital (Westmead Hospital), Sydney/Melbourne site

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	Sites=2
Research design	Retrospective diagnostic study
Aim	To examine the relationship between measures of cortical, subcortical, medial temporal and global brain volumes for discriminating between PSP and PD using MRV vs. clinical diagnosis.
Population	**PSP:** diagnostic criteria established by the National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy Inc for PSP. **PD:** diagnostic criteria according to the United Kingdom Parkinson's disease brain bank criteria **Normal Controls:** age and sex matched controls without neurological, psychiatric or neuroradiological abnormalities were recruited from spouses, care givers and friends of the patients in addition to hospital and community volunteers. Entry criteria for controls included functional independence on the Barthel's Activities of Daily Living Scale (ADL) as well as scores of zero on the Clinical Dementia Rating Scale, >27 on the Mini-Mental State Geriatric Depression Scale ➢ Exclusion criteria for disease and control cases: history of ischaemic heart disease, cardiac/coronary artery surgery, major head injury, drug/alcohol abuse, major psychiatric or focal neurological disorders, and structural lesions including substantial white matter change on proton density and T2-weighted MRI brain images.
Intervention	MRI scan: Three dimensional magnetisation –prepared rapid gradient-echo sequences 9.7/4/1/12 [TR (repetition time)/ TE (echo time)/NEX (number of excitations)/FA (flip angle), 246 X1.02 mm thick contiguous transverse slices were acquired for detection of structural abnormalities. One rater performed all MRI volume measurements from the MPRAGE dataset using ANALYZE 7.5 software. The volumetric analyses were performed 6 months following completion of all clinical assessments and MRI scan acquisitions at a separate site in Melbourne. Investigator was blinded to patient identity and clinical diagnosis. All disease and control cases underwent the same standardised specialist neurological assessment administered by one clinician with history and physical examinations performed within 2 weeks of MRI acquisition. An experienced neuroradiologist reviewed all MRI films. Investigators were blinded to patient identity and clinical diagnosis. Protocol for measurement of various cranial volumes specified.
Comparison	Retrospective clinical diagnosis of patients with PSP and PD
Outcome	Volumetric variables; Clinicoradiological correlations; Predictive statistics (sensitivity, specificity for clinical diagnosis of PSP and PD vs. MRV diagnosis)

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<table>
<tr><td>Characteristics</td><td>Patient characteristics
<table>
<tr><th></th><th>Controls</th><th>PSP</th><th>PD</th></tr>
<tr><td>Gender</td><td>14:9</td><td>14:7</td><td>13:4</td></tr>
<tr><td>Mean age (years)</td><td>71.5</td><td>70.3</td><td>67.7</td></tr>
<tr><td>Mean disease duration (months)</td><td>N/A</td><td>47.7</td><td>94.3</td></tr>
<tr><td>Total UPDRS score</td><td>0.6</td><td>45.1</td><td>32.3</td></tr>
<tr><td>Hoehn and Yahr stage</td><td>0</td><td>3.8</td><td>2.6</td></tr>
</table>
Disease severity differed between groups (UPDRS scores t=2.4, P=0.02; H&Y scores t=4.4, p<0.001) and durations (mean disease duration t=-4.1, p<0.001).</td></tr>
<tr><td>Results</td><td><u>Predictive statistics- sensitivity, specificity</u>
➢ A discriminant function analyses was performed to determine whether the volume measures could be useful predictors of diagnostic group
➢ This resulted in two significant canonical discriminant functions. The second discriminant function added significantly to the discrimination provided by the first (Wilk's lambda=0.79, x^2=77.73 d.f.=10, p<0.001).
➢ The cross validated classification of PSP was very good, with a sensitivity of 95.2% (20 out of 21) and a specificity of 90.9% (20 out of 22) relative to the other two groups.
➢ No significant discriminant findings between Parkinson's disease patients and controls.</td></tr>
<tr><td>SIGN quality rating</td><td>+</td></tr>
<tr><td>Evidence hierarchy grading</td><td>DSIb</td></tr>
<tr><td>Comments</td><td>➢ Age, and sex matched.
➢ Disease severity differed between groups
➢ Clinical diagnoses criteria specified
➢ Investigators were blinded to patient identity and clinical diagnosis
➢ Homogeneity in scanning technique
➢ No clinical diagnostic follow-up post MRI
➢ Sensitivity/specificity data available</td></tr>
<tr><td>NCC CC ID</td><td>123</td></tr>
</table>

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DIAG 4c – section 5.9

Evidence Table **DIAG4c** How effective is magnetic resonance spectroscopy vs long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Author / title / reference / yr	Clarke, C. E. & Lowry, M. 2001, "Systematic review of proton magnetic resonance spectroscopy of the striatum in parkinsonian syndromes", *European Journal of Neurology.*, vol. 8, no. 6, pp. 573-577.
N=	11 studies N= 3 – 151 IPD range N= 4 –97 Control range Sites=multiple
Research design	Systematic review of mixed study designs
Aim	(1) Clarifying the role of MRS in the differential diagnosis of parkinsonian syndromes; (2) Informing decisions about future work.
Population	Parkinsonian syndromes
Intervention	Magnetic resonance spectroscopy of striatal structures
Comparison	Clinical diagnoses
Outcome	NAA/Cr and N-acetylaspartate/choline levels changes in various parkinsonian sub-groups
Characteristics	No details regarding the population characteristics
Results	One multinational study with as many IPD patients as the remaining studies combined, failed to identify and difference in NAA/Cr or NAA/Cho ratios between IPD cases and healthy controls (means of defining IPD diagnosis not stated). Subgroups defined on age have not been analysed. 6 further studies found no significant differences between IPD and controls One study found NAA/Cho ratios were reduced in de novo Vs controls but not significantly reduced in cases with complications, and this was confirmed by 2 other studies one of which also showed reduced NAA/Cr in IPD with or without complications. Findings of reduced NAA/Cho and NAA/Cr ratios have been made in both MSA and IPD

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	populations. Authors state that "It is contended that no clear conclusions on the change in metabolite concentrations and ratios should be drawn from such heterogeneous results". More research is needed before conclusions can be reached
SIGN quality rating	+
Evidence hierarchy grading	DS III
Comments	➢ Database searches are limited to Medline, with identified studies reference lists analysed and conference proceedings identified ➢ Short description of research methodology ➢ No formal quality assessment of studies documented ➢ Correspondence with authors confirms that informal evaluation of study quality and description given in discussion ➢ Significant heterogeneity in study methodologies and outcome measures ➢ Population characteristics limited.
Studies Included	Davie et al. 1995; 1997; Ray Chaudhuri et al., 1996; Ellis et al., 1996; 1997; Hu et al. 1998; Clarke et al., 1997; 2000; Cruz et al., 1997; Tedeschi et al., 1997; Turjanski et al., 1997; Tan et al., 1998; Federico et al., 1999; Ross et al., 1999; Simoes-Ribeiro et al., 1999.
NCC CC ID	17

DIAG 6 – section 5.6

Evidence Table **DIAG4a** How effective is magnetic resonance imaging vs long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Author / title / reference / yr	Schocke, M. F. H., Seppi, K., Esterhammer, R., Kremser, C., Jaschke, W., Poewe, W., & Wenning, G. K. 2002, "Diffusion-weighted MRI differentiates the Parkinson variant of multiple system atrophy from PD", *Neurology.*, vol. 58, no. 4, pp. 575-580.
N=	N=28 Total participants ➢ N=10 Multiple System Atrophy-striatonigral degeneration type (MSA-P) ➢ N=11 Parkinson's disease (PD)

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<table>
<tr><td></td><td>➢ N=7 Healthy controls

Location=Parkinson's out-patient clinic, Austria Sites=1</td></tr>
<tr><td>Research design</td><td>Retrospective diagnostic study with a 1.5-year follow-up.</td></tr>
<tr><td>Aim</td><td>Can diffusion-weighted imaging discriminate between MSA-P and PD?</td></tr>
<tr><td>Population</td><td>MSA-P (probable) clinical diagnosis according to established criteria (Gilman et al. 1998)
PD (probable) clinical diagnosis according to established criteria (Hughes et al 1992)
A detailed clinical history and a careful neurologic examination were performed to exclude the presence of parkinsonian disorders.</td></tr>
<tr><td>Intervention</td><td>MRI Protocol
Conventional dual-echo fast spin-echo and DWI sequences were performed in all patients and healthy volunteers using a 1.5T whole-body MR scanner and a circular polarized head coil. The dual-echo spin-echo sequence had a repetition time of 3,500 ms, echo times of 22 and 90 ms, a slice thickness of 2mm, a matrix of 256X256 pixels, and a field of view of 200 ms. This sequence was performed twice providing 2 X 15 slices that were interleaved without any gap. DWI scans were acquired using a spin-echo type of echoplanar imaging (EPI) sequence with diffusion-sensitising gradients switched in slice direction and three different b-values (30, 300, and 1,100 s/mm^2). Sequential sampling of k-space was used with an effective echo time of 123 ms, a bandwidth of 1250 Hz/pixel, and an acquisition matrix of 128 X128, which was interpolated to 256 X256 during image calculation. The DWI sequence provided 20 consecutive slices with a slice thickness of 3 mm and a field of view of 230 mm. The acquisition time of each DWI sequence was 5 seconds.

➢ Two blinded independent raters evaluated the conventional dual-echo fast spin scans for the presence or absence of putaminal atrophy and hyperintensity, those findings occurring significantly more often in patients with MSA than in controls and patients with PD.</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis of MSA-P vs. PD vs. healthy controls</td></tr>
<tr><td>Outcome</td><td>➢ Inter-rater reliability
➢ Subregional Apparent Diffusion Coefficient (ADC) on Diffusion Weighted Images (DWI) in early MSA-P compared with early PD.
➢ Sensitivity, specificity, positive predictive value, and interrater reliability of DWI abnormalities.
➢ MSA-P related structural changes on conventional MRI.</td></tr>
<tr><td>Characteristics</td><td><table><tr><th>Group (n)</th><th>Mean age at DWI</th><th>Mean disease</th></tr></table></td></tr>
</table>

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		duration at DWI
PD (11)	64	2.8
MSA (10)	64	2.9
Controls (7)	59	-

- Patient age was not significantly different between groups at the time of MRI examination.
- There were no significant differences in disease duration of patients with PD and patients with MSA-P.
- Patients with MSA-P (median, 38) had significantly higher UPDRS OFF scores than patients with PD (median 26, p=0.001).
- The Hoehn and Yahr OFF stages of both patient groups were similar (p>0.1).

Results

Inter-rater reliability

- DWI: inter-rater reliability of the segmentation procedure was 0.88 for the first measurement and 0.91 (pearson correlation coefficient) for the second. The inter-rater reliability was 0.94 for rater 1 and 0.90 for rater 2 (pearson correlation coefficient).
- MR: Putaminal atrophy k=0.81, putaminal hyperintense rim k=0.83

Subregional ADC on DWI in early MSA-P compared with early PD.

- Patients with MSA-P had higher putaminal rADC (median 0.791X 10^3 mm^2/s) than both patients with PD (median 0.698X10^3 mm^2/s, p<0.001) and healthy volunteers (median 0.727X10^3 mm^2/s, p<0.001)
- There were no significant differences in putaminal rADC between patients with PD and healthy volunteers
- None of the putaminal rADC values in the PD and control group surpassed the lowest value in the MSA-P group
- There was no significant group differences in the rADC values in other brain regions such as pons, substantia nigra, globus pallidus, caudate nucleus, thalamus, or grey and white matter.

- Sensitivity, specificity, positive predictive value, and interrater reliability of DWI abnormalities.

Diffusion-weighted imaging and MRI differentiates the Parkinson variant of Multiple System Atrophy from PD and healthy controls (see table below).

Validity Measures	Putamen rADC > 0.760 X 10^{-3} mm^2/s %	Putaminal hyperintense rim, %	Putaminal atrophy %
Sensitivity (MSA-P vs PD)	100	80	60

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Specificity (MSA-P vs PD)	100	91	100
Positive Predictive value (MSA-P vs PD)	100	89	100
Sensitivity (MSA-P vs PD and controls)	100	80	60
Specificity (MSA-P vs PD and controls)	100	94	100
PPV (MSA-P vs PD and controls)	100	89	100

MSA-P related structural changes on conventional MRI.

- Putaminal atrophy was seen exclusively in patients with MSA-P (60% of the patients with MSA-P)
- 80% of patients with MSA-P exhibited a putaminal hyperintense rim, which was seen in only one patient with a clinical diagnoses of PD (see table below)
- Follow-up examination 1.5 years after MRI examination revealed no atypical features or loss of levo-dopa response.

DWI and MRI data

Group (n)	Putamen rADC > 0.760 X 10 ^{3} mm^{2}⁄s median range	Putaminal atrophy, n	Putaminal hyperintense rim, n
PD (11)	0.698 (0.585-0.759)	0	1
MSA (10)	0.791 (0.760-1.032)	6	8
Controls (7)	0.727 (0.635-0.754)	0	0

SIGN quality rating	+
Evidence hierarchy grading	DS II
Comments	➢ Patients matched for age and disease duration and Hoehn & Yahr OFF stage. ➢ Patients with MSA-P (median, 38) had significantly higher UPDRS OFF scores than patients with PD (median 26, p=0.001)-reflecting differences in the natural history of these disorders. ➢ Clinical diagnosis according to established criteria by a movement disorder specialist experienced in PD. ➢ Two blinded independent raters evaluated the MRI scans.

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	➢ Inter-rater reliability specified. ➢ No long term clinical diagnostic follow-up ➢ Homogeneity in scanning technique (images were acquired by the same scanner and protocol). ➢ Short disease duration (PD=2.8 years; MSA-P=2.9 years)
NCC CC ID	130

Evidence Table **DIAG4a** How effective is magnetic resonance imaging vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Author / title / reference / yr	Bhattacharya, K., Saadia, D., Eisenkraft, B., Yahr, M., Olanow, W., Drayer, B., & Kaufmann, H. 2002, "Brain magnetic resonance imaging in multiple-system atrophy and Parkinson disease: A diagnostic algorithm", *Archives of Neurology.*, vol. 59, no. 5, pp. 835-842.
N=	N=39 Total participants ➢ N=14 Multiple System Atrophy-Predominant Parkinsonism participants (MSA-P) ➢ N=4 Multiple System Atrophy-marked Cerebella ataxia (MSA-C) ➢ N=21 Parkinson's disease (PD) Location=Mount Sinai Medical Centre, New York Sites=1
Research design	Retrospective diagnostic study
Aim	To determine concordance between clinical and MR imaging-based diagnoses of MSA-P and PD.
Population	➢ Parkinson's disease as diagnosed according to the UK Brain Bank criteria. ➢ MSA (MSA-C/MSA-P) as diagnosed according to published criteria (Gilman et al., 1998)
Intervention	***MRI Protocol*** Sagittal T1-weighted images (repetition/time/echo time, 600/14 seconds; slice thickness, 5 mm), axial intermediate and T2-weighted sequences (repetition time /echo time, 2500/30-90 seconds; slice thickness, 5 mm), and inversion recovery axial T1 images (repetition time/echo time/inversion time, 2500/20/800 seconds; slice thickness, 4 mm).

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<table>
<tr><td></td><td>Radiological diagnosis based on:
MSA-P: Moderate to severe putaminal abnormalities or mild putaminal change together with brainstem or cerebellar abnormality.
PD: Near-normal MR images with few or no abnormalities, or the presence of only mild abnormality in the putamen, brainstem, or cerebellum.
MSA-C: Cerebellar changes in the brainstem or cerebellum were moderate or severe regardless of putaminal change.
➢ In addition, the neuroradiologists used their overall impression to assign a diagnosis.</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis of Multiple System Atrophy vs. Parkinson’s disease</td></tr>
<tr><td>Outcome</td><td>Concordance between radiological and clinical diagnoses</td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><th>Groups</th><th>Male/female n</th><th>Mean age years</th><th>Mean disease duration years</th></tr>
<tr><td>MSA</td><td>13/5</td><td>59</td><td>5</td></tr>
<tr><td>MSA-P</td><td>9/5</td><td>59</td><td>5</td></tr>
<tr><td>MSA-C</td><td>All men</td><td>57</td><td>4</td></tr>
<tr><td>PD</td><td>15/6</td><td>64</td><td>7</td></tr>
</table>
➢ Patients in all groups had similar ages.
</td></tr>
<tr><td>Results</td><td>
Concordance between radiological and clinical diagnoses
➢ Neuroradiologists diagnosed 5 patient’s with a clinical diagnoses of MSA-P as having PD (Patients with MSA-P wrongly diagnosed radiologically as having PD had significantly shorter disease duration (4 vs. 6 years; p=0.05) although they were of similar age. “Brain MR imaging may be of limited value in patients with MSA-P early in their disease, as it may show only mild abnormalities”)
➢ Neuroradiologist diagnosed 2 patients with clinical diagnoses of PD as having MSA-P.
➢ Neuroradiologist diagnosed 1 patient with clinical diagnoses of MSA-C as having PD.
<table>
<tr><th>Brain MR imaging findings in patients with MSA-P with concordant radiological diagnosis of MSA-P and nonconcordant radiological diagnosis of PD</th><th>Diagnosis of MSA-P</th><th>Diagnosis of PD</th><th>P value</th></tr>
<tr><td>Mean age years</td><td>61</td><td>57</td><td>0.25</td></tr>
</table>
</td></tr>
</table>

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	Mean disease duration	6	4	0.05
	Putamen N (%)	7 (78)	4 (80)	> 0.99
	Lateral slitlike hyperintensity	7 (78)	4 (80)	>0.99
	Lateral slitlike hyperintensity >1	5 (71)	0	0.09
	Low signal (body)	8 (89)	3 (60)	0.51
	Low signal >1 (body)	6 (75)	0	0.03
	Atrophy	5 (56)	1 (20)	0.30
	Atrophy>1	2 (40)	0	0.51
	Brainstem No (%) Brainstem atrophy	8 (89)	2 (40)	>0.99
	Cerebellum No % Cerebellar atrophy	5 (56)	2 (40)	>0.99
SIGN quality rating	+			
Evidence hierarchy grading	DS II			
Comments	➢ Matched age groups. ➢ Not known whether level of severity between the groups is matched. ➢ Two experienced neuroradiologists rated the MRI blind to the clinical diagnosis ➢ No inter-rater reliability ➢ Clinical diagnoses criteria specified ➢ Bases of radiological diagnoses specified ➢ No clinical diagnostic follow-up post MRI ➢ No sensitivity/specificity/predictive values data but concordance data available			
NCC CC ID	13			

Evidence Table
Diag 6
How effective is positron emission tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with parkinsonian syndrome?

Bibliographic reference	Schreckenberger M, Hagele S, Siessmeier T, Buchholz H-G, Armbrust-Henrich H, Rosch F *et al*. The

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	dopamine D<inf>2</inf> receptor ligand ¹⁸F- desmethoxyfallypride: An appropriate fluorinated PET tracer for the differential diagnosis of parkinsonism. *European Journal of Nuclear Medicine & Molecular Imaging* 2004;**31**:1128-35.
Study type	Diagnostic
Evidence level	++
Study objective	To investigate the clinical suitability of this 18F-DMFP PET tracer in the differential diagnosis of patients with parkinsonism.
Number of patients	N=35 parkinsonism patients N=16 idiopathic PD (IPD) N=19 atypical PD (APD) Location: Germany sites: single
Patient characteristics	35 patients with parkinsonism (18 women, 17 men, mean age 64.9 ± 9.1 years, range 43-77 years, median 65 years) and 16 healthy male controls (mean age 38.5 ± 9.5 years, range 26-64 years). Patients were recruited by neurological outpatient department for movement disorders that were diagnosed clinically as either idiopathic parkinsonian syndrome (IPD) or atypical parkinsonian syndrome (APD). The APD group comprised of 15 patients with MSA and 4 with PSP. The mean value on the UPDRS part III was 31.3 (median 34) and the mean value on the Hoehn and Yahr scale was 2.3 (median 2). The clinical diagnosis of IPD was based on the UK PDS brain bank criteria. The clinical diagnosis of MSA or PSP followed published proposed diagnostic criteria.
Intervention	18F-DMFP PET scan- see paper for details
Comparison	Clinical diagnosis
Length of follow-up	None stated
Outcome measures	Sensitivity, specificity, accuracy, positive and negative predictive values
Effect size	➢ F-DMFP uptake ratios revealed significantly ($p<0.01$) reduced ratios in the APD patients compared with the normal subjects and IPD patients for total striatum- as well as separately for the caudate nucleus and putamen ➢ Controls had slightly higher uptake values but the difference was not significant ➢ The correlation analysis of the caudate to the putaminal F-DMFP uptake within the normal controls and within the IPS group and the APS group revealed significant ($p<0.001$) correlations between the two striatal structures for each group ➢ The results of the 'region-of-interest' (ROC) analysis performed to assess the diagnostic accuracy

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	of F-DMFP imaging for the differential diagnosis of APS versus IPS show the areas under the curve for the caudate, the putaminal and the total striatal uptake ratios were 0.86 ± 0.007, 0.81 ± 0.07 and 0.84 ± 0.07, respectively ➢ The difference between the areas for the caudate and the putaminal F-DMFP uptake ratio were significant (p<0.05) ➢ Based on these results, a threshold value of 2.495 (caudate uptake ratio) a specificity, sensitivity, accuracy of 100%, 74%, and 86% respectively ➢ Using this threshold, the positive and negative predictive values for the diagnosis of APS were 100% and 76%
Source of funding	Government
Additional comments	➢ 3 experienced nuclear medicine physicians who were blinded to the clinical-neurological diagnosis ➢ No long-term follow-up ➢ Small sample size
Citation	
NCC CC ID (Ref Man)	19838

Evidence Table **Diag 6** How effective is positron emission tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with parkinsonian syndrome?	
Bibliographic reference	Juh R, Kim J, Moon D, Choe B, Suh T. Different metabolic patterns analysis of Parkinsonism on the ¹⁸F-FDG PET. *European Journal of Radiology* 2004;**51**:223-33.
Study type	Diagnostic
Evidence level	+
Study objective	To evaluate the differentation of IPD, PSP and MSA based on an anatomical standardisation with spatial normalisation approach, using predefined volumes of interest on a voxel-by-voxel basis technique and diagnostic yield of 18FDG PET scans using statistical parametric mapping 2 (SPM2)
Number of patients	N=24 parkinsonian patients N=8 IPD N=9 MSA N=7 PSP N=12 controls

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<table>
<tr><td></td><td>Location: South Korea sites: single</td></tr>
<tr><td>Patient characteristics</td><td>
<table>
<tr><td></td><td>Controls</td><td>PD</td><td>MSA</td><td>PSP</td></tr>
<tr><td>Mean age, y</td><td>67.8 ± 14.4</td><td>67.9 ± 10.7</td><td>57.9 ± 9.2</td><td>67.6 ± 4.83</td></tr>
<tr><td>Male: female</td><td>9:13</td><td>3: 5</td><td>4:5</td><td>3:4</td></tr>
<tr><td>Disease duration, y</td><td>-</td><td>35.3 ± 26.3</td><td>28.5 ± 7.2</td><td>30 ± 18.5</td></tr>
<tr><td>Hoehn and Yahr stage</td><td>-</td><td>2.3 ± 1.1</td><td>2.0 ± 0.6</td><td>2.7 ± 1.0</td></tr>
</table>
Clinical status was assessed using the UPDRS. Patients were aged >50 years, had a clinical diagnosis of PD based on the UK brain bank criteria and their disease was at Hoehn and Yahr stages II-IV when assessed in off state. 22 age-matched healthy controls were examined and served as controls for the comparison between patients with Parkinsonism. They had no history of central nervous system disease and their neurological examinations were normal.</td></tr>
<tr><td>Intervention</td><td>18 FDG-PET- see paper for details</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis</td></tr>
<tr><td>Length of follow-up</td><td>None stated</td></tr>
<tr><td>Outcome measures</td><td>P values of significance between groups</td></tr>
<tr><td>Effect size</td><td>The multi-group discriminate analysis was carried out after a cross-validation using hypometabolic region from SPM2 analysis
➢ For IPD
➢ Sensitivity of 75% (6/8 IPD) and a specificity of 100% in IPD patients
➢ For MSA
➢ Sensitivity 100% (9/9 MSA) and specificity of 87% MSA patients
➢ For PSP
➢ Sensitivity of 86% (6/7) PSP and a specificity of 94% in PSP patients

Groups were analysed using the extent threshold 100 voxel level with a P (uncorrected) ≤ 0.01
<table>
<tr><td>Group analysis (extent z value, threshold 100 voxel, p<0.001)</td><td>IPD < control (n of 8 (%))</td><td>MSA < control (n of 9 (%))</td><td>PSP < control (n of 7 (%))</td></tr>
<tr><td>Frontal</td><td>6 (75)</td><td>5 (55)</td><td>4 (57)</td></tr>
<tr><td>Parietal</td><td>3 (37)</td><td>3 (33)</td><td>1 (14)</td></tr>
<tr><td>Temporal</td><td>4 (50)</td><td>3 (33)</td><td>2 (28)</td></tr>
<tr><td>Occipital</td><td>-</td><td>-</td><td>-</td></tr>
</table></td></tr>
</table>

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	Cingulated	4(50)	-	6 (86)
	Caudate	3 (37)	1 (11)	4 (57)
	Putamen	-	4 (44)	3 (43)
	Thalamus	1(12)	1 (11)	5 (71)
	Midbrain	1 (12)	1 (11)	5 (71)
	Pons	-	5 (55)	1 (14)
	Cerebellum	-	4 (44)	1 (14)
Source of funding	Private sector and government			
Additional comments	➢ Blinding of investigators not stated ➢ Small sample size ➢ No follow-up			
Citation				
NCC CC ID (Ref Man)	19839			

Evidence Table

Q6

How effective is Positron Emission Tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?

Author / title / reference / yr	Eidelberg, D., Moeller, J. R., Ishikawa, T., Dhawan, V., Spetsieris, P., Chaly, T., Belakhlef, A., Mandel, F., Przedborski, S., & Fahn, S. 1995, "Early differential diagnosis of Parkinson's disease with 18F-fluorodeoxyglucose and positron emission tomography", *Neurology.*, vol. 45, no. 11, pp. 1995-2004.
N=	N=15 early stage Parkinson's disease (EPD) N=9 atypical unilateral parkinsonism (APD) N=15 control subjects Location: NY, USA
Research design	Diagnostic study
Aim	To use ^{18}F-fluorodeoxyglucose (FDG) and PET to assess whether EPD can be detected by a characteristic pattern of regional metabolic asymmetry

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Population	*EPD* A diagnosis of EPD was made if the patient had ''pure'' unilateral parkinsonism (at least two of the following: tremor, rigidity, and akinesia) without a history of known causative factors and did not have dementia, supranuclear glaze abnormalities, myoclonus, apraxia, autonomic deficits, or ataxia. *APD* No clinical criteria listed. **Controls** Recruited by advertisement among hospital personnel of North Shore University Hospital and spouses of PD patients in local support groups. Exclusion criteria: history of neurologic or psychiatric illness; prior exposure to neuroleptic agents or drug use; medical history of hypertension, cardiovascular disease, and diabetes mellitus; and an abnormal neurologic examination.
Intervention	FDG/PET to quantitatively assess nigrostriatal dopaminergic metabolic function, Subscaled subprofile model (SSM) to assess regional metabolic data, topographical profile rating (TPR) computes the expression of the profile identified in the SSM analysis, FDOPA/PET measures striatal FDOPA uptake
Comparison	Clinical diagnosis
Outcome	Statistical significance in discrimination of experimental groups and % of correct classifications.
Characteristics	*EPD* Hoehn and Yahr stage I Mean age 59.1 $\pm$ 12 years; mean disease duration 4.3 $\pm$ 2.8 years; 6 women, 9 men All responded to levodopa ($\geq$ 20% change in UPDRS motor scores) All patients family histories were negative for neurological illness; T2 MRI was normal in all EPD patients *APD* Mean age 44.6 $\pm$ 14.0; mean disease duration 2.7 $\pm$ 2.2 years; 4 women, 5 men Poor or absent responses to levodopa (<20% change in UPDRS motor score) *Controls*

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	Mean age 53.4 ± 14.6
Results	*FDG/PET Glucose metabolism* ➢ δrCMRGlc values did not differ significantly from normal ➢ Discriminant analysis based on δrCMRGlc values revealed a linear combination of basal ganglia and thalamic values that discriminated the three clinical groups (EPD vs. normal: p<0.001; EPD vs. APD p<0.02) ➢ Discriminant function analysis correctly classified 29/39 (74%) members of entire study sample, miscategorising 5/15 normal subjects, 1/15 EPD patients and 4/9 APD patients **Subscaled subprofile model (SSM)** ➢ Analysis of 10 EPD_1 patients and 10 normal subjects- subject scores were found to be significantly elevated in the disease group (p<0.0001) and discriminated these from controls p<0.0001-a discrimination function based on these scores separated the two groups 'perfectly' *TPR analysis* ➢ Analysis of 5 EPD_2 patients, 9 APD patients and five other controls a discriminant function analysis based on the subject scores correctly classified 18/19 (95%) of subjects- all EPD_2 and APD patients were correctly classified- one normal subject (age 63) was classified incorrectly as belonging to the EPD_2 group ➢ Across the entire study sample topographic contrast profile subject scores accurately discriminated EPD patients from normal subjects p<0.0001; and APD patients from EPD patients p<0.0001 ➢ A discriminant function analysis based on these scores correctly classified 37/39 (95%) members of the sample, miscategorising two normal subjects *FDOPA/PET* ➢ Analysis of 11 EPD patients, 5 APD patients and 10 age-matched normal control subjects ➢ Contralateral striatal values were abnormally reduced in both the EPD and APD groups (caudate p<0.02; putamen p<0.0001) ➢ EPD patients were accurately discriminated from normal subjects by contralateral putamen values (p<0.0001) and to a lesser degree by caudate values (p<0.01) ➢ APD patients were also discriminated from controls on these measures: putamen (p<0.001) and caudate (p<0.005) ➢ A discrimination function based on contralateral putamen values correctly classified 11 EPD patients and all normal subjects ➢ APD did not differ from EPD in measures of either putamen or caudate

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SIGN quality rating	+
Evidence hierarchy grading	DS II
Comments	➢ No detail on who performed clinical diagnosis or when this was done in regards to the study commencement ➢ Blinding of investigators to clinical diagnosis during analysis of data not specified ➢ No sensitivity/specificity or other diagnostic outcome measures ➢ Criteria for APD diagnosis not given ➢ Mean age of APD subjects much less than EPD subjects ➢ Demographics of control subjects (besides age) not given
NCC CC ID	291

Evidence Table Q6 How effective is Positron Emission Tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?	
Author / title / reference / yr	Sawle, G. V., Playford, E. D., Burn, D. J., Cunningham, V. J., & Brooks, D. J. 1994, "Separating Parkinson's disease from normality. Discriminant function analysis of fluorodopa F 18 positron emission tomography data", *Archives of Neurology*, vol. 51, no. 3, pp. 237-243.
N=	N=41 patients with Parkinson's disease N=28 healthy volunteers Location: post-graduate teaching hospital in London, UK
Research design	Diagnostic study
Aim	To identify clinically normal subjects who may have preclinical Parkinson's disease
Population	*PD* Diagnosed used the criteria for 'definite Parkinson's disease' as set out by the UK Parkinson's Disease Society

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	Brain Bank *Controls* The healthy volunteers were examined carefully and found no evidence of bradykinesia, rest tremor, or rigidity
Intervention	PET scan: fluorodopa F 18 striatal uptake analysis All drug therapy was stopped for a minimum of 12h before scanning. All subjects received 100mg of carbidopa 1 hour before and 50mg immediately before tracer injection to inhibit peripheral aromatic amino acid decarboxylase. After a ten minute transmission scan, each subject received approximately 145 ± 47 MBq of fluorodopa F 18 by intravenous infusion over 2 minutes. 28 dynamic emission scans were collected over 2 hours.
Comparison	Clinical diagnosis
Outcome	Probability (%) of being assigned to the correct patient group using PET discriminant function analysis
Characteristics	**PD group**: 29 male, 12 female; aged 58 ± 11 Hoehn and Yahr stage, mean 2.7 ± 1.0 Thirteen patients were levodopa (and dopamine agonist) naïve The remaining 26 patients were on an average levodopa dose of 575± 397. mg/day Five patients were taking dopamine agonists and 12 were taking selegiline **Control group**: 16 male, 12 female; aged 58± 14 years None of the control subjects were taking any medication
Results	By using discriminant function analysis, all of the normal and control subjects were correctly assigned to the appropriate diagnostic category using either input functions (tissue or plasma) **Tissue input function for PD diagnostic discrimination**: ➢ The probability for individual subjects being assigned to the correct diagnostic category 86% for one patient, 93% for one control, and 99% or greater for all other patients and controls **Plasma input function for PD diagnostic discrimination**: ➢ All subjects were correctly assigned to their diagnostic groups with a probability of 99% or greater except for one control subject (who was assigned a probability of 58% and the reasons are discussed in length in the paper)
SIGN quality rating	+
Evidence hierarchy	DS II

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grading	
Comments	➢ The paper does not state whether the investigators analysing the scans are blind to the clinical diagnosis ➢ The paper does not use long-term clinical follow-up as the reference standard ➢ Diagnostic outcomes such as sensitivity, specificity, PPV and NPV values are not given ➢ Does not state the what type of clinician (neurologist, radiologist, geriatricians) was involved in the clinical diagnosis and scan analysis or their level of expertise ➢ Criteria for diagnosis of PD given ➢ Long-term follow-up of some of the control subjects: no decline in F18 uptake observed
NCC CC ID	213

DIAG7 – section 5.5

Evidence Table **Q 7** How effective is Single Photon Emission Computed Tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?	
Author / title / reference / yr	Benamer, H. T., Oertel, W. H., Patterson, J., Hadley, D. M., Pogarell, O., Hoffken, H., Gerstner, A., & Grosset, D. G. 2003, "Prospective study of presynaptic dopaminergic imaging in patients with mild parkinsonism and tremor disorders: part 1. Baseline and 3-month observations", *Movement Disorders.*, vol. 18, no. 9, pp. 977-984.
N=	N=62 patients suspected of Parkinson's disease N=24 patients did not meet diagnostic criteria for PD or ET N=38 patients who did meet diagnostic criteria for PD N=14 volunteers Location: UK and Germany Sites: 2 centres
Research design	Diagnostic study
Aim	A diagnostic study to determine the ability of SPECT to detect PD cases as confirmed by clinical assessment at 3 months
Population	Patients from movement disorder clinics with suspicion of PD

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<table>
<tr><td></td><td>Exclusions: Patients with other causes of parkinsonism or tremor (including MSA, PSP, cerebrovascular disease, hyperthyroidism, and tremorogenic drugs) were excluded.
Exclusions were applied to drug treatments, including amphetamine, anti-anorexia and obesity treatments, and sympathomimetics including some nasal decongestants; and standard co-morbid medical disorders were excluded. Amoxapine and benztropine were not allowed for 4 weeks before entry.</td></tr>
<tr><td>Intervention</td><td>SPECT assessment: intravenous [123I]-FP- CIT was given over 15 seconds followed by a saline flush, and SPECT imaging was conducted 3 to 6 hours later. One observer in each centre, blind to clinical data, undertook visual assessment of striatal uptake.</td></tr>
<tr><td>Comparison</td><td>Clinical assessment: features were assessed according to the standardised UPDRS descriptions, and graded, none, possible, or definite</td></tr>
<tr><td>Outcome</td><td>Sensitivity: % of correctly diagnosed patients from SPET analysis compared to clinical diagnosis</td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><th></th><th>Patients not fulfilling diagnostic criteria for PD or ET (n=24)</th><th>Patients fulfilling diagnostic criteria for PD and UPDRS ≤ 16 (n=38)</th><th>Healthy controls (n=14)</th></tr>
<tr><td>Age years, (SD)</td><td>63 (9)</td><td>60 (9)</td><td>59 (12)</td></tr>
<tr><td>Sex, male</td><td>17 (71%)</td><td>21 (55%)</td><td>7 (50%)</td></tr>
<tr><td>Symptom duration (SD)</td><td>3 (4)</td><td>3 (7.1)</td><td>-</td></tr>
<tr><td>UPDRS (SD)</td><td>5.5 (3.3)</td><td>12.2 (3.8)</td><td>-</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>

Based on clinical criteria 38/ 62 patients fulfilled diagnostic criteria for PD at baseline
Of these 33 (87%) were scored visually abnormal (sensitivity 87%)
While 10 (42%) of those not fulfilling clinical criteria scored visually abnormal
The 3 month diagnosis remained probable PD in 35 cases, of which 33 (94%) had an abnormal SPECT result
Of 9 patients not fulfilling PD criteria, but with a clinical diagnosis of possible PD at baseline and 3 months, 8 (89%) had abnormal SPECT scans
When Brain Bank criteria were strictly applied (using definite rather than possible clinical features) the proportion of cases with abnormal scans increased (100% of 3 cases with three definite features; 90% of 21 cases with at least two definite features including bradykinesia) at the expense of sensitivity
Of 11 cases (10 with an initial PD clinical diagnosis) in which the baseline working diagnosis was inconsistent with dopaminergic imaging results, the diagnosis was amended (independent of SPECT results) at the 3-month review in seven cases.

</td></tr>
<tr><td>SIGN quality rating</td><td>++</td></tr>
</table>

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Evidence hierarchy grading	DS Ib
Comments	➢ Baseline and 3-month UPDRS motor score and modified Hoehn and Yahr (H&Y) rating were conducted blind to SPECT-data ➢ Patients were selected from movement disorder clinics on the suspicion that they might have PD, and thus at an early stage of disease progression ➢ Access to SPECT results was allowed to both parties after 3 months on ethical and clinical grounds ➢ 3 month follow-up is short ➢ Study to be extended with blinded clinical outcomes assessors ➢ Clinical features may not be clear in early presentation
NCC CC ID	425

Evidence Table **Q 7** How effective is Single Photon Emission Computed Tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?	
Author / title / reference / yr	Booij J, Speelman JD, Horstink MW, Wolters EC. The clinical benefit of imaging striatal dopamine transporters with [123I]FP-CIT SPET in differentiating patients with presynaptic parkinsonism from those with other forms of parkinsonism. *European Journal of Nuclear Medicine.* 2001;28:266-72.
N=	N= 33 possible parkinsonism patients Location = Holland
Research design	Diagnostic study
Aim	To explore the value of FP-CIT SPET in cases where clinical diagnosis of the form of parkinsonism was inconclusive, i.e. associated with some serious element of uncertainty when referred by movement disorder specialists.
Population	A mixed Parkinsonian population. All cases where diagnosis was judged inconclusive from the referring movement disorder specialist
Intervention	For SPET imaging: intravenous administration of approximately 110 MBq [123i] FP-CIT specific activity >185

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	MBq/nmol, was completed and SPET image acquisition was performed at 3 h.
Comparison	Clinical follow up to a period of 25-51 months (mean 38 months, SD 7 months) Assessment was made on clinical signs compatible with Parkinson's disease according to the United Kingdom Parkinson's Disease brain bank criteria.
Outcome	Positive and negative predictive values of SPET vs. clinical follow-up diagnosis
Characteristics	Age = 51yrs (range 17 to 73 yrs)
Results	➢ Nine patients showed degeneration of the nigrostriatal dopaminergic system on SPET ➢ Each of these patients was clinically diagnosed to have presynaptic parkinsonism after a minimum of 2 years' clinical follow-up (positive predictive value=100%) ➢ From 24 negative SPECT results 19 patients had normal images and were clinically determined not to have presynaptic parkinsonism, while in 3 patients a clinical diagnosis was not established but presynaptic parkinsonism was excluded. ➢ Two subjects whose images did not reveal nigrostriatal degeneration were clinically judged to have presynaptic parkinsonism in the follow-up period. (Negative predictive value of the scan 22/24=92%).
SIGN quality rating	++
Evidence hierarchy grading	DS Ib
Comments	➢ The study population of inconclusive diagnosis represents a difficult population to determine a strong diagnosis of PD from presynaptic deficit ➢ Dopamine therapy may have limited the ability of the imaging test to identify degeneration of nigrostriatal pathway ➢ Analyses of SPECT were performed blind to the clinical data
NCC CC ID	467

Evidence Table **Q 7** How effective is Single Photon Emission Computed Tomography vs long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?	
Author / title /	2000, "A multicenter assessment of dopamine transporter imaging with DOPASCAN/SPECT in parkinsonism.

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<table>
<tr><td>reference / yr</td><td>Parkinson Study Group.[see comment]", Neurology., vol. 55, no. 10, pp. 1540-1547.</td></tr>
<tr><td>N=</td><td>N=43 Parkinson’s disease (PD) patients
N=17 Progressive Supranuclear Palsy (PSP) patients
N=14 Essential Tremor (ET) patients
N=22 controls

Locations: USA Sites: multiple (5)</td></tr>
<tr><td>Research design</td><td>Diagnostic</td></tr>
<tr><td>Aim</td><td>To use a multi-centre study to evaluate the diagnostic accuracy of DOPASCAN and SPET in patients with PD, PSP, and ET in five sites with difference multi-detector SPET systems</td></tr>
<tr><td>Population</td><td>Clinical criteria for each group listed (very detailed see paper)
Exclusion and inclusion criteria listed (very detailed see paper)
Recruitment: consecutive series of patients (PD, PSP, and ET) were recruited through the movement disorders centre at each participating site. Controls were recruited either from the community at large or through personal contact with the study participants</td></tr>
<tr><td>Intervention</td><td>Eligible patients and controls were injected with 5mCi dose of DOPASCAN. All participants received Lugol’s solution before [^{123}I]-β-CIT injection. Projection data was acquired 24 + 2 hours following injection at each participating site on different multi-detector systems. Both masked visual interpretation and ROI analysis were performed at each site and at a core analysis centre.</td></tr>
<tr><td>Comparison</td><td>Standard clinical criteria as applied by the movement disorder specialists were the reference standard for each of the diagnostic groups</td></tr>
<tr><td>Outcome</td><td>Sensitivity: % of patients correctly assigned as parkinsonian by SPET analysis
Specificity: % of patients correctly assigned as non-parkinsonian by SPET analysis</td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><th>Demographics</th><th>PD (n=43)</th><th>PSP (n=17)</th><th>ET (n=14)</th><th>Controls (n=22)</th></tr>
<tr><td>Mean age (yrs) ± SD</td><td>68 ± 7.8</td><td>72 ± 5.6</td><td>69 ± 10</td><td>67± 8.0</td></tr>
<tr><td>Men %</td><td>70</td><td>59</td><td>57</td><td>45</td></tr>
<tr><td>UPDRS score, mean ± SD</td><td>38 ± 17</td><td>59 ± 23</td><td>-</td><td>-</td></tr>
<tr><td>Medications %</td><td></td><td></td><td></td><td></td></tr>
<tr><td>L-dopa</td><td>84</td><td>24</td><td>-</td><td>-</td></tr>
<tr><td>Dopamine agonists</td><td>37</td><td>12</td><td>-</td><td>-</td></tr>
<tr><td>Anti-tremor (propanolol or primidone)</td><td>-</td><td>-</td><td>43</td><td>-</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>➢ No significant differences in the mean age of the different experimental groups</td></tr>
</table>

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	➢ Visual analysis of SPET and DOPASCAN ➢ Images from 89/96 individuals were declared evaluable by at least 2/3 of readers ➢ The sensitivity was 0.98 and specificity was 0.83 for comparing parkinsonism (PD+ PSP) vs. non-parkinsonian (ET+ controls) ➢ 5/6 patients incorrectly classified as PD/PSP were ET patients
SIGN quality rating	++
Evidence hierarchy grading	DS 1b
Comments	➢ Diagnostic criteria applied blind to SPET results ➢ SPET analysis blinded to clinical diagnosis ➢ No long-term clinical follow-up ➢ No details on disease duration ➢ No details on expertise of physicians assigning the initial clinical diagnoses
NCC CC ID	475

Evidence Table **Q 7** How effective is Single Photon Emission Computed Tomography vs long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?	
Author / title / reference / yr	Benamer, T. S., Patterson, J., Grosset, D. G., Booij, J., de Bruin, K., van Royen, E., Speelman, J. D., Horstink, M. H., Sips, H. J., Dierckx, R. A., Versijpt, J., Decoo, D., Van Der, L. C., Hadley, D. M., Doder, M., Lees, A. J., Costa, D. C., Gacinovic, S., Oertel, W. H., Pogarell, O., Hoeffken, H., Joseph, K., Tatsch, K., Schwarz, J., & Ries, V. 2000, "Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group", *Movement Disorders.*, vol. 15, no. 3, pp. 503-510.
N=	N=158 parkinsonism patients [Idiopathic Parkinson's disease (IPD), Multiple System Atrophy (MSA), and Progressive Supranuclear Palsy (PSP)] N=27 essential tremor (ET) patients N=35 healthy volunteers

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<table>
<tr><td></td><td>Location: Europe Sites: 6 centres</td></tr>
<tr><td>Research design</td><td>Diagnostic study</td></tr>
<tr><td>Aim</td><td>To evaluate whether visual assessment of [^{123}I]-FP-CIT Single Photon Emission Computerized Tomography (SPET) images can differentiate between parkinsonism and essential tremor (ET)</td></tr>
<tr><td>Population</td><td>Parkinsonism patients fulfilling the UK PD Society Brain Bank Criteria step 1 (bradykinesia with rigidity and/or tremor)
ET patients with a diagnosis of definite ET fulfilling Findley and Koller criteria
MSA patients met criteria for the Consensus Committee of the American Autonomic Society and American Academy of Neurology
PSP patients met the clinical research diagnostic criteria of the National Institute of Neurological Disorders and Stroke and the Society for PSP
Exclusion criteria: evidence of Cerebrovascular disease, other structural brain disease, dementia, head injury, or encephalitis</td></tr>
<tr><td>Intervention</td><td>An IV injection of [^{123}I]-FP-CIT containing activity in the range 111-185MBq was given over approximately 15 seconds followed by saline flush. SPET imaging was conducted 3-6 hours after injection. SPET images were obtained using a specific-site gamma camera system. Each system provided transverse slices with clear visualization of the striatum.</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis</td></tr>
<tr><td>Outcome</td><td>Sensitivity: % of parkinsonism cases identified by institutional and consensus reading of scan images compared to clinical diagnosis
Specificity: % of ET cases identified by institutional and consensus reading of scan images compared to clinical diagnosis</td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><th></th><th>Parkinsonism (n=158)</th><th>ET (n=27)</th><th>Volunteers (n=35)</th></tr>
<tr><td>Age in years (STD)</td><td>62.8 (9.0)</td><td>64.1 (8.8)</td><td>61.1 (8.7)</td></tr>
<tr><td>Sex- male%</td><td>63.8</td><td>69</td><td>42.9</td></tr>
<tr><td>Race % white</td><td>98.8</td><td>100</td><td>94.3</td></tr>
<tr><td>Height cm (STD)</td><td>170.4 (8.6)</td><td>169 (10)</td><td>170.4 (7.6)</td></tr>
<tr><td>Weight kg (STD)</td><td>72 (12.3)</td><td>74.7 (20.4)</td><td>74.4 (11.8)</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>

177 (84.3%) diagnosed clinically as parkinsonism and 33 (15.7%) as ET
Parkinsonism patients were further classified as 145 (82%) IPD, 22 (12%) MSA, and 10 (6%) PSP

<table>
<tr><th></th><th>Parkinsonism</th><th>ET</th><th>Healthy volunteers</th></tr>
</table>
</td></tr>
</table>

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			Intention-to-treat (n=158)	Per-protocol (n=115)	Intention-to-treat (n=27)	Per-protocol (n=16)	Intention-to-treat (n=35)	Per-protocol (n=26_
	Institutional Read	Normal	4 (2.5%)	4 (3.5%)	27 (100%)	16 (100%)	34 (97.1%)	26 (100%)
		Abnormal	154 (97.5%)	111 (96.5%)	0 (0%)	0 (0%)	1 (2.9%)	0 (0%)
	Consensus Blind read	Normal	8 (5.1%)	6 (5.2%)	25 (92.6%)	15 (93.8%)	33 (94.3%)	24 (92.3%)
		Abnormal	150 (94.9%)	109 (94.8%)	2 (7.4%)	1 (6.3%)	2 (5.7%)	2 (7.7%)
	➢ The institutional read and the blinded read did not differentiate between IPD, MSA and PSP ➢ Institution read: sensitivity for the clinical diagnosis of parkinsonism was 97% and specificity for ET was 100% ➢ Consensus blind read: sensitivity 95% and specificity 93%							
SIGN quality rating	++							
Evidence hierarchy grading	DS Ib							
Comments	➢ Each centre assessed the images blind to the clinical data and a blinded consensus was undertaken ➢ Visual assessment was performed by one neurologist with limited experience in assessing [^{123}I]-FP-CIT images and four experienced nuclear medicine physicians ➢ Each panel member evaluated blind images and agreement of 3 members out of five was taken as consensus ➢ No evidence of study centre effect ➢ No details on who performed clinical diagnosis and when this diagnosis occurred in respect to start of study							
NCC CC ID	484							

Evidence Table **Q 7** How effective is Single Photon Emission Computed Tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?	
Author / title / reference / yr	Asenbaum, S., Pirker, W., Angelberger, P., Bencsits, G., Pruckmayer, M., & Brucke, T. 1998, "[123I]beta-CIT and SPECT in essential tremor and Parkinson's disease", *Journal of Neural Transmission.*, vol. 105, no. 10-12, pp. 1213-1228.
N=	N=29 Idiopathic Parkinson’s disease (PD) patients

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	N=32 Essential Tremor (ET) patients N=30 controls Location: Vienna, Austria
Research design	Diagnostic
Aim	To investigate [^{123}I]-β-CIT and SPET for differentiating ET and PD
Population	Controls: not on medication and no central neuropsychiatric disorders All patients were in Hoehn and Yahr stage I, with a mean duration of 1.8 years (range 0.3 to 5 years) Exclusion criteria: major depressive illness, dementia, or other neurological signs besides parkinsonism
Intervention	[^{123}I]-β-CIT and SPET: subjects received a mean dose of 133MBq of [^{123}I]-β-CIT intravenously. All persons were investigated 20 hours after tracer administration.
Comparison	Patients examined neurologically by two experienced neurologists
Outcome	Sensitivity: Specificity:
Characteristics	**PD (n=29)** 10 female, 19 male; age range 39-81 years, mean age 61 years **ET (n=32)** 19 female, 13 male; age range 31-83 years, mean age 63 years **Controls (n=30)** 20 female, 10 male; age range 21-75 years, mean age 45 years
Results	➢ Visual evaluation: ➢ All patients with PD had relatively high activities in the caudate, whereas putamen could hardly be differentiated ➢ Contralateral striatum to clinical symptoms was more severely affected ➢ No abnormalities in the visualization of the basal ganglia could be seen in ET patients ➢ Age differed significantly between controls and patient groups ($p<0.001$) ➢ Discriminant function analysis: ➢ The highest discriminator was contralateral putamen/cerebellum (PC) binding ratio ➢ Whereas ipsilateral caudate/cerebellum (CC) binding ratio was the least discriminator ➢ Taking PC and CC binding ratios contra-and ipsilaterally to clinical symptoms as factors together- all PD patients were correctly classified (sensitivity and specificity 100%) ➢ Striatum/cerebellum (SC) binding ratio and PC binding ratio as factors discriminated PD patients with a high sensitivity of 98.3% (PD vs. controls and ET) and even SC binding ratio alone produced a sensitivity of 94.9%

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	(PD vs. controls) and 96.7% (PD vs. ET) ➢ Control vs. ET had a low sensitivity of 59.7%
SIGN quality rating	++
Evidence hierarchy grading	DS 1b
Comments	➢ Patients with PD were untreated or stopped medication 12 hours prior to tracer administration ➢ No clinical criteria listed for diagnosis of PD ➢ Experienced neurologists performed clinical diagnosis ➢ SPET analysis performed by investigator blinded to clinical diagnosis
NCC CC ID	507

Evidence Table **Q 7** How effective is Single Photon Emission Computed Tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?	
Author / title / reference / yr	Acton, P. D., Mozley, P. D., & Kung, H. F. 1999, "Logistic discriminant parametric mapping: a novel method for the pixel-based differential diagnosis of Parkinson's disease", *European Journal of Nuclear Medicine.*, vol. 26, no. 11, pp. 1413-1423.
N=	N=42 Parkinson's disease N=23 Healthy controls Location=Philadelphia, USA Sites=3 (2x movement disorder clinic, 1x university medical centre)
Research design	Diagnostic study with retrospective clinical diagnostic comparison
Aim	To distinguish between Parkinson's disease patients and age-matched healthy controls using a novel SPET pixel-based technique and logistic discriminant analysis to distinguish between a group of PD patients and age-matched healthy controls.
Population	Parkinson's disease:

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	A specialist in the field confirmed all diagnoses All patients suffered from at least two of the four cardinal features of the disease, which was verified at the time of scanning. The selection criteria included a history of having a favourable response to dopamine replacement therapy. **Exclusion criteria:** Patients with only one of the four cardinal features of the disease who did not have a favourable response to dopamine replacement therapy at some time during their illness. Patients taking selective serotonin reuptake inhibitors were excluded because the half-lives of these medications are too long. **Inclusion criteria:** All patients were on dopamine replacement therapy Drugs that act or could act on presynaptic transporters were discontinued for seven half-lives before study.
Intervention	SPECT Imaging of binding of technetium 99m labelled TROTDAT-1 to dopamine transporters using a novel pixel-based technique and logistic discriminant analysis in PD patients. A dose of 740 MBq (20mCi) of [^{99m} Tc] TRODAT-1 was injected; 3 to 5 hours after the injection dynamic SPET scans of the brain.
Comparison	Clinical diagnosis
Outcome	Sensitivity and specificity for SPET vs. clinical diagnosis in differentiating Parkinson's patients from controls
Characteristics	*Parkinson's disease* Subgroups: Training group- (well-defined Parkinsonian symptoms) N=17 Methodology testing group N=25 (4 of these had hemi-Parkinson's disease) Male/female N=27/15 Mean age 65.1 yrs Mean time between symptom onset and participation=7.4 yrs **Healthy controls** Male/female N=13/10 Mean age=58.4 yrs Age-matched controls
Results	Optimum pixel-level probability threshold, pt was varied from 0.5 to 0.999 in order to determine the optimum level for differentiating Parkinson's patients from controls. The optimum value occurred at around pt=0.94 LDPM

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	➢ Logistic discrimination parametric mapping (LDPM) correctly classified all PD patients (**sensitivity was 100%**) and misclassified one control the (**specificity 95%**) ➢ When logistic discriminant parametric mapping (LDPM) was applied to the test group of four early onset PD patients, all were correctly diagnosed as having hemi-PD SPM ➢ Statistical parametric mapping (SPM) of individual subjects gave a **sensitivity of 24%** (10 out of 42 PD patients). None of the control group had significant differences compared individually against the rest of the group- **specificity 100%.**
SIGN quality rating	+
Evidence hierarchy grading	DSII
Comments	➢ All diagnoses were confirmed by a specialist in the field- and mean time between symptom onset and participation is given ➢ Clinical diagnoses criteria specified ➢ Blinding of investigators not specified- but results consistent with studies who did employ blinding techniques ➢ Controls - age matched ➢ Level of disease severity not specified ➢ Homogeneity in scanning technique ➢ No clinical diagnostic follow-up post SPECT
NCC CC ID	196

Evidence Table **Q 7** How effective is Single Photon Emission Computed Tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?	
Author / title / reference / yr	Acton, P. D., Mozley, P. D., & Kung, H. F. 1999, "Logistic discriminant parametric mapping: a novel method for the pixel-based differential diagnosis of Parkinson's disease", *European Journal of Nuclear Medicine.*, vol. 26, no. 11, pp. 1413-1423.

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N=	N=42 Parkinson's disease N=23 Healthy controls Location=Philadelphia, USA Sites=3 (2x movement disorder clinic, 1x university medical centre)
Research design	Diagnostic study with retrospective clinical diagnostic comparison
Aim	To distinguish between Parkinson's disease patients and age-matched healthy controls using a novel SPET pixel-based technique and logistic discriminant analysis to distinguish between a group of PD patients and age-matched healthy controls.
Population	Parkinson's disease: A specialist in the field confirmed all diagnoses All patients suffered from at least two of the four cardinal features of the disease, which was verified at the time of scanning. The selection criteria included a history of having a favourable response to dopamine replacement therapy. **Exclusion criteria:** Patients with only one of the four cardinal features of the disease who did not have a favourable response to dopamine replacement therapy at some time during their illness. Patients taking selective serotonin reuptake inhibitors were excluded because the half-lives of these medications are too long. **Inclusion criteria:** All patients were on dopamine replacement therapy Drugs that act or could act on presynaptic transporters were discontinued for seven half-lives before study.
Intervention	SPECT Imaging of binding of technetium 99m labelled TROTDAT-1 to dopamine transporters using a novel pixel-based technique and logistic discriminant analysis in PD patients. A dose of 740 MBq (20mCi) of [^{99m} Tc] TRODAT-1 was injected; 3 to 5 hours after the injection dynamic SPET scans of the brain.
Comparison	Clinical diagnosis
Outcome	Sensitivity and specificity for SPET vs. clinical diagnosis in differentiating Parkinson's patients from controls
Characteristics	*Parkinson's disease* Subgroups: Training group- (well-defined Parkinsonian symptoms) N=17 Methodology testing group N=25 (4 of these had hemi-Parkinson's disease) Male/female N=27/15

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	Mean age 65.1 yrs Mean time between symptom onset and participation=7.4 yrs **Healthy controls** Male/female N=13/10 Mean age=58.4 yrs Age-matched controls
Results	Optimum pixel-level probability threshold, pt was varied from 0.5 to 0.999 in order to determine the optimum level for differentiating Parkinson's patients from controls. The optimum value occurred at around pt=0.94 LDPM ➢ Logistic discrimination parametric mapping (LDPM) correctly classified all PD patients (**sensitivity was 100%**) and misclassified one control the (**specificity 95%**) ➢ When logistic discriminant parametric mapping (LDPM) was applied to the test group of four early onset PD patients, all were correctly diagnosed as having hemi-PD SPM ➢ Statistical parametric mapping (SPM) of individual subjects gave a **sensitivity of 24%** (10 out of 42 PD patients). None of the control group had significant differences compared individually against the rest of the group- **specificity 100%.**
SIGN quality rating	+
Evidence hierarchy grading	DSII
Comments	➢ All diagnoses were confirmed by a specialist in the field- and mean time between symptom onset and participation is given ➢ Clinical diagnoses criteria specified ➢ Blinding of investigators not specified- but results consistent with studies who did employ blinding techniques ➢ Controls - age matched ➢ Level of disease severity not specified ➢ Homogeneity in scanning technique ➢ No clinical diagnostic follow-up post SPECT

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NCC CC ID	196

Evidence Table **Q 7** How effective is Single Photon Emission Computed Tomography vs long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?	
Author / title / reference / yr	Varrone, A., Marek, K. L., Jennings, D., Innis, R. B., & Seibyl, J. P. 2001, "[(123)I]beta-CIT SPECT imaging demonstrates reduced density of striatal dopamine transporters in Parkinson's disease and multiple system atrophy", *Movement Disorders.*, vol. 16, no. 6, pp. 1023-1032.
N=	N=157 Parkinson's Disease (PD) patients N=26 MSA patients Location: New Jersey, USA
Research design	Diagnostic study
Aim	To evaluate whether SPET imaging with [^{123}I]β-CIT alone or in combination with clinical rating scales provides additional diagnostic accuracy in distinguishing between PD and MSA compared to clinical evaluation alone.
Population	**PD:** Inclusion criteria: older than 35 years, at least two of the following (bradykinesia, resting tremor, rigidity, postural instability, or freezing phenomenon) one of which is rest tremor or bradykinesia **MSA:** (Including striatonigral degeneration [SND] and Shy-Drager syndrome [SDS]) diagnosed with a known negative unsustained or inadequate response to L-dopa with at least two of the following: (bradykinesia, resting tremor, postural reflex impairment, or freezing phenomenon); with concurrent presence of cerebellar dysfunction, symptomatic autonomic failure, or pyramidal signs **Recruitment**: Yale Movement Disorder Centre
Intervention	[^{123}I]β-CIT SPECT imaging: SPET studies were performed 21± 2 hours after intravenous administration of 217 ± 18 MBq of [^{123}I]β-CIT.
Comparison	Clinical diagnosis
Outcome	Sensitivity: % of correctly diagnosed PD patients based on SPET analysis compared to clinical diagnosis Specificity: % of correctly assigned controls based on SPET analysis compared to clinical diagnosis

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<table>
<tr><td>Characteristics</td><td>
<table>
<tr><th>Patient group</th><th>Age (yr) mean</th><th>Gender Male/Female</th><th>Mean illness duration* (yr)</th><th>Hoehn & Yahr stage mean</th><th>UPDRS total mean</th><th>UPDRS motor mean</th></tr>
<tr><td>PD (n=157)</td><td>61</td><td>102/55</td><td>4 (0.3-23)</td><td>1.7</td><td>30.1</td><td>18.4</td></tr>
<tr><td>MSA (n=26)</td><td>66</td><td>19/7</td><td>4 (0.2-10)</td><td>2.8</td><td>50.1</td><td>31</td></tr>
<tr><td>MSA-SND (n=14)</td><td>67</td><td>10/4</td><td>4 (0.2-10)</td><td>3.2</td><td>57.7</td><td>35.1</td></tr>
<tr><td>MSA-SDS (n=12)</td><td>65</td><td>9/3</td><td>4 (1.0-8)</td><td>2.4</td><td>41.1</td><td>26.3</td></tr>
</table>
* Illness duration was calculated as interval between onset of symptoms and the day of the SPET scan
</td></tr>
<tr><td>Results</td><td>
➢ Gender distribution in PD not significantly different that MSA group
➢ Compared with PD patients MSA were significantly older (P<0.05) and more severely impaired (P<0.001)
➢ MSA patients showed a more pronounced reduction in DAT density than PD patients in the striatum ipsilateral to the more affected side of the body (p<0.01)
➢ The reduction of striatal DAT density was 49 ± 13% and 42 ± 20% of normal control values in PD and MSA respectively
➢ No differences in putamen to caudate ratios were found in the two groups
➢ Logistic regression analysis:
➢ 2 models
➢ Model 1: Hoehn and Yahr stage, age corrected ipsilateral striatum V3'' and asymmetry index of striatum
➢ If the cut-off for group classification was estimated from the sample size of PD n=127 and MSA n=21
➢ Sensitivity and specificity were both 81% for this model
➢ Model 2: Hoehn and Yahr stage, age-corrected contralateral caudate V3'' and asymmetry index of striatum
➢ If the cut-off for group classification was estimated from the sample size of PD n=131 and MSA n=20
➢ Sensitivity was 77% and specificity was 83% for this model
➢ Analyses of ROC curves showed that the boundary of odds estimate corresponding to the highest overall accuracy yielded a very low sensitivity (35% in the first model and 27% in the second model) and a high specificity (96% in the first model and 98% in the second model)
</td></tr>
<tr><td>SIGN quality rating</td><td>+</td></tr>
<tr><td>Evidence hierarchy grading</td><td>DS II</td></tr>
<tr><td>Comments</td><td>
➢ Do not know who made initial diagnosis or when last diagnosis was made in respect to study initiation
➢ No long-term clinical follow-up
➢ No blinding of investigators reported (though no visual assessment which reduces bias)
</td></tr>
</table>

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	➢ MSA group significantly older and more progressed in disease
NCC CC ID	453

Evidence Table **Q 7** How effective is Single Photon Emission Computed Tomography vs long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?	
Author / title / reference / yr	Lokkegaard, A., Werdelin, L. M., & Friberg, L. 2002, "Clinical impact of diagnostic SPET investigations with a dopamine re-uptake ligand", *European Journal of Nuclear Medicine & Molecular Imaging.*, vol. 29, no. 12, pp. 1623-1629.
N=	N=80 Total participants ➢ N=16 Probable PD ➢ N= 41 Possible PD ➢ N=19 Possible Parkinsonism plus ➢ N=4 Possible drug-induced parkinsonism Location= Neurological department, Bispebjerg Hospital, Denmark Sites=1
Research design	Diagnostic study with retrospective clinical diagnosis based on clinical records
Aim	To evaluate the impact of [^{123}I]-ß-CIT SPET on the diagnosis and clinical management of patients with a primary, tentative diagnosis of parkinsonism.
Population	➢ Probable PD ➢ Possible PD ➢ Possible Parkinsonism plus ➢ Possible drug-induced parkinsonism As diagnosed retrospectively from clinical records by one specialist in neurology blinded to the result of the scan. The clinical diagnoses were based on generally established clinical criteria- specified.
Intervention	**SPET protocol** Patients received 120 MBq I-B-CIT i.v. The SPET scan was performed 20 h after the [^{123}I]-ß-CIT injection, when a steady state had been reached. The same specialist in nuclear medicine interpreted all scans immediately after the

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	investigation. The criteria for a normal scan were based on data from the literature.
Comparison	Retrospective clinical diagnosis
Outcome	Sensitivity and specificity of SPET diagnosis compared to clinical diagnosis
Characteristics	**Probable PD** Duration of disease=13.5yrs *Possible PD* Duration of disease=5.9yrs **Possible Parkinsonism plus** Duration of disease N=3.4 **Possible drug-induced parkinsonism** Duration of disease N=4.5 No further patient characteristics per diagnostic group.
Results	➢ The result of the [^{123}I]-ß-CIT SPET investigations correlate with the later retrospective clinical diagnoses ➢ 3/60 PD patients were classified as having a diagnosis other than PD or PP at the time of evaluation (false positives) ➢ 2/25 subjects with a normal scan results, two were classified as having a diagnosis of either PD or PP at the time of evaluation (false negatives). When "borderline changes" (N=5) were excluded the [^{123}I]-ß-CIT SPET **sensitivity = 97%, Specificity = 88%** The five investigations with borderline changes were re-analysed by an investigator blinded to the clinical diagnosis at the time of evaluation. When they were included in the analyses on the basis of the most likely diagnosis: **sensitivity = 97%, specificity = 83%**
SIGN quality rating	+
Evidence hierarchy grading	DS II
Comments	➢ Lacking patient characteristics per diagnostic group. ➢ Not clear whether the diagnostic groups differed significantly in age, disease duration, or disease severity ➢ Clinical diagnosis was carried out following SPET diagnosis, retrospectively from clinical records by one specialist in neurology blinded to the result of the scan. ➢ Not clear whether SPET scanning was carried out blind to the initial clinical diagnosis. ➢ Sensitivity, specificity data available

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	➢ No clinical diagnostic follow-up post SPET
NCC CC ID	439

Evidence Table **Q 7** How effective is Single Photon Emission Computed Tomography vs long-term clinical follow-up in determining an accurate diagnosis in patients with a Parkinsonian syndrome?	
Author / title / reference / yr	Prunier, C., Tranquart, F., Cottier, J. P., Giraudeau, B., Chalon, S., Guilloteau, D., De Toffol, B., Chossat, F., Autret, A., Besnard, J. C., & Baulieu, J. L. 2001, "Quantitative analysis of striatal dopamine D2 receptors with 123 I-iodolisuride SPECT in degenerative extrapyramidal diseases", *Nuclear Medicine Communications.*, vol. 22, no. 11, pp. 1207-1214.
N=	N=17 Total participants ➢ N=9 Parkinson's disease (PD) ➢ N=8 Parkinson's disease-plus syndrome (MSA + PSP) Location=France Site= N=1
Research design	Diagnostic study with 2-year prospective follow-up of clinical diagnosis.
Aim	To determine the value of iodolisuride SPECT in discriminating Parkinson's from the most frequent Parkinson-plus syndromes
Population	PD Diagnosed according to the United Kingdom Parkinson's disease Society Brain Bank criteria **MSA + PSP** Diagnosed according to the NINDS-SPSP criteria for PSP and those of Quinn for MSA. After 2 years follow-up response to dopamine therapy and the progressive development of other neurological signs (pyramidal syndrome, cerebellar syndrome, neuropsychological disorders, supranuclear palsy, orthostatic hypotension, pseudobulbar syndrome and genital and bladder disorders) were taken into account for the diagnoses.
Intervention	Iodolisuride (3-(9,10-didehydro-2-iodo-6-methyl-8α-ergolinyl1)-1,1-diethyl urea (^{123}I-lisuride) was injected

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	intravenously (185 MBq) to all patients, corresponding to 0.02-0.07 ng.Kg^{-1} of body weight of iodolisuride, labelled with 1.7-2.8 MBq of ^{123}I.
Comparison	Clinical diagnoses
Outcome	➢ Sensitivity of Iodolisuride SPET scan vs. clinical diagnosis in accurately diagnosing PD, MSA and PSP ➢ Specificity same as above ➢ Positive predictive value same as above ➢ Negative predictive value same as above
Characteristics	*PD* M/F N= 7/2 Mean age=59.8 yrs Hoehn and Yahr=1.8 *MSA & PSP* MSA N=4, PSP N=4 M/F N=7/1 Mean age=71.6 yrs Hoehn and Yahr=2.9
Results	➢ When comparing patient group's SPECT results and clinical classification- sensitivity, specificity and predictive values for each ratio was calculated according to their respective cut-off value: **Striatum/Occipital lobe** **Sensitivity** 88.8% **Specificity** 75% **Positive predictive value** 80% **Negative predictive value** 85.7% **Caudate nucleus/Occipital lobe** **Sensitivity** 77.7%

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	Specificity **62.5%** **Positive predictive value** 70% **Negative predictive value** 71.4% **Putamen/Occipital lobe** **Sensitivity** 77.7% **Specificity** 62.5% **Positive predictive value** 70% **Negative predictive value** 71.4% No correlation was found between SPECT data and duration of disease or Hoehn and Yahr staging.
SIGN quality rating	+
Evidence hierarchy grading	DS II
Comments	➢ N=9 (narrow population) ➢ Age, disease duration and Hoehn and Yahr staging given and taken into account ➢ Diagnostic criteria specified ➢ 2 year prospective follow-up of diagnostic classification ➢ Blinding of investigator to clinical diagnosis not specified ➢ In all patients all dopamine treatment was withdrawn 7 days before SPECT examinations to avoid possible interaction with ILIS ➢ Results consistent with other studies
NCC CC ID	459

DIAG7b – section 5.5b

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Evidence Table **Diag 7** How effective is single photon emission computed tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Bibliographic reference	Chou KL, Hurtig HI, Stern MB, Colcher A, Ravina B, Newberg A *et al*. Diagnostic accuracy of [99mTc]TRODAT-1 SPECT imaging in early Parkinson's disease. *Parkinsonism & Related Disorders* 2004;**10**:375-9.
Study type	Diagnostic
Evidence level	+
Study objective	To determine the diagnostic accuracy of TRODAT imaging in distinguishing patients with early stage PD from normal individuals.
Number of patients	N=29 PD patients N=38 controls Location: USA sites: single
Patient characteristics	Initial inclusion criteria for undergoing imaging were: age > 35 years; Hoehn and Yahr stage of 2 or less; and disease duration of PD symptoms less than 2 years or UPDRS motor score off medications <25. Patients were examined within three months of imaging with UPDRS and Hoehn and yahr staging whole off medication for at least 12 hours to assess severity of illness. The patients were then followed for a mean of 2.1 years (range 1.4 to 3.1) during which they had to satisfy the UK PDS braink bank criteria for PD in order to be included in the analysis. Patient characteristics: 20 men and 9 women; age range 3-75 years, mean 59.2 ± 11.8, mean duration since symptom onset was 21.9 months (range 3-48, SD ± 12.4), were matched with 38 healthy volunteers (21 men, 17 women, age range 36-83, mean 60.8 ± 13.0). The volunteers had no history of neurologic or psychiatric disease, and were not taking medications other than oral contraceptives.
Intervention	TRODAT imaging (see paper for details)
Comparison	Clinical diagnosis
Length of follow-up	2.1 years follow-up of clinical diagnosis
Outcome measures	Sensitivity and specificity and positive and negative likelihood ratios (LR) (e.g. positive LR= sensitivity/ (1-specificity))
Effect size	➢ 34 patients were imaged; 29 qualified for the study ➢ of the 5 excluded: 2 had been diagnosed with multiple system atrophy, one with progressive

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supranuclear palsy, and 2 had psychogenic movement disorders

Region	Sensitivity	Specificity	Positive LR	Negative LR
Caudate				
Ipsilateral	0.31	0.84	1.94	0.82
Contralateral	0.55	0.82	3.06	0.55
Mean	0.48	0.84	3.00	0.62
Anterior putamen				
Ipsilateral	0.55	0.79	2.62	0.57
Contralateral	0.76	0.84	4.75	0.29
Mean	0.66	0.89	6.00	0.38
Posterior putamen				
Ipsilateral	0.72	0.76	3.00	0.37
Contralateral	0.83	0.87	6.38	0.20
Mean	0.79	0.92	9.88	0.23

- Quantitative imaging analysis of TRODAT uptake using the mean value of the ipsilateral and contralateral posterior putamen resulted in the greatest area under the region-of-interest curve (0.92) and the greatest accuracy, with a sensitivity of 0.79 and a specificity of 0.92
- 6/29 patients were classified as normal because their TRODAT binding was above the cut-off that best differentiated patients from controls
- There were no statistically significant differences between these six patients and the 22 whose TRODAT uptake fell below the cut-off point in terms of age, gender, UPDRS motor scores, UPDRS tremor subscores or duration of disease

Source of funding	Government funding
Additional comments	➢ Investigators not blinded ➢ No clinical follow-up stated ➢ Small sample size
Citation	
NCC CC ID (Ref Man)	19817

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Evidence Table
Diag 7
How effective is single photon emission computed tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?

Bibliographic reference	Jennings DL, Seibyl JP, Oakes D, Eberly S, Murphy J, Marek K. (123I) beta-CIT and single-photon emission computed tomographic imaging vs clinical evaluation in Parkinsonian syndrome: unmasking an early diagnosis. *Archives of Neurology* 2004;**61**:1224-9.
Study type	Diagnostic
Evidence level	++
Study objective	To evaluate the diagnostic accuracy of dopamine transporter imaging using (^{123}I) β- CIT in patients with suspected parkinsonian syndrome
Number of patients	N=35 patients with suspected parkinsonian syndrome (PS) Location: USA sites: single
Patient characteristics	Community neurologists identified patients with suspected PS but in whom they had diagnostic uncertainty. PS was defined as PD and related striatal dopamine-deficient syndromes including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), striatal nigral degeneration, and corticobasalganglionic degeneration.

Characteristics	All subjects recruited (n=35)
Mean age, y (range)	66.8 (46.2 – 81.7)
Men (%)	63
Mean symptom duration, y (range)	2.4 (0.3-7.6)
Unilateral symptoms, no (%)	13 (37.1)
Resting tremor	25 (71.4)
Rigidity	29 (82.9)
Bradykinesia	34 (97.1)
Gait disturbance	30 (85.7)
Postural instability	14 (40.0)
2 of 3 cardinal symptoms	32 (91.4)

Intervention	(^{123}I) β- CIT imaging (see paper for details)
Comparison	6-month follow-up clinical diagnosis was assigned by a movement disorder specialist blind to imaging (gold standard diagnosis)
Length of follow-up	6-month follow-up

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<table>
<tr><td>Outcome measures</td><td>Sensitivity, specificity</td></tr>
<tr><td>Effect size</td><td>

The mean diagnostic certainty at baseline for the community neurologists was 71.7% and the movement disorders experts (MDE) was 82.7%
Community neurologists assigned a diagnostic positive PS or negative PS at baseline, prior to the imaging study
The diagnosis of community neurologists at the time of referral was positive in 30/35 patients
The initial diagnosis positive PS was assigned by MDE1 (unblinded to imaging data) in 31/35 cases and by MDE2 (blinded to imaging data) in 25/35 cases
There was disagreement among the community neurologists and the initial clinical diagnosis of MDE 1in 7/35 cases, the diagnosis of MDE2 in 9/35, the visual imaging diagnosis in 12/35 and the quantitative imaging in 12/35
The visual and quantitative imaging diagnoses disagreed in 3/35 cases

The gold standard diagnosis was positive PS in 25 cases and negative PS in 10 cases
Comparing the diagnosis of the community neurologists at referral with the gold standard diagnosis, there was disagreement in 9 (25.7%) of 35 cases
The baseline diagnosis of MDE1 and MDE2 disagrees with the gold standard in 7 (20.0%) of 35 on average
Comparing the imaging diagnoses with the gold standard diagnosis, there was disagreement in 3 (8.6%) of 35 cases for the visual imaging diagnosis and 2 (5.7%) of 35 for the quantitative imaging diagnosis
Other diagnoses assigned by the gold standard included: essential tremor (5), psychogenic parkinsonism (2), primary dystonia (2), and drug-induced parkinsonism (1)

Table: using gold standard diagnosis as reference
<table>
<tr><th>Diagnosis</th><th>No. of patients with PS</th><th>No. of patients without PS</th><th>Sensitivity</th><th>Specificity</th></tr>
<tr><td>Primary neurologist baseline</td><td></td><td></td><td></td><td></td></tr>
<tr><td>PS</td><td>23</td><td>7</td><td>0.92</td><td>0.30</td></tr>
<tr><td>No PS</td><td>2</td><td>3</td><td></td><td></td></tr>
<tr><td>Unblinded MDE 1 baseline</td><td></td><td></td><td></td><td></td></tr>
<tr><td>PS</td><td>24</td><td>7</td><td>0.96</td><td>0.30</td></tr>
<tr><td>No PS</td><td>1</td><td>3</td><td></td><td></td></tr>
<tr><td>Blinded MDE 2 baseline</td><td></td><td></td><td></td><td></td></tr>
<tr><td>PS</td><td>22</td><td>3</td><td>0.88</td><td>0.70</td></tr>
</table>
</td></tr>
</table>

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	No PS	3	7		
	Visual imaging analysis				
	PS	24	2	0.96	0.80
	No PS	1	8		
	Quantitative imaging analysis				
	PS	23	0	0.90	.100
	No PS	2	10		
Source of funding	Non-profit and private sector				
Additional comments	➢ Blinded raters ➢ Inter-rater reliability ➢ Clinical follow-up (needs to be longer-term) ➢ Small sample size				
Citation					
NCC CC ID (Ref Man)	19818				

Evidence Table
Diag 7
How effective is single photon emission computed tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?

Bibliographic reference	Huang WS, Lee MS, Lin JC, Chen CY, Yang YW, Lin SZ *et al*. Usefulness of brain 99mTc-TRODAT-1 SPET for the evaluation of Parkinson's disease. *European Journal of Nuclear Medicine & Molecular Imaging* 2004;**31**:155-61.
Study type	Diagnostic
Evidence level	++
Study objective	To classify the patterns of 99m-Tc-TRODAT-1 SPET and to test its clinical feasibility for evaluation of the presence and severity of PD.
Number of patients	N=188 patients with PD N=45 controls Location: Taiwan sites: single
Patient characteristics	Diagnosis of PD was made according to generally accepted criteria. At least two of the following

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	symptoms were required for a clinical diagnosis of idiopathic PD: resting tremor, akinesia, and rigidity, and favourable response to dopamine therapy. All PD patients were scored with Hoehn and Yahr scale (range, I-IV). Stage I: n=32, 14 men, 18 women, mean age 64 years, range 47-78 Stage II: n=30, 14 men, 16 women, mean age 67 years, range 53-80 Stage III: n=54, 31 men, 23 women, mean age 64 years, range 47-79 Stage IV: n=58, 34 men and 24 women, mean age 67 years, range 50-80 Stage V: n=14, 10 men, 4 women, mean age 69 years, range 62-78 45 age-matched healthy subjects (16 men, 29 women, mean age 66 years, range 47-80) served as controls. None had a history of neuropsychiatric disorder or family history of movement disorders.
Intervention	TRODAT
Comparison	Clinical examination
Length of follow-up	6-month follow-up
Outcome measures	Sensitivity, specificity
Effect size	➢ Visual analysis revealved better radioactivity contrast between striatum and adjacent brain tissue in healthy subjects than in PD subjects ➢ The striatal or putaminal uptake in PD patients decreased progressively with disease severity according to both visual inspection and semi-quantitative analysis ➢ The inter-observer agreement for the presence of PD was 0.85; it was 0.88 for the rough visual scale and 0.81 for the fine visual scale ➢ There was relatively poor inter-observer agreement in disease stages II and V ➢ With reference to the clinical Hoehn and Yahr Scale (HYS) the agreement for averaged inspection was 0.52, for the fine visual scale was 0.71, for the rough visual scale and 0.85 for evaluating the presence of disease ➢ The sensitivity and specificity of averaged visual inspection in the detection of PD based on the clinical HYS were 98% and 86% ➢ Comparable sensitivity and specificity (98% and 88% respectively) for clinical PD were achieved with image findings
Source of funding	None stated
Additional comments	➢ Raters were blinded ➢ Clinical follow-up involving re-assessment of diagnosis not stated ➢ 6-month follow-up not long-term

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	➢ Poor inter-observer agreement ➢ Good sample size
Citation	
NCC CC ID (Ref Man)	19820

Evidence Table
Diag 7
How effective is single photon emission computed tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?

Bibliographic reference	Weng YH, Yen TC, Chen MC, Kao PF, Tzen KY, Chen RS *et al*. Sensitivity and specificity of 99mTc-TRODAT-1 SPECT imaging in differentiating patients with idiopathic Parkinson's disease from healthy subjects. *Journal of Nuclear Medicine* 2004;**45**:393-401.
Study type	Diagnostic
Evidence level	+
Study objective	To further investigate the clinical correlations and the age-specific sensitivity and specificity of this new approach in the diagnosis of patients with idiopathic PD that manifests in patients >50 years of age.
Number of patients	N=118 N=78 PD patients N=40 controls participants Location: Taiwan sites: single
Patient characteristics	78 PD patients (38 women, 40 men; mean age 68.6 ± 6.1 yr, age range 51-77 years) whose clinical symptoms commenced after the age of 50 years were enrolled. MRI images of the brain, in all patients, were normal, except for mild cortical atrophy. 60 patients met the criteria for probable PD and 18 patients met the criteria for possible PD because the symptoms were present for <3 years. The PD group was divided into 3 groups based on their age when undergoing SPET:

	50-59 years (n=11)	60-69 years (n=44)	70-79 years (n=23)	Total (n=79)
Mean age, y	55.1 ± 1.0	65.1 ± 2.9	72.3 ± 2.7	65.8 ± 6.1
Age of onset, y	51.2 ± 3.2	58.6 ± 4.8	63.6 ± 7.2	59.3 ± 6.7
Duration, y	3.9 ± 2.6	6.6 ± 4.5	8.7 ± 5.2	6.5 ± 4.7
Hoehn and Yahr	1.9 ± 1.2	2.6 ± 1.3	2.9 ± 1.0	2.5 ± 1.2

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	<table><tr><td>UPDRS</td><td>35.8 ± 23.2</td><td>53.2 ± 29.0</td><td>58.7 ± 23.1</td><td>50.6 ± 27.4</td></tr><tr><td>UPDRS III</td><td>23.6 ± 16.6</td><td>33.3 ± 17.1</td><td>37.5 ± 15.4</td><td>32.0 ± 17.1</td></tr></table>The control group included 40 age-matched healthy volunteers (21 women and 19 men) from 49 to 79 years old (mean age 63.2 ± 9.1 years). For comparison to the PD group 3 sub-groups were formed: n=15 (50-59 years) mean age 52.3 ± 3.8; n=15 (60-69 years) mean age 64.9 ± 2.3 years); and n=10 (70-79 years) mean age 73.2 ± 3.6 years).
Intervention	99mTc-TRODAT-1 – for protocol see paper (slice thickness and in-plane size was 2.9mm)
Comparison	Clinical examination
Length of follow-up	None stated
Outcome measures	Sensitivity and specificity of TRODAT technique used to distinguish PD from control images
Effect size	➢ A marked decrease in TRODAT-1 uptake in the striatum was easily observed in patients ➢ Reduction of uptake was most pronounced in the putamen contralateral the dominant symptomatic side ➢ The mean binding ratios of all defined regions in the PD group were significantly lower than those in the control group (p<0.0001) ➢ The mean putamen/caudate ratios were significantly lower than those in the control group (p<0.0001) ➢ Loss of dopamine agonist transporter (DAT) was most severe in contralateral putamen compared with the controls, followed by ipsilateral putamen, contralateral caudate, and ipsilateral caudate ➢ The selective loss of DAT was the characteristic finding in the PD patients ➢ In the control group TRODAT-1 binding ratios were symmetric- whereas PD patients were significantly asymmetric ➢ Using the region of interest (ROC) curve analysis- only the contralateral putamen/occipital and contralateral putamen/caudate had 100% sensitivity and specificity in discriminating PD patients from the healthy subjects ➢ With further analysis in 3 difference age-specific groups separately, all binding ratios, except caudate/occipital ratios and ipsilateral putamen/caudate ratios, showed 100% sensitivity and specificity ➢ The decrease TRODAT-1 binding in the striatum was extremely reliable in diagnosis of PD ➢ There was an age-specific cut-off level for disease diagnosis ion different regions of the striatum Early-stage patients ➢ Early stage PD patients with unilateral symptoms (Hoehn and Yahr I) 23 PD patients (mean age

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	61.6 ± 6.2 years, range 51-69) were compared separately to 26 healthy age-matched controls (mean age 59.2 ± 6.5 years, range 50-67) ➢ The striatal/occipital, putamen/occipital and contralateral putamen/caudate ratios had 100% sensitivity and specificity in discriminating early-stage PD from healthy subjects in two different age-specific groups ➢ No sexual differences in TRODAT binding ➢ Blinding ratios also declined with age in control groups ➢ Reduction of binding ratios was correlated with the UPDRS and Hoehn and Yahr staging (p<0.0001) in PD group
Source of funding	Government
Additional comments	➢ All images underwent blind review by one nuclear physician ➢ No diagnostic criteria stated ➢ Time from clinical diagnosis to scan not stated ➢ Small sample size ➢ No long-term follow-up
Citation	
NCC CC ID (Ref Man)	19821

Evidence Table **Diag 7** How effective is single photon emission computed tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Bibliographic reference	Catafau AM, Tolosa E, Laloux P, Vander BT, Van Zandijcke M, De Geeter F *et al*. Impact of dopamine transporter SPECT using ¹²³I-Ioflupane on diagnosis and management of patients with clinically uncertain parkinsonian syndromes. *Movement Disorders* 2004;**19**:1175-82.
Study type	Diagnostic
Evidence level	+
Study objective	To investigate the clinical impact of 123I-Ioflupane SPET in patients with clinically uncertain parkinsonian syndromes.
Number of patients	N=120 patients

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	Location: European centres sites: 15
Patient characteristics	Patients were considered eligible for the study when the clinical data posed significant uncertainty to the neurologist to establish a clinical diagnosis of parkinsonism. Criteria of uncertainty were assessed by referring neurologists, and included at least one of the following: only one of the three cardinal signs of parkinsonism, with or without asymmetry; two signs without bradykinesia; atypical signs; signs of mild intensity; poor response to LD and lack of disease progression. Patients with established clinical diagnosis were excluded, as where those where the uncertainty was related to differentation between idiopathic PD, MSA or PSP. All patients except 2 were Caucasians, with an average age of 65.5 ± 11.2 years, mean Hoehn and Yahr stage 2.0 ± 0.8 and median duration of disease was 3.8 years; 69% of patients had bradykinesia, 74% tremor, 63% rigidity, and 36% postural instability. Signs were unilateral in 62% of patients. At baseline 67 patients were classified as suspected presynaptic PS (59 PD, 8 other PS), 26 as suspected non-presynaptic PS (16 essential tremor) and 25 as inconclusive.
Intervention	Single intravenous injection of 123-I-Ioflupane and underwent SPET scan. The scan was carried out and reported by neuroimaging expert nuclear medicine physicians that were not blinded to patients' clinical data.
Comparison	Clinical diagnosis: classified presynaptic (parkinsonism associated with nigrostriatal degeneration such as PD, MSA, PSP), suspected non-presynaptic PS (other parkinsonism without nigrostriatal degeneration including suspected essential tremor) or inconclusive. Diagnosis and classification were based on neurologists' judgement rather than application of formal criteria. After reviewing SPET images and corresponding clinical data, neurologists were again asked to provide a diagnosis, taking into account the results of the SPET image as only additional information.
Length of follow-up	None stated
Outcome measures	Change in diagnosis
Effect size	Diagnosis ➢ At baseline 67 patients were classified as suspected presynaptic PS (59 PD, 8 other PS), 26 as suspected non-presynaptic PS (16 essential tremor) and 25 as inconclusive. ➢ The most common reason for uncertainty in the diagnosis was the presence of atypical signs (57%) followed by signs of mild intensity (52%) SPET ➢ 123-I-Ioflupane images could be classified in 117 of 118 (99.2%; 95%CI 65.4 to 100.0) of cases ➢ In only one patient was it not possible to classify an image because of doubts between and abnormal type 1 patterns

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	➢ In a substantial proportion of patients, the results of the image did not correspond with the suspected diagnosis (36% with a suspected diagnosis of presynaptic PS had a normal scan, and 54% with a suspected diagnosis of non-presynaptic PS had an abnormal scan) ➢ Of the cases classified initially s inconclusive, 68% showed abnormal pattern Diagnosis ➢ Initial diagnosis was changed after I-Ioflupane SPET in 61 patients (52%), 42% with an initial diagnosis of presynaptic PS, and 54% with a diagnosis of non-presynaptic PS ➢ After imaging 76% of inconclusive patients (n=19) were re-classified as presynaptic PS (n=14) or non-presynaptic (n=5), leaving 6 patients in the inconclusive category ➢ 16 patients classified initially as presynaptic or non-presynaptic PS were reclassified as inconclusive after SPET imaging review ➢ After SPET imaging review 12 patients changed from presynaptic PS to inconclusive (75% with normal image) and 4 patients changed from non-presynaptic PS to inconclusive (75% with normal image) ➢ 100% of patients with a final diagnosis of presynaptic PS had an abnormal image result (in one patient the image could not be classified) ➢ Whereas 94% of patients with a final diagnosis of non-presynaptic PS hd a normal image result ➢ In only two patients with abnormal scans was the diagnosis non-presynaptic PS (essential tremor and vascular parkinsonism) Confidence in diagnosis ➢ After SPET imaging, confidence in a diagnosis of PS was increased when presynaptic PS was the final diagnosis (from 58.4 $\pm$ 22.2 % at baseline to 88.4 $\pm$ 14.1%; n=63, p<0.0001) ➢ Confidence in a diagnosis of PS was decreased when non-presynaptic was the final diagnosis (from 40.3 $\pm$ 20.5% to 9.7 $\pm$ 19.4%; n=33, p<0.0001) ➢ In 51 patients, clinical diagnosis was confirmed after SPET imaging ➢ In 39 presynaptic PS patients- confidence was increased from 62.7 to 89.2% ➢ And in 12 patients with non-presynaptic PS confidence decreased from 45.0 to 12.1% Clinical management ➢ Changes in planned clinical management after SPET were recorded in 85 patients (72% of cases), changes involving therapy in most cases (46%), mainly because new therapy was initiated (35%) Tolerance ➢ Adverse events were recorded in 7 patients of which 4 were not considered to be drug related and resolved spontaneously without medical intervention

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	Withdrawals ➢ 5 patients did not return to the hospital for SPECT scanning ➢ Tolerance was assessed on 120 patients and 118 patients (59 men and 59 women) were considered for the efficacy study endpoints because 2 patients were on prohibited medications and thus were excluded despite having received a dose of 123-I-Ioflupane
Source of funding	Private sector
Additional comments	➢ Unblinded ➢ No long term follow-up ➢ Power calculations provided ➢ Large sample size
Citation	
NCC CC ID (Ref Man)	19823

Evidence Table **Diag 7** How effective is single photon emission computed tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Bibliographic reference	Van Laere K, De Ceuninck L, Dom R, Van Den EJ, Vanbilloen H, Cleynhens J *et al*. Dopamine transporter SPECT using fast kinetic ligands: ¹²³I-FP- beta-CIT versus ^{99m}Tc-TRODAT-1. *European Journal of Nuclear Medicine & Molecular Imaging* 2004;**31**:1119-27.
Study type	Diagnostic
Evidence level	+
Study objective	To compare 99mTc-TRODAT-1 and 123I-FP-β-CIT regarding both the differential diagnostic accuracy and the sensitivity for detection of disease progression.
Number of patients	N=76 IPD patients N=20 controls Location: Belgium sites: single
Patient characteristics	Between November 1999 and December 2002, a total of 96 patients (mean age 63.0 ± 11.2 years, mean disease duration 2.0 ± 1.3 years, 57 men, 39 women) were included. In both groups 10 patients with normal presynaptic function were included as control population, based on a final clinical diagnosis of essential tremor or medication-induced extrapyramidal symptoms. All other patients were classified as having idiopathic PD based on UK PDS brain bank criteria. There were no significant differences between groups below.

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<table>
<tr><td></td><td>
<table>
<tr><th>Characteristics</th><th>Controls (n=10)</th><th>IPD patients (n=39)</th><th>Controls (n=10)</th><th>IPD patients (n=37)</th></tr>
<tr><td>Mean age, y</td><td>59.8 ± 15.8</td><td>61.6 ± 10.7</td><td>66.1 ± 10.6</td><td>64.3 ± 10.4</td></tr>
<tr><td>Gender (M: F)</td><td>6:4</td><td>23:16</td><td>5:5</td><td>23:14</td></tr>
<tr><td>Mean disease duration, y</td><td>1.73 ± 1.58</td><td>2.11 ± 1.34</td><td>1.84 ± 1.59</td><td>2.07 ± 1.37</td></tr>
<tr><td>Modified Hoehn and Yahr stage</td><td>-</td><td>1.19 ± 0.33</td><td>-</td><td>1.27 ± 0.48</td></tr>
<tr><td>L-dopa at time of scan (mean: mg)</td><td>N= 2 (425)</td><td>N=12 (390)</td><td>N=1 (375)</td><td>N=22 (490)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>99mTc-TRODAT-1(TR) and 123I-FP-β-CIT (FP) imaging (see paper for details)</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis based on long-term follow-up (follow-up not stated)</td></tr>
<tr><td>Length of follow-up</td><td>None stated</td></tr>
<tr><td>Outcome measures</td><td>Sensitivity, specificity</td></tr>
<tr><td>Effect size</td><td>

Several semi-quantitative parameters were investigated and compared for the two radio-ligands
The binding index of the caudate head, the putamen, both regions summed and putamen-to-caudate ratios
Also the minimal (L v R) values for these indices and the value contralateral to the clinically affected side (for unilateral disease, H&Y <2) were investigated
The 95%CI in the FP group for both putamen binding index and the putamen/caudate ratio showed no overlap with normal values
A distinct broad overlap was observed in the TR group, especially with respect to the putamen/caudate ratio

Discriminant analysis
<table>
<tr><th>ROI/ratio</th><th colspan="3">FP-CIT</th><th colspan="3">TRODAT-1</th></tr>
<tr><th>a. All subjects</th><th>Sensitivity</th><th>Specificity</th><th>Accuracy</th><th>Sensitivity</th><th>Specificity</th><th>Accuracy</th></tr>
<tr><td>1. Putamen *</td><td>88.5</td><td>80.0</td><td>86.8</td><td>82.5</td><td>60.0</td><td>78.2</td></tr>
<tr><td>2. Caudate *</td><td>70.5</td><td>60.0</td><td>68.4</td><td>70.3</td><td>45.0</td><td>64.9</td></tr>
<tr><td>3. Putamen/caudate *</td><td>85.9</td><td>85.0</td><td>85.8</td><td>70.3</td><td>50.0</td><td>66.0</td></tr>
<tr><td>Combination (1+2+3)</td><td>92.3</td><td>90.0</td><td>91.8</td><td>83.8</td><td>60.0</td><td>78.7</td></tr>
<tr><td>4. Putamen min **</td><td>92.3</td><td>70.0</td><td>87.8</td><td>83.8</td><td>80.0</td><td>83.0</td></tr>
<tr><td>5. Caudate min **</td><td>69.2</td><td>60.0</td><td>67.3</td><td>75.7</td><td>60.0</td><td>72.3</td></tr>
<tr><td>6. Putamen/caudate min **</td><td>87.2</td><td>80.0</td><td>85.7</td><td>75.5</td><td>70.0</td><td>75.5</td></tr>
<tr><td>Combination (4+5+6)</td><td>94.9</td><td>80.0</td><td>91.8</td><td>83.8</td><td>80.0</td><td>83.0</td></tr>
</table>
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	<table><tr><th>ROI/ratio</th><th colspan="3">FP-CIT</th><th colspan="3">TRODAT-1</th></tr><tr><th>b. H&Y stage < 2 (lateralised)</th><th>Sensitivity</th><th>Specificity</th><th>Accuracy</th><th>Sensitivity</th><th>Specificity</th><th>Accuracy</th></tr><tr><td>7. Putamen contralateral</td><td>94.6</td><td>85.7</td><td>93.2</td><td>91.7</td><td>70.0</td><td>87.0</td></tr><tr><td>8. Caudate contralateral</td><td>78.4</td><td>57.1</td><td>75.0</td><td>75.0</td><td>60.0</td><td>71.7</td></tr><tr><td>9. Putamen/caudate contralateral</td><td>91.9</td><td>85.7</td><td>90.9</td><td>69.4</td><td>70.0</td><td>69.9</td></tr><tr><td>Combination (7+8+9)</td><td>94.6</td><td>85.7</td><td>93.2</td><td>91.7</td><td>70.0</td><td>87.0</td></tr></table>* Average of both sides: all data included irrespective of disease lateralisation (i.e. without a priori clinical information) ** Minimal binding index or minimal putamen/caudate ratio, irrespective of any clinical information ➢ Discriminant analysis with cross-validation showed maximal classification accuracy for FP of 93% for the binding index in the putamen contralateral to the initial clinically affected side (sensitivity 95% and specificity 86%) in H&Y < 2 subgroup ➢ For the TR group the corresponding values were 87% accuracy, 92% sensitivity and 70% specificity ➢ The putamen binding index contralateral to the most affected side (or in the absence of clinical information, the minimal putamen binding index) was the most discriminative index for both tracers ➢ The highest specificity was also obtained from the putamen binding index or from the putamen/caudate ratio
Source of funding	University research grant
Additional comments	➢ No mention of blinding ➢ No long-term follow-up ➢ Small sample sizes
Citation	
NCC CC ID (Ref Man)	19824

Evidence Table **Diag 7** How effective is single photon emission computed tomography vs. long-term clinical follow-up in determining an accurate diagnosis in patients with a parkinsonian syndrome?	
Bibliographic reference	Popperl G, Radau P, Linke R, Hahn K, Tatsch K. Diagnostic performance of a 3-D automated quantification method of dopamine D<inf>2</inf> receptor SPECT studies in the differential diagnosis of parkinsonism. *Nuclear Medicine Communications* 2005;**26**:39-43.
Study type	Diagnostic

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Evidence level	+
Study objective	To evaluate the diagnostic performance of a recently introduced three-dimensional automated quantification method in a large group of parkinsonian patients.
Number of patients	N=101 patients with parkinsonian syndromes N=49 idiopathic parkinsonian syndromes (IPS) N=52 non-idiopathic parkinsonian syndromes (non-IPS) Location: Germany Sites: single
Patient characteristics	A total number of 101 consecutive patients (67 men and 34 women) with clinically confirmed parkinsonian syndromes referred from specialised movement disorder clinics. 49 patients suffered from IPS, 52 patients from non-IPS with the clinical diagnosis based on the positive or negative response to an apomorphine test and/or dopamine replacement therapy. The two patient groups were comparable in age, with a mean age of the IPS patients of 65 $\pm$ 8 years (range 36-81 years) and a mean age of the non-IPS patient group of 70 $\pm$ 9 years (range 53-85 years).
Intervention	123I-IBZM SPET (see paper for details)
Comparison	Clinical diagnosis
Length of follow-up	None stated
Outcome measures	Sensitivity and specificity
Effect size	➢ Quantitative data of the manual and automated evaluation were separately categorised in true positive and false positive, and true negative and false negative findings using the results of the clinical investigations as the 'gold standard' ➢ At optimal decision thresholds sensitivity and specificity were 87% and90% for automated and 85% and 90% for manual method ➢ This diagnostic performance was obtained at a striatal/frontal cortex ratio of 1.42 for the automated and 1.60 for the manual quantification respectively ➢ The total area under the curve was 0.92 for the automated and 0.93 for the manual method, showing no statistical difference ➢ The area under the ROC curve corresponding to a false positive fraction from 0% to 20% was 0.163 for the automated and 0.166 for the manual evaluation, also showing no statistically

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	significant difference
Source of funding	None stated
Additional comments	➢ Blinding of raters not specified ➢ Criteria for clinical diagnosis not UK PDS brain bank criteria ➢ Number of raters not stated ➢ Large sample size
Citation	
NCC CC ID (Ref Man)	19822

DIAG 8 – section 5.11

Evidence Table **Q 8** How effective is objective smell testing vs. long-term clinical follow-up in determining an accurate diagnosis in patients with suspected Parkinson's disease?	
Bibliographic reference	Muller, A., Mungersdorf, M., Reichmann, H., Strehle, G., & Hummel, T. 2002, "Olfactory function in Parkinsonian syndromes", *Journal of Clinical Neuroscience.*, vol. 9, no. 5, pp. 521-524.
Study type	Diagnostic study: prospective follow-up (6-12 months) clinical diagnosis
Evidence level	DS II
Number of patients	N= 50 Parkinson's syndrome (PS) patients ➢ N=29 clinically diagnosed idiopathic Parkinson's disease (IPD) ➢ N=21 no definite diagnosis at time of testing Location: Department of Neurology, University of Dresden Medical School Sites=1
Patient characteristics	Mean age 57.7 years (range 38-80) 15 women; 35 men Mean duration of PS symptoms 5.8 years (range 3 months to 17yr) Patients with Parkinson's syndrome were included in this study which, consisted of patients already

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	clinically diagnosed with IPD and patients with no diagnosis at the time of testing 2 patients were not treated pharmacologically; 48 patients received various Anti-PD medication Number of patients at Hoehn and Yahr (H&Y) stages: I=6; I,5=1; II=21; II,5=8; III=11; IV=3 On questioning of olfactory deficits 23/50 patients reported a decrease in olfactory function None of the patients had an infection of the upper respiratory tract at the time of testing
Intervention	***'Sniffin Sticks': standardized psychophysical olfactory test*** Odorants were presented in 'pen-like' odour dispensing devices For odour presentation the pen's cap was removed for approximately 3 seconds The pen's tip was placed ~ 2cm in front of both nostrils (testing was performed bilaterally) Duration of testing ~ 30 min Odour threshold test: 3 pens presented in randomised order- 2 pens containing the solvent - 1 pen contained the odorant at a certain dilution- subjects had to identify the odour containing pen Odour discrimination test: triplets of pens presented in randomised order- 2 containing the same odorant- the third containing a different odour-subjects had to identify 'different odour' pen For the above 2 tests subjects were blindfolded to prevent visual identification of pens Odour identification test: 16 common odours were presented- identification of individual odorants was performed using a list of 4 descriptors- interval between odours 20-30 seconds
Comparison	Clinical diagnosis made by a team of experienced neurologists (Diagnostic evaluation included PET F-dopa scans for patients with questionable diagnosis)
Length of follow-up	6-12 months
Outcome measures	Odour threshold, discrimination, and identification results were presented as a composite 'TDI score' to quantify olfactory function; sensitivity and specificity for the discrimination of IPD
Effect size	Functional anosmia <16 TDI score- definitions for hyposmia vary in relation to the subject's age- for example subjects aged between 16 and 35 yr the following definitions apply: severe hyposmia (16-20), moderate hyposmia (21-25), mild hyposmia (26-30), and normosmia >30 ***IPD*** ➢ 51% (n=19) presented with anosmia; 35% (n=13) with severe hyposmia, and 14% (n=5) with moderate hyposmia Multiple system atrophy (MSA), supranuclear palsy (PSP), and corticobasal degeneration (CBD):

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	➢ After an additional observation period of 6-12 months 4 patients with moderate hyposmia were clinically diagnosed as non IPD: 3 patients diagnosed as MSA and 1 patient as PSP ➢ 4 patients clinically diagnosed as MSA had mild hyposmia ➢ One patient with mild hyposmia clinically diagnosed as CBD ➢ Four patients clinically diagnosed as CBD, MSA, misdiagnosed PS, or psychogenic movement disorder presented with normosmia ➢ When comparing olfactory sensitivity between 3 different types of IPD (tremor-dominant type, akinetic rigid- dominant type, and equivalent (neither tremor nor akinesia are dominant) and MSA a significant effect for group ($F [3,41]=9.88$, $p<0.001$) post-hoc Bonferroni tests indicated no differences between 3 types of IPD ➢ Olfactory sensitivity for each of the 3 IPD groups was significantly lower than for MSA ($p<0.002$) ➢ Odour threshold test: ($F [3,41]=4.92$, $p=0.005$); odour discrimination ($F[3,41]=7.12$, $p=0.001$) and odour identification ($F[3,41)=6.20$, $p=0.001$) ➢ There were no significant correlations between the TDI score, duration of disease ($p=0.41$) or scoring on Hoehn and Yahr scale ($p=0.90$) ➢ When comparing olfactory sensitivity between IPD patients scoring higher than 2 on the H&Y and those scoring ≤ 2, no significant difference was found ($p=0.81$) ➢ **Differentiation between MSA and IPD at a <u>cut-off TDI score of 19.5</u>, psychophysical testing (sniffin' sticks) a sensitivity of 78%, specificity of 100%, positive predictive value 100%, negative predictive value 50%** ➢ **<u>Cut-off TDI score of 24.8</u>: sensitivity 100%, specificity 63%, positive predictive value 93%, and negative predictive value100%**
Source of Funding	None stated
Additional comments	➢ Aim: To reinvestigate the diagnostic value of psychophysical olfactory testing (using 'Sniffin Sticks') to differentiate IPD from non-IPD ➢ Definitions for hyposmia apply to an age range of 16-35 years- the patient group in the paper has an age range of 38-80 years (mean 57.7) ➢ Investigators were blind to the initial diagnosis when administering the 'sniffin stick' test ➢ Investigators were blind to 'sniffin stick' results when making follow-up clinical diagnosis ➢ PD patients were not initially re-diagnosed for this study by a blind neurologist-instead previous diagnosis from the clinics where they were recruited were applied (time from last diagnosis to

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	study commencement therefore not stated) ➢ No diagnostic criteria stated for either initial clinical diagnosis or final clinical diagnosis ➢ No healthy age-matched controls- comparison group was MSA group Prospective study: follow-up 6-12 months
Citation	
NCC CC ID (Ref Man)	700

Evidence Table
Q 8
How effective is objective smell testing vs. long-term clinical follow-up in determining an accurate diagnosis in patients with suspected Parkinson's disease?

Bibliographic reference	Double, K. L., Rowe, D. B., Hayes, M., Chan, D. K., Blackie, J., Corbett, A., Joffe, R., Fung, V. S., Morris, J., & Halliday, G. M. 2003, "Identifying the pattern of olfactory deficits in Parkinson disease using the brief smell identification test", *Archives of Neurology.*, vol. 60, no. 4, pp. 545-549.
Study type	Diagnostic study: retrospective clinical diagnosis
Evidence level	DS II
Number of patients	N=101 Total Participants ➢ N=49 Parkinson's disease (PD) ➢ N=52 Controls Location: Sydney, Australia Sites: multiple
Patient characteristics	Study group consisted of 101 Caucasian subjects (49 with PD and 52 controls)

	Controls (n=52)	PD (n=49)	H&Y I (n=20)	II (n=20)	III (n=9)
Male/female	22/30	26/23	11/9	9/11	3/5
Age yrs (mean)	71 (10)	68 (8)	65 (7)	71 (8)	67 (9)
Disease duration yrs	NA	5 (1)	4 (1)	5 (1)	9 (2)
UPDRS motor score (mean)	0.6 (0.2)	16 (1.3)	8.5 (1)	19 (2)	27 (3)

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Abnormal Olfaction No. (%)	12 (23)	40 (82)	16 (80)	16 (80)	8 (89)
Smokers No (%)	23 (44)	23 (47)	7 (35)	6 (30)	5 (55)

PD

All subjects were assessed by a neurologist specializing in movement disorders
The presence and severity of parkinsonian symptoms were determined and quantified by means of the motor section (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS)
All subjects categorized according to Hoehn and Yahr criteria
All motor testing was performed with patients taking medication
Cognitive function was assessed using a neuropsychological tool to identify dementia
Subjects also completed a questionnaire concerning motor dysfunction history, smell or taste problems, current medications, previous surgical interventions, and current and past smoking habits
Diagnosis of PD was made according to the criteria of Gelb et al

Controls

Required the absence of any neurologic or neuropsychological signs or symptoms of PD
Subjects exhibiting any evidence of dementia or atypical Parkinsonism features were excluded
Controls with family history of PD were also excluded

3/49 PD and 4/52 controls reported surgical procedures involving the sinus, septal or nasal region

Intervention	B-SIT: an abridged, validated version of the UPSIT incorporating the 12 scratch-and-smell odours The test is given with a freshly scratched odour-impregnated panel a maximum of twice before being required to make a forced choice from 4 possible alternative answers The number of correct answers from 12 possible correct answers were summed and compared with predetermined values defining 'normal' or 'abnormal' olfactory function according to age and sex (Doty

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	et al., 1996)
Comparison	Retrospective clinical diagnosis
Length of follow-up	None stated (retrospective study)
Outcome measures	Sensitivity, specificity, positive and negative predictive values for diagnostic accuracy of B-SIT vs. clinical diagnosis
Effect size	➢ Abnormal olfactory function was present in 40 (82%) of non-demented PD subjects compared to 12 (23%) controls ➢ There was no interaction between total B-SIT score and a history of smoking, PD duration, or PD severity (UPDRS and H&Y scales) Discriminant analysis results for the B-SIT test: ➢ **Sensitivity 82%, specificity 82%, positive predictive value 77%, negative predictive value 77%, p value <0.001** ➢ Differences in odour identification between PD and control groups were found in 8/12 odours tested ➢ The use of 12 odours correctly classified 81% of cases (44 controls [85%] and 38 patients with PD [76%]) Data indicated that 5 our of the 12 B-SIT odours (gasoline, banana, pineapple, smoke, and cinnamon) are required to adequately discriminate patients with PD from controls with low-probability of false-positive diagnoses
Source of Funding	Australian Brain Foundation, Sydney; The Neurology Research Fund of the Royal North Shore Hospital, Sydney; and research salary grants from the National Health and Medical Research Council of Australia, Canberra; and New South Wales State Government salary support and anonymous donations.
Additional comments	➢ The aim of the study was to utilize the Brief Smell Identification Test (B-SIT) test to identify a selective pattern of olfactory deficits to discriminate between patients with PD from controls ➢ Investigators did not state whether diagnostic tests were performed blindly or independently ➢ No differences between sites discussed: possibility for heterogeneity in smell-test methods as well as diagnostic criteria ➢ No long-term clinical follow-up stated
Citation	
NCC CC ID (Ref Man)	699

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Evidence Table **Q 8** How effective is objective smell testing vs. long-term clinical follow-up in determining an accurate diagnosis in patients with suspected Parkinson's disease?	
Bibliographic reference	Doty, R. L., Bromley, S. M., & Stern, M. B. 1995, "Olfactory testing as an aid in the diagnosis of Parkinson's disease: development of optimal discrimination criteria", *Neurodegeneration.*, vol. 4, no. 1, pp. 93-97.
Study type	Diagnostic study: retrospective clinical diagnosis
Evidence level	DS III
Number of patients	N=180 Parkinson's disease (PD) patients N=612 controls (4 age-matched controls for each PD patient in the ≤ 60 and ≥ 70 years subject groups) Location: Pennsylvania, New Jersey, and California USA sites: 3
Patient characteristics	Primarily subjects with early-stage PD Number of subjects at Hoehn and Yahr (H&Y) stages I-III: 102,55,23 respectively At the time of testing 31 patients were unmedicated The duration of parkinsonian symptoms ranged from 3 months to 48 years (median 5.0 yrs) All subjects scored 35 or better on the Picture Identification Test Recruitment: Controls: randomly selected from a database of over 2500 subjects maintained at the University of Pennsylvania Smell and taste centre- includes individuals who had been administered UPSIT PD: outpatients from the Department of Neurosurgery at St.Barnabas Medical Centre, Livingstone, NJ, the department of neurology, graduate hospital, Philadelphia, Pennsylvania, and the California Parkinson's foundation, San Jose, California
Intervention	UPSIT test: (University of Pennsylvania Smell Identification Test) In this test the subject is required to identify, in a 4-alternative multiple-choice format, each of 40 odorants presented on microencapsulated 'scratch and sniff' labels, and the subject is required to provide an answer even if no smell is perceived (the test is forced-choice).

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	The number of items out of 40 that were answered correctly served as the dependent measure.
Comparison	Retrospective clinical diagnosis
Length of follow-up	None stated (retrospective study)
Outcome measures	Sensitivity and specificity of UPSIT test diagnosis compared to clinical examination diagnosis
Effect size	➢ Sensitivity and specificity estimates were calculated for values at and below 32 of the possible 40 UPSIT scores (0,5 and 10-40) (chance performance =10) ➢ Age group ≤ 60 years, male, UPSIT cut-off score 31, sensitivity 91% and specificity 88% ➢ Age group ≤ 60 years, female, UPSIT cut-off score 33, sensitivity 79% and specificity 85% ➢ **Age group 61-70 years, male, UPSIT cut-off score, 25, sensitivity, 81% and specificity 82%** ➢ **Age group 61-70 years, female, UPSIT cut-off score 30, sensitivity, 80% and specificity 88%** ➢ Age group ≥ 71 years, male, UPSIT cut-off score 22, sensitivity 76% and specificity 78% ➢ Age group ≥ 71 years, female, UPSIT cut-off score 25, sensitivity 78% and specificity 82% ➢ These cut-off (discriminatory) UPSIT scores decrease as a function of age for each of the study groups On average lower UPSIT scores are needed to define PD-related pathology for the males than for females
Source of Funding	Grant from the National Institute on Deafness and Other Communication Disorders and grant from the National Institute of Aging.
Additional comments	➢ **Aim**: To assess olfactory dysfunction in the evaluation of Parkinson's disease, specifically using the University of Pennsylvania Smell Identification Test (UPSIT) to discriminate between PD patients and age-matched controls ➢ Clinical diagnostic criteria not stated ➢ Investigators did not state whether diagnostic tests were performed blindly or independently ➢ No differences between sites discussed: possibility for heterogeneity in smell-test methods as well as diagnostic criteria ➢ PD patients were not re-diagnosed for this study by a blind neurologist-instead previous diagnosis from the clinics where they were recruited were applied (time from last diagnosis to study commencement therefore not stated) ➢ Authors state: 'since the PD subjects of our study were already identified as having PD, sensitivity and specificity estimates obtained cannot be viewed as comparable to classical sensitivity and specificity estimates obtained by epidemiologists' ➢ No long-term clinical follow-up stated
Citation	

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NCC CC ID (Ref Man)	708

Evidence Table
Q 8
How effective is objective smell testing vs. long-term clinical follow-up in determining an accurate diagnosis in patients with suspected Parkinson's disease?

Bibliographic reference	Wenning, G. K., Shephard, B., Hawkes, C., Petruckevitch, A., Lees, A., & Quinn, N. 1995, "Olfactory function in atypical parkinsonian syndromes", *Acta Neurologica Scandinavica.*, vol. 91, no. 4, pp. 247-250
Study type	Diagnostic study
Evidence level	DS III
Number of patients	N=169 total N=118 idiopathic Parkinson's disease patients (IPD) N=29 Multiple System Atrophy patients (MSA) N=15 progressive supranuclear palsy patients (PSP) N=7 Corticobasal degeneration patients (CBD) N=123 controls
Patient characteristics	Diagnostic criteria for MSA given by Quinn et al, PSP given by Lees et al., and ''in the absence of diagnostic criteria CBD was diagnosed in the presence of a typical picture described by Riley et al'' Controls: Recruited from Ipswitch Hospital and British telecom staff

	IPD	MSA	PSP	CBD	Control
Mean age (years)	59.4	58.6	65.5	67.1	46.4
Standard deviation	± 11.6	± 8.6	± 8.1	± 5.1	± 17.3
Male-female ratio	0.98	1.90	2.80	1.30	0.67

Intervention	UPSIT test: 40-odorant forced-choice test All MSA subjects tested at National Hospital for Neurology and Neurosurgery, London; IPD and healthy controls tested at Ipswitch hospital, Suffolk; PSP and CBD patients self-administered the test
Comparison	Atypical parkinsonian syndromes test scores and control subject test scores
Length of follow-up	Non stated

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Outcome measures	Sensitivity of test to include IPD patients and specificity of test to exclude non-IPD patients
Effect size	➢ **A cut-off score of 25 between IPD and atypical parkinsonian groups yielded a sensitivity of 77% and a specificity of 85% for the differentiation of IPD from other parkinsonian syndromes** ➢ A lower cut-off score increased the specificity at the expense of sensitivity and vice versa ➢ UPSIT scores were outside the lower limit of 95% confidence interval in: ➢ 60/118 (50.8%) of PD patients ➢ 9/29 (31%) of MSA patients ➢ 3/15 (20.0%) of PSP patients ➢ And none of the CBD patients ➢ There was a significant inverse correlation between age and UPSIT scores in controls (P=0.01) as well as PD (p=0.01) and MSA (p=0.029) but not in PSP or CBD groups
Source of Funding	UK Parkinson's disease society
Additional comments	➢ The difference in sex and age of controls compared to patients groups was taken into consideration in the statistical analysis ➢ Self-administration of tests for PSP and CBD groups not objective? ➢ No blinding of investigators to clinical diagnosis stated ➢ Poor reference standard (differential diagnosis not comparison to clinical diagnosis) ➢ Diagnostic criteria for IPD not stated (brain bank???)
Citation	
NCC CC ID (Ref Man)	707

Evidence Table **Q 8** How effective is objective smell testing vs. long-term clinical follow-up in determining an accurate diagnosis in patients with suspected Parkinson's disease?	
Bibliographic reference	Hawkes, C. H., Shephard, B. C., & Daniel, S. E. 1997, "Olfactory dysfunction in Parkinson's disease", *Journal of Neurology, Neurosurgery & Psychiatry.*, vol. 62, no. 5, pp. 436-446.
Study type	Diagnostic study
Evidence level	DS III

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Number of patients	N=96 Parkinson's disease N=96 controls
Patient characteristics	Parkinson's disease group: Aged: 27-81 years (mean 57 years), 49 men and 47 women Patient were obtained consecutively from neurological inpatients and outpatients All were examined neurologically at least once and were considered to have IPD All patients had intact nasal passages All patients scored 27/30 or more on mini-mental test Nearly all IPD patients were receiving levodopa and selegiline 6 patients were taking long-term tricyclic antidepressants 2 were on long-term lithium carbonate for affective disorder Controls: Aged: 18-78 (mean 41.7 years), 39 men, 57 women Recruited from healthy members of hospital and British telecom staff
Intervention	UPSIT test- uses strips of paper inmpregnated with microencapsulated odours, which are released on scratching the strip with a pencil. There are 40 different odours and a forced choice is made from four possible answers
Comparison	Healthy controls
Length of follow-up	None stated
Outcome measures	Sensitivity of test for selecting IPD patients (i.e. percentage of patients scoring incorrectly) Specificity of test for not selecting controls (i.e. percentage of controls scoring correctly)
Effect size	➢ The UPSIT fort he patients with Parkinson's disease were significantly lower than those for controls (P<0.0001) ➢ Only 26% (25 of 96) of the patients with Parkinson's disease had a score within the level expected for 95% of our healthy controls ➢ There was no evidence of quadratic effects ➢ Out of the 40 odorants a combination of **pizza and wintergreen** was the best discriminator with a **sensitivity of 90% and a specificity of 86%** ➢ **Pizza** (oregano smell) was the best single discriminant: **sensitivity 76% and 90% specificity** ➢ Inclusion of a third odorant did not improve separation between controls and PD group ➢ No correlation between disease duration and UPSIT score (r=0.074) ➢ Odours that were most readily misidentified were lemon, pizza, wintergreen, rose and clove

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Source of Funding	A grant from the United Kingdom Parkinson's disease Society
Additional comments	➢ Aim: To evaluate olfactory function in Parkinson's disease ➢ This study does not compare the results of the UPSIT test to clinical diagnosis ➢ Young control group- could contribute towards significance of the results? ➢ Predominantly female control group compared to patient group ➢ Forced choice: 25% chance of correct answer ➢ From questionnaire also included in the study only 28% of patients with PD were aware of an olfactory impediment ➢ Does not state blinding of investigators to clinical diagnosis ➢ Does not list criteria for clinical diagnosis (brain bank??)- poor reference standard??
Citation	
NCC CC ID (Ref Man)	703

Evidence Table **Diag 8** How effective is objective smell testing vs. long-term clinical follow-up in determining an accurate diagnosis in patients with suspected Parkinson's disease?	
Bibliographic reference	Katzenschlager R, Zijlmans J, Evans A, Watt H, Lees AJ. Olfactory function distinguishes vascular parkinsonism from Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry* 2004;**75**:1749-52.
Study type	Diagnostic
Evidence level	+
Study objective	To compare olfactory function in vascular parkinsonism and Parkinson's disease (PD) diagnosed according to published clinical diagnostic criteria.
Number of patients	N=14 vascular parkinsonism patients N=18 PD patients N=27 controls Location: sites:
Patient characteristics	Eligible patients had to fulfil published clinical diagnostic criteria. MMSE score of ≤24 was an exclusion

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<table>
<tr><td></td><td>criterion. L-dopa response was determined based on the participants subjective assessment and the case notes, but was not used as an exclusion criterion for vascular parkinsonism. Consecutive patients attending a movement disorders clinical and fulfilling above criteria were asked to participate. Parkinson's disease was diagnosed based on the Queen Square Brain bank criteria.
<table>
<tr><td></td><td>Vascular parkinsonism</td><td>PD</td><td>Controls</td></tr>
<tr><td>Mean age, y (range)</td><td>74.1</td><td>70.6 (64-85)</td><td>72.6 (63-85)</td></tr>
<tr><td>Mean disease duration, (range)</td><td>6.6</td><td>9.1 (2 to 17)</td><td>-</td></tr>
</table>
Mean age and disease duration did not differ significantly between groups.</td></tr>
<tr><td>Intervention</td><td>University of Pennsylvania smell identification test (UPSIT). Patients are required to make a forced choice from 4 possible answers for each item, even if no odour is perceived.</td></tr>
<tr><td>Comparison</td><td>Clinical diagnosis</td></tr>
<tr><td>Length of follow-up</td><td>None stated</td></tr>
<tr><td>Outcome measures</td><td>Sensitivity, specificity</td></tr>
<tr><td>Effect size</td><td>➢ The mean UPSIT score in the vascular parkinsonism group was 26.1 (95%CI 23.1 to 29.0) which was significantly different from PD: mean UPSIT score 17.1 (95%CI 14.5 to 19.7); 95%CI of the difference 5.2 to 12.7; p<0.0001
➢ Mean UPSIT in normal controls was 27.6 (95%CI 25.6 to 29.4)
➢ The difference between PD and controls was significant (95%CI –13.5 to –7.6; p<0.0001)
➢ While the difference between vascular parkinsonism and controls was non-significant (p=0.32)

➢ In this elderly age group an UPSIT score of >22 had a sensitivity of 85.7% for detecting vascular parkinsonism and a specificity of 88.9% for distinguishing vascular parkinsonism from controls
➢ As subjects' age distribution spanned ages where considerable changes in olfactory normally occur- the authors analysed separate cut-off values for two age groups (65-75 and 76-88 years)
➢ The cut-off value showing the best balance between sensitivity and specificity was ≤ 23 in 65-75 with 100% sensitivity and 85.7% specificity
➢ In the 76-88 group, an UPSIT score of ≤ 22yeilded a sensitivity of 85.7% and a specificity of 80%</td></tr>
<tr><td>Source of funding</td><td>None stated</td></tr>
<tr><td>Additional comments</td><td>➢ Blinding of raters to clinical diagnosis not stated
➢ No long-term follow-up
➢ Criteria for diagnosis stated
➢ Small sample size</td></tr>
<tr><td>Citation</td><td></td></tr>
</table>

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NCC CC ID (Ref Man)	19807

TxNP1 – section 6.5

Evidence Table **TxNP1** Is MAO-B vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Ives, N., Stowe, R. L., Marro, J., Counsell, C., Macleod, A., & Clarke, C. E. Monoamine oxidase type B inhibitors in early Parkinsons's disease: A meta analysis of 17 randomised trials involving 3525 patients. 2004.
Study type	Meta-analysis: 17 randomised trials
Evidence level	1++
Study objective	To quantify more reliably the benefits and risks of monoamine oxidase type B inhibitors (MAOBI) in early Parkinson's disease.
Number of patients	N=3525 early Parkinson's disease patients
Patient characteristics	Early disease patients: patients who had no history of motor complications and were untreated or had received limited (generally less than 12 months) exposure to anti-parkinsonian medication
Intervention	13 trials- selegiline, 3- lazabemide, 1-rasagiline
Comparison	Placebo or levodopa
Length of follow-up	6 weeks to 10 years
Outcome measures	Mortality and UPDRS rating scale (other outcome measure to be included for TxMN1)
Effect size	Mortality ➢ Mortality data was available from 9 trials of selegiline and one of lazabemide ➢ UK-PDRG study reported 76/271 deaths in selegiline arm compared with 44/249 deaths in levodopa arm (odd ratio=1.57, 95%CI 1.09 to 2.30, p=0.015) ➢ Other trials showed no excess mortality between MAOBI groups and controls (15.5% v 18.2%;odds ratio= 1.02, 95% CI 0.84 to 1.25, p=0.8)

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	➢ Taking all available data, 287 (20%) deaths occurred in 1436 MAOBI patients compared to 257 (21%) in 1215 control patients (odds ratio=1.13, 95%CI 0.94 to 1.34, p=0.2) ➢ No significant heterogeneity between trials p=0.6 even including the UK-PDRG study Clinical disability rating scales ➢ Data was only available from 6 trials of selegiline ➢ UPDRS scores at 3 months were: • Total score: 2.7 (95%CI 1.4 to 4.1, p=0.00009); • Motor score: 1.8 (95%CI 0.8 to 2.7, p=0.0004) and • Activities of daily Living scores: 0.9 points (0.5 to 1.4, p=0.00007) • All better with selegiline than controls ➢ The large DATATOP study accounted for over 65% of the patients analysed and over 79% of patients in the MAOBI v placebo comparison ➢ Combined results from the other two studies of MAOBI v placebo were consistent with those from the DATATOP and significant independently (p=0.004)
Source of funding	Government funding
Additional comments	➢ Robust search strategy ➢ Systematic review of literature from 1966 to December 2003 ➢ Inclusion criteria for trials listed ➢ Two investigators independently scored the methodological quality of the included studies ➢ Tests for heterogeneity were used ➢ All trials double-blind (15/17 double blind) ➢ Not all studies intention-to-treat analysis ➢ Trials included for these outcome measure reported here: Lees et al (1995), Kirollos et al (1996), Olanow (1995), Caraceni et al (2001), Tetrud et al (1989), Larsen et al (1999), Pruntek (1999), Myllyla et al (1992), Myllyla et al (1995), Myllyla et al (1997)
NCC CC ID (Ref Man)	2739

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Evidence Table

TxNP1

Is MAO-B vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?

Bibliographic reference	2004, "A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease", *Arch.Neurol.*, vol. 61, no. 4, pp. 561-566.
Study type	Double-blind, parallel group, randomised, delayed start clinical trial
Evidence level	1++
Study objective	To compare the effects of early and later initiation of rasagiline on progression of disability in patients with Parkinson's disease (PD).
Number of patients	N=404 patients with early PD N=134 rasagiline 1 mg/d N=132 rasagiline 2 mg/d N=138 placebo/delayed rasagiline group Location: US and Canada Sites:32
Patient characteristics	Inclusion criteria: subjects must be older than 35 years, had idiopathic PD confirmed by the presence of at least 2 of cardinal signs (resting tremor, bradykinesia, and rigidity) and had disease severity not greater than Hoehn and Yahr stage III.
Intervention	Rasagiline 1 or 2 mg/d for 1 year
Comparison	Placebo for 6 months followed by rasagiline 2 mg/d for 6 months

Characteristics	Rasagiline 1mg/d	Rasagiline 2 mg/d	Delayed rasagiline
Age, y (SD)	60.8 ± 10.1	60.2 ± 11.4	60.4 ± 10.9
Disease duration, y (SD)	0.92 ± 1.28	1.13 ± 1.31	0.90 ± 1.08
Male sex (%)	82 (67.2)	68 (57.1)	89 (68.5)
UPDRS score (Total)	24.4 ± 11.5	25.1 ± 9.1	23.9 ± 10.9
UPDRS score (Motor)	17.6 ± 9.1	17.5 ± 7.2	17.0 ± 8.3
UPDRS score (ADL)	5.95 ± 3.41	6.53 ± 3.22	6.01 ± 3.32
Hoehn and Yahr	1.84 ± 0.48	1.85 ± 0.47	1.84 ± 0.49

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<table>
<tr><td>Length of follow-up</td><td>52 weeks</td></tr>
<tr><td>Outcome measures</td><td>Change in total Unified Parkinson’s disease Rating Scale (UPDRS) from baseline to 12 months</td></tr>
<tr><td>Effect size</td><td>

Subjects were examined at baseline and at 4,8,14,20,26,32,42 and 52 weeks after randomisation
380/404 entered the active treatment phase- 9 withdrew immediately after entering-leaving 371
33 subjects who withdrew or began dopaminergic therapy immediately were older (p=0.04) and had higher total UPDRS scores at baseline (p<0.001)
There were no significant differences in baseline characteristics among the 371 subjects
259 (69.8% of the 371 subjects completed the active phase without starting additional therapy

UPDRS

52-week total UPDRS score/ changes in total UPDRS from baseline- mean (SD) for 371 subjects:
1 mg rasagiline 27.45 (± 14.18)/ 3.01 (±8.26)
2 mg rasagiline 27.10 (±11.90)/ 1.97 (±7.49)
Delayed 2mg rasagiline 28.02 (±14.17)/ 4.17 (±8.83)

Table: change from baseline in efficacy variables between 371 subjects (effect size, 95% CI, p value)
<table>
<tr><td>Variable</td><td>Rasagiline 1mg/d vs. delayed rasagiline 2 mg/d</td><td>Rasagiline 2 mg/d vs. delayed rasagiline 2 mg/d</td></tr>
<tr><td>UPDRS total*</td><td>-1.82 (-3.64 to 0.01, p= 0.05)</td><td>-2.29 (-4.11 to –0.487, p= 0.01)</td></tr>
<tr><td>UPDRS motor*</td><td>-1.06 (-2.47 to 0.34)</td><td>-0.99 (-2.39 to 0.41)</td></tr>
<tr><td>UPDRS ADL</td><td>-0.48 (-1.15 to 0.19)</td><td>-0.96 (-1.64 to –0.29, p=0.005)</td></tr>
<tr><td>UPDRS Mental*</td><td>0.16 (-0.09 to 0.42)</td><td>-0.07 (-0.33 to 0.19)</td></tr>
<tr><td>Hoehn and Yahr Score</td><td>0.08 (-0.01 to 0.17)</td><td>0.04 (-0.05 to 0.13)</td></tr>
<tr><td>Schwab/ England</td><td>-0.21 (-1.47 to 1.04)</td><td>-0.15 (-1.41 to 1.11)</td></tr>
</table>

The model used to determine effect sizes includes a treatment x centre interaction
The comparison of responders between the group receiving 2 mg/d rasagiline for 1 year and the delayed 2 mg/d rasagiline group was significant p=0.04
The comparison between the 1mg/d rasagiline and 2 mg/d rasagiline groups was not significant p=0.93
There were no differences between groups in the time to start additional therapy during one year of follow-up

</td></tr>
<tr><td>Source of funding</td><td>Pharmaceutical company</td></tr>
<tr><td>Additional comments</td><td>

Enrolment period from November 1997 to June 1999
At enrolment patients could be treated with anticholinergics but other anti-parkinsonian medications

</td></tr>
</table>

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	were not permitted ➢ Blinding of investigators ➢ Intention-to-treat analysis: based on 91.8% of the original cohort who enrolled- only those entered and began the active treatment phase were analysed with intention-to-treat ➢ Centre interaction was part of data analysis ➢ Comparability between sites for all outcome measures not stated ➢ Methods of randomisation and allocation concealment methods not stated
NCC CC ID (Ref Man)	2764

Evidence Table **TxNP1** Is MAO-B vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease? **TxMN1** What is the effectiveness of MAO-B vs. placebo or levodopa in the treatment of early Parkinson's disease?	
Bibliographic reference	Macleod AD, Counsell CE, Ives N, Stowe R. Monoamine oxidase B inhibitors for early Parkinson's disease. The Cochrane Database of Systematic Reviews 2005, Issue 3.
Study type	Cochrane review meta-analysis: 10 randomised trials
Evidence level	1++
Study objective	To assess the evidence from randomised controlled trials for the effectiveness and safety of long-term use of MAO-B inhibitors in early PD
Number of patients	N=2422 early Parkinson's disease patients
Patient characteristics	Early disease patients: patients were starting parkinsonian treatment for the first time (or had started treatment in the last 12 months) and where the majority of patients were classified as Hoehn-Yahr stage II or less. Trial including a significant proportion of patients with motor fluctuations (greater than 10%) were excluded.
Intervention	9 trials- selegiline, 1- lazabemide
Comparison	Placebo or levodopa
Length of follow-up	1 to 9.2 years, mean follow-up 5.8 years (studies with < 1 year of follow-up were excluded)

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Outcome measures	Deaths at the end of follow-up, changes in UPDRS motor scores and ADL scores from baseline, levadopa requirements, development of motor fluctuations, dyskinesias, adverse events and withdrawals.
Effect size	Mortality ➢ All the studies reported data on deaths at the end of follow-up ➢ There was a non-significant increase in deaths amongst patients treated with MAO-B inhibitors compared with those given control (OR 1.15; 95%CI 0.92 to 1.44, p=0.21) with no significant heterogeneity. The result remained non-significant when the unadjusted data (not adjusted for differing lengths of follow-up in each group) from the UK-PDRG (RR) 1998 study were used. Mean change in UPDRS motor score from baseline to one year on treatment ➢ Data from 5 studies was available for analysis. ➢ All the studies favoured treatment with MAO-B inhibitors. The weighted mean difference (WMD) was –3.81 (95%CI –5.36 to –2.27). This shows that the mean decline in the motor impairment score at one year was nearly 4 points (out of a total scale of 108 points) less in participants treated with MAO-B inhibitors than those treated with control. ➢ Although this result is highly statistically significant (p<0.00001) its clinical significance is unclear. ➢ There was significant heterogeneity amongst the studies in this analysis however this was entirely attributable to the PSG 1996 study which used lazabemide. The results suggest that lazabemide (WMD –1.35; 95%CI –3.09 to 0.39) has a significantly weaker effect than selegiline (WMD –4.55; 95%CI –5.62 to –3.47, p=0.002). Mean change in UPDRS ADS score from baseline to one year on treatment ➢ Data from 5 studies was available for analysis. ➢ All the studies favoured treatment with MAO-B inhibitors. The WMD was –1.5 (95%CI –2.53 to –0.48, p=0.004) that is the scores were about one and a half points better (out of a total score of 52 points) after one year in patients treated with MAO-B inhibitors. ➢ There was an apparent difference in effect between the studies using selegiline (WMD –2.23; 95%CI –2.84 to –1.61) and the study that used lazabemide (WMD –0.47; 95%CI –1.31 to 0.37). This accounted for the substantial heterogeneity in this analysis. Subgroup analysis showed a highly significant difference between the two types of MAO-B inhibitor used (p=0.0006). Mean change in UPDRS total score from baseline to the end of washout ➢ Data from 3 studies was available for analysis.

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	➢ The mean duration of follow-up for this analysis was 1.1 years and the length of the washout was between 2 weeks and 2 months. ➢ Meta analysis yielded a WMD was –3.15 (95%CI –5.48 to –0.82, p=0.008) that is the increase in score severity from baseline to the end of washout was about three points less in the treatment group. Heterogeneity was low. Levodopa requirements ➢ Data from 3 studies was available for analysis as they assessed this outcome at a comparable follow-up period of one year. ➢ The mean duration of follow-up for this analysis was 1.1 years and the length of the washout was between 2 weeks and 2 months. ➢ The combined OR was 0.53 (95%CI 0.36 to 0.79), significantly in favour of MAO-B inhibitors (p=0.01) with no significant heterogeneity ➢ The California 1089 study reported these data at 3 years by which time only one patient (in the seefiline arm) did not require levodopa. In the other two studies all the patients were receiving levodopa at the end of 4 years of follow-up (Finland 1997; Swedish PSG 1998). Motor fluctuations ➢ Data from 5 studies was available for analysis. ➢ The mean weighted duration of follow-up for this analysis was 3.4 years. ➢ The overall effect was significantly in favour of MAO-B inhibitors (OR 0.75; 95% CI 0.59 to 0.94. p=0.01) with no heterogeneity. However, this results was very dependent on the adjusted results of the UK-PDRG study (adjusted for different durations of follow-up in each group) and if the unadjusted results are used the overall result becomes non-significant. ➢ Results were not reported for 336 patients in these five studies. A modified worst-case analysis was performed which also made the results non-significant (OR 1.02, 0.53 to 1.95). The authors therefore judged that the motor fluctuation result was not robust in sensitivity analyses. Dyskinesias ➢ Data from 4 studies was available for analysis. ➢ The mean duration of follow-up was 3.5 years. ➢ No difference between intervention and control was found (OR 0.98; 95% CI 0.76 to 1.26). Re-

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	analysis using the raw data from the UK- PDRG trial did not alter the results (OR 0.99). Patients with adverse events ➢ Data from 4 studies reported the number of patients with significant adverse events. ➢ There was a non-significant trend for more adverse events with MAO-B inhibitors (OR 1.38; 95%CI 0.92 to 2.06, p=0.12). ➢ Five studies reported data on nausea. More patients in the MAO-B inhibitor group reported nausea but the overall difference was not significant (OR 1.64; 95%CI 0.85 to 3.17). ➢ None of the 4 studies which reported data on blood pressure found lower mean blood pressures in patients in the MAO-B arms (thus no evidence to support postural hypotension concerns). Withdrawals ➢ Six studies reported the number of withdrawals due to adverse events at the end of follow-up ➢ There were significantly more withdrawals with MAO-B inhibitors (OR 2.36; 95% CI 1.32 to 4.20, p=0.004) and with no significant heterogeneity. ➢ All 10 trials reported data on total number of withdrawals by end of follow up. There was no significant difference in the number of withdrawals between the MAO-B inhibitor and control arms (OR 0.93; 95%CI 0.74 to 1.16).
Source of funding	The Health Foundation UK (support).
Additional comments	➢ Robust search strategy ➢ Systematic review of literature from 1966 to August 2004 ➢ Inclusion criteria for trials listed ➢ All data were extracted by two reviewers and cross-checked. ➢ Tests for heterogeneity were used ➢ 9/10 trials double-blind (the UK-PDRG 2001 study was unblinded) ➢ Not all studies intention-to-treat analysis ➢ The authors conclude, “MAO-B inhibitors do not appear to delay disease progression but may have a beneficial effect on motor fluctuations. There was no statistically significant effect on deaths although the confidence interval does not exclude a small increase with MAO-B inhibitors. At present we do not feel these drugs can be recommended for routine use in the treatment of early Parkinson’s disease but further randomised controlled trials should be carried out to clarify, in particular, their effect on deaths and motor complications”. ➢ Trials included: California 1989, DATATOP 1993, Finland 1997, Norway Denmark 1999, PSG 1996, SELEDO 1999, Swedish PSG 1998, UK 1996, UK-PDRG (RR) 1998, UK-PDRG 2001 and

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	US 1995.
NCC CC ID (Ref Man)	19938

TxNP2 – section 6.4

Evidence Table **Q TxNP2** Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Whone, A. L., Watts, R. L., Stoessl, A. J., Davis, M., Reske, S., Nahmias, C., Lang, A. E., Rascol, O., Ribeiro, M. J., Remy, P., Poewe, W. H., Hauser, R. A., Brooks, D. J., & REAL-PET Study Group 2003, "Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study", *Annals of Neurology*, vol. 54, no. 1, pp. 93-101.
Study type	RCT, double-blind
Evidence level	1+
Study objective	To compare the rates of loss of dopamine-terminal function in de novo patients with clinical and ^{18}F-dopa PET evidence of early PD, randomised to receive either levodopa or ropinirole.
Number of patients	N=162 idiopathic Parkinson's disease (IPD) N=87 Ropinirole N=75 L-dopa Location: multi-national sites: 34 neurological centres
Patient characteristics	➢ Baseline demographics and disease characteristics were similar for the two groups ➢ Clinical diagnosis of idiopathic Parkinson's disease by local neurologist ➢ Patients were aged between 30 to 75 years of age ➢ Hoehn and Yahr stages I to II.5 ➢ Symptom duration of 2 years or less ➢ Patients had not previously received treatment with L-dopa or dopamine agonists and were enrolled if they were considered by their local neurologist to require it
Intervention	Ropinirole initial dose of 0.75 mg/ day (0.25 mg 3 times per day)
Comparison	Levodopa initial dose of 50 mg/day (plus placebo twice per day)
Length of follow-up	2 years
Outcome measures	^{18}F-dopa PET at 4 weeks and 2 years (mean percentage reduction in side to side averaged putamen

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	^{18}F-dopa uptake as measured as an influx constant (Ki) Dosing and clinical end-points
Effect size	**Imaging** **<u>Region of interest:</u>** ➢ **Analysis showed a significant difference in loss of putamen Ki between ropinirole (n=68) and L-dopa (n=59) p=0.022** ➢ **Treatment estimates indicated mean reductions in putamen Ki of 13.4% (standard error (SE) 2.14) for ropinirole and 20.3% (SE 2.35) for L-dopa (95% CI, 0.65 to 13.06) a relative difference of 34%** **<u>Statistical parametric mapping (SPM):</u>** ➢ **Analyses showed less reduction in Ki (P<0.005) in the putamen and substantia nigra with ropinirole compared with L-dopa** ➢ **The greatest Ki decrease within each group was the putamen** ➢ **Treatment estimates indicated mean reductions in the putamen Ki of the following: ropinirole, 14.1% (SE 1.58); L-dopa, 22.9% (SE 1.70); 95% CI, 4.24 to 13.3 a relative difference of 38%** ➢ **Between group SPM showed two regions of significantly greater loss in the ^{18}F-dopa uptake in the L-dopa group compared with the ropinirole group (posterior dorsal putamen and substantia nigra bilaterally)** ➢ **No regions had a greater loss in the ropinirole group compared with the L-dopa group (p<0.05)** ➢ **<u>Comparison of amplitudes of change</u>:** ➢ **In the nigra, indicated a significant difference in favour ropinirole (p=0.025)** ➢ **Treatment estimates indicated a mean (SE) 4.3% (3.67) increase in substantia nigra Ki for ropinirole compared with a –7.5% (3.94) decrease for L-dopa (mean treatment difference 11.9; 95% CI, 1.3 to 22.4)** **<u>Dosing</u>** ➢ **Over the first 4 weeks of the study, doses were escalated to 3x daily regimens of ropinirole 3 mg/d, or L-dopa 300mg/d** ➢ **Mean doses of both treatments increased throughout the trial** **<u>Clinical end-points</u>** ➢ **Motor function during treatment at 2 years was superior with L-dopa compared with ropinirole (95%CI 3.54 to 9.14)** ➢ **<u>CGI global improvement scale</u> during the first year of the study (odds ratio, 0.72; 95%CI 0.36 to 1.45, p=0.367) favouring ropinirole** ➢ **Significantly fewer patients in ropinirole group developed <u>dyskinesia</u> compared with L-dopa (odds ratio 0.09, 95%CI 0.02 to 0.29, p<0.001)** ➢ **There was also a significant difference in favour of ropinirole in time to develop dyskinesias (hazard ratio 8.28, (95%CI, 2.46 to 27.93, p<0.001)** **<u>Adverse events</u>** ➢ **Similar proportions of patients (87 ropinirole, 75 L-dopa) reported non-serious adverse events** ➢ **Nausea and somnolence were the most commonly reported adverse events (both were more common in patients receiving ropinirole than in those receiving L-dopa)** ➢ **Hallucination, depression and confusion occurred in less than 10% of patients in each treatment**

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	➢ **Serious adverse events were experienced by 18 ropinirole and 17 L-dopa treated patients** ➢ **Adverse events led to a withdrawal of 14.9% in the ropinirole group and 5.3% in the L-dopa group**
Source of Funding	The study was contracted by a pharmaceutical company
Additional comments	➢ Randomization performed used a computer-generated coding memo system ➢ Titration was flexible to a max of 24mg/d Ropinirole or 1000mg/d L-dopa ➢ If symptoms remained inadequately controlled patients could receive open-label supplemental L-dopa ➢ Amantadine and anticholinergic medications were permitted but at a fixed dose form study onset ➢ Concomitant selegiline was no permitted and discontinued at least 6 weeks before study initiation ➢ 74% of the ropinirole group and 73% of the L-dopa group completed the trial ➢ Enrolment between June 1997 to April 1999 ➢ Methods of allocation concealment detailed ➢ Power calculations detailed ➢ Not intention-to-treat analysis (68/87 (78%) ropinirole PET scans analysed and 59/75 (79%) L-dopa scans analysed ➢ 68% of patients had scans that were evaluated ➢ Power assumed 30% of patients would have scans that could not be evaluated ➢ Study close but not adequately powered??
Citation	
NCC CC ID (Ref Man)	808

Evidence Table **Q 8** Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Marek, K. 2002, "Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression", *JAMA*, vol. 287, no. 13, pp. 1653-1661.
Study type	RCT, parallel group, double-blind
Evidence level	1++
Study objective	To compare rates of dopamine neuron degeneration after initial treatment of early PD with pramipexole vs. levodopa by means of β-CIT SPET imaging

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<table>
<tr><td>Number of patients</td><td>N=82 patient with early Parkinson's disease (PD)
N=42 pramipexole
N=40 levodopa

Location: US and Canada Sites: 17 Academic movement disorder clinics</td></tr>
<tr><td>Patient characteristics</td><td>➢ Inclusion criteria: adults ages >30 years who had IPD for less than 7 yrs and required dopaminergic antiparkinsonian therapy at time of enrolment
<table>
<tr><th></th><th>Pramipexole (n=42)</th><th>Levodopa (n=40)</th></tr>
<tr><td>Age, years (SD)</td><td>61.9 (10.8)</td><td>60.1 (11.1)</td></tr>
<tr><td>No. (%) of male patients</td><td>27 (65.9)</td><td>24 (58.5)</td></tr>
<tr><td>Years since diagnosis</td><td>1.3 (1.4)</td><td>1.6 (1.9)</td></tr>
<tr><td>No. (%) of patients with prior levodopa use</td><td>11 (26.2)</td><td>11 (27.5)</td></tr>
<tr><td>No. (%) of patients with prior selegiline use</td><td>19 (45.2)</td><td>14 (35.0)</td></tr>
<tr><td>UPDRS rating scale Total (SD)</td><td>34.6 (13.1)</td><td>30.6 (11.4)</td></tr>
<tr><td>Striatal β-CIT uptake (SD)</td><td>3.04 (0.72)</td><td>2.91 (0.66)</td></tr>
<tr><td>Caudate β-CIT uptake (SD)</td><td>4.07 (0.86)</td><td>3.90 (0.83)</td></tr>
<tr><td>Putamen β-CIT uptake (SD)</td><td>2.01 (0.68)</td><td>1.93 (0.56)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Patricipants allocated to receive pramipexole 0.5 mg 3 times per day with a levodopa placebo (patients with residual disability the dosage was escalated during the first 10 weeks, and open-label levodopa could be added)</td></tr>
<tr><td>Comparison</td><td>Participants allocated to receive carbidopa/levodopa 25/100 mg 3 times per day, with pramipexole placebo</td></tr>
<tr><td>Length of follow-up</td><td>10-week dose escalation period, followed by 21 month maintenance period (23.5 month total)</td></tr>
<tr><td>Outcome measures</td><td>Percentage change from baseline in striatal [^{123}I] β-CIT uptake after 46 months
The percentage changes in the striatum, caudate and putamen were assessed after 22 and 36 months
Clinical severity was assessed using the UPDRS 12 hours off anti-Parkinsonian medications</td></tr>
<tr><td>Effect size</td><td>➢ Participants were imaged before the baseline visit and just before the 23.5 month visit
➢ 53% in the pramipexole group required supplemental levodopa compared with 39% in the levodopa group (hazard ratio, 1.54; 95% CI, 1.09 to 2.17; p=0.02)
➢ Rate of decline in striatal [^{123}I] β-CIT uptake from baseline was significantly reduced in the group treated initially with pramipexole compared with group treated initially with levodopa</td></tr>
</table>

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Change in [^{123}I] β-CIT uptake after treatment with pramipexole (P) or levodopa (L)
(% Change from baseline, mean)

	22 months			34 months			46 months		
Site	P	L	P value	P	L	P value	P	L	P value
Striatum	-7.1	-13.5	.004	-10.9	-19.6	.009	-16.0	-25.5	.01
Putamen	-7.9	-16.9	.005	-11.4	-24.2	.001	-17.1	-28.1	.03
Caudate	-6.4	-11.8	.02	-10.3	-17.2	.04	-15.2	-24.1	.01

- **The mean total and mean motor UPDRS scores were reduced in the levodopa group at 22 months compared to baseline and the pramipexole group, but were not significantly different by 34 or 46 months**

Change in UPDRS (''defined off'') after initial treatment with pramipexole (P) or levodopa (L)

	22 months			34 months			46 months		
UPDRS Score	P	L	P value	P	L	P value	P	L	P value
Total	0.9	-3.3	.02	2.5	0.7	.40	4.1	4.0	.61
Motor	0.0	-2.5	.04	0.2	-0.5	.57	1.0	2.1	.84

- **There was a correlation between the percentage loss of striatal [^{123}I] β-CIT uptake from baseline with change in total UPDRS score from baseline in all patients**

Source of Funding	Pharmaceuticals company, non-profit organization, and government funding
Additional comments	➢ Patients were enrolled between November 1996 to August 1997 ➢ All imaging evaluations took place at Yale University ➢ No participants were lost to follow-up ➢ The baseline characteristics of the 82 participants enrolled in the SPET sub-study were similar to those of the entire cohort ➢ Patients in the levodopa group took an average of 406 mg/d by the end of the trial ➢ Patients in the pramipexole group took on average 2.78 mg/d by the end of the trial ➢ Patients that dropped-out of trial were described ➢ Patients were randomised in 1:1 ratio, using computer-generated randomisation plan that included stratification by investigator and blocking ➢ Allocation concealment methods described ➢ Scans were analysed by a blinded technologist ➢ Both groups had patients with prior amantadine and anticholinergic use ➢ Comparability of results between sites not addressed

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	➢ Results reported were not by intention-to-treat analysis ➢ 33/42 (78%) pramipexole analysed and 32/40 (80%) analysed in L-dopa group ➢ 80% of participants were analysed for treatment effects ➢ No statistical powering detail ➢ Small sample size (n=82)
Citation	
NCC CC ID (Ref Man)	809

Evidence Table **TxNP2** Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Hely, M. A., Morris, J. G., Traficante, R., Reid, W. G., O'Sullivan, D. J., & Williamson, P. M. 1999, "The sydney multicentre study of Parkinson's disease: progression and mortality at 10 years", *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 67, no. 3, pp. 300-307.
Study type	Randomised, levodopa-controlled, double-blind
Evidence level	1+
Study objective	To compare mortality in the study's cohort of patients on either bromocriptine or levodopa therapy, to see if bromocriptine lessens mortality.
Number of patients	N=126 Parkinson's disease patients Location: Australia Sites: multi-centre
Patient characteristics	➢ Patients were recruited with Hoehn and Yahr stage I to III ➢ 70 men and 56 women ➢ (More detail in original study published of the first 5 years- included in systematic review ID24)
Intervention	Low dose bromocriptine (≤ 30g/day)
Comparison	Low dose levodopa-carbidopa (≤600/150 mg/day)
Length of follow-up	10-13 years
Outcome measures	Mortality, Hoehn and Yahr stages, adverse events
Effect size	➢ 4 patients were lost to follow-up (n=122) ➢ Of the 10 patients who did not complete first 6 months of the study (phase I), 8 were accounted for

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	at 10 years by telephone or personal examination ➢ 50 (38%) of patients (34 men, 16 women) died during the first 10 years ➢ 63 (48%) had died by the last follow-up (maximum 13 years) ➢ The standardized mortality ratio (SMR) for the whole cohort was 1.58 (95%CI, 1.21 to 2.02) indicating a higher rate of death than the age-matched population (p<0.001) Bromocriptine ➢ At 10 years there were 29/63 (46%) deaths in the bromocriptine-treatment group patients ➢ At max. 13 years there were 33/63 (52%) deaths in this group ➢ The mean time of taking bromocriptine was 22.4 months ➢ The mean time from ceasing bromocriptine until death was 63.7 months Levodopa ➢ There were 21/67 (31%) deaths in the levodopa-carbidopa treatment group ➢ At max. 13 years there were 30/67 (45%) deaths Progression of modified Columbia Rating Score ➢ Randomisation to bromocriptine or continued use of bromocriptine for 1 year or more did not influence deterioration in Columbia score by 10 or 20 points Progression of Hoehn and Yahr stages ➢ There was no significant difference between the groups for progression through Hoehn and Yahr stages Adverse events (reasons for stopping bromocriptine therapy: ➢ Confusion (11), postural hypotension (6), lack of efficacy (2), peripheral oedema, Raynaud's phenomenon, and abnormal liver function (1 each).
Source of Funding	Initial study (first 5 years) was funding Pharmaceutical company. Continuation of study (present study) follow-up was funded was administered by a non-profit organization and local hospital.
Additional comments	➢ 10 year follow-up of study included in systematic review which included 5-year follow-up ➢ Few patients remained on bromocriptine alone for more than 2years ➢ Patients recruited between 1984 and 1987 ➢ Patients considered to have atypical parkinsonism before 5 years were excluded from analysis ➢ Only two patients were on bromocriptine monotherapy when they died, the other patients were receiving levodopa-carbidopa alone or in combination with bromocriptine ➢ Author's conclusions: they were unable to show any protective effect from bromocriptine on longevity or disease progression in new patients with Parkinson's disease ➢ No detail on randomisation methods (probably included 5 year study)

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	➢ Allocation concealment and blinding of investigators not detailed (probably included 5-year publication) ➢ Intention-to-treat poorly addressed ➢ Comparability of results from different sites not addressed
Citation	
NCC CC ID (Ref Man)	2184

Evidence Table
TxNP2
Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?

Bibliographic reference	Montastruc, J. L., Desboeuf, K., Lapeyre-Mestre, M., Senard, J. M., Rascol, O., & Brefel-Courbon, C. 2001, "Long-term mortality results of the randomized controlled study comparing bromocriptine to which levodopa was later added with levodopa alone in previously untreated patients with Parkinson's disease", *Movement Disorders*, vol. 16, no. 3, pp. 511-514.
Study type	Prospective randomised open controlled study
Evidence level	1+
Study Objective	To compare long-term mortality of L-dopa versus L-dopa plus bromocriptine treated early PD patients
Number of patients	N=58 Parkinson's disease patients N=28 levodopa alone group (L-dopa) N=30 bromocriptine alone then later plus levodopa (L-dopa/Br) Location: France Sites: one
Patient characteristics	➢ Idiopathic PD patients met UK PD Brain Bank criteria ➢ Recruited with Hoehn and Yahr stage 1 to 3 ➢ Exclusion criteria: patients suffering from evolutive intercurrent diseases ➢ No significant differences between groups at baseline

Characteristics	L-dopa/Br (n=30)	L-dopa (n=28)
Men	20	16
Women	10	12
Age at randomisation (SD)	59.4 (8.7)	62.2 (7.4)

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	Disease duration before entry, years (SD)	2.5 (1.8)	2.6 (2.7)
	Follow-up duration, years (in January 2000) (SD)	10.3 (3.4)	10.1 (2.6)
Intervention	Bromocriptine (52 (SEM 5) mg/day) to which L-dopa (471 (SEM 46) mg/day) was later added		
Comparison	L-dopa only (569 (SEM 47) mg/day)		
Length of follow-up	Mean 10.3 years		
Outcome measures	Mortality		
Effect size	➢ 17 patients (29.3%) died during the follow-up ➢ Mean survival time was 13.9 years (0.6) from onset of treatment ➢ 9 deaths in the L-dopa/Br group (30%) and 8 deaths in L-dopa group (28.6%) ➢ Probability of survival at 10 years was 79% (95%CI, 71.4 to 86.6) in the L-dopa/Br group and 72.9% (95%CI, 63.3 to 82.6%) in L-dopa group ➢ Survival from onset of treatment in L-dopa/Br and L-dopa groups were not significant (p=0.93) ➢ Baseline characteristics such as increasing stage of disease and increasing age (by 10 years) were significantly associated to a higher risk of death (L-dopa/Br vs. L-dopa) ➢ Hazard ratio (disease stage) 2.33 (95%CI, 1.48 to 3.66) ➢ Hazard ratio (age) 1.94 (95%CI, 1.30 to 2.89) ➢ Treatment group and duration of disease were not significant (L-dopa/Br vs. L-dopa) ➢ Hazard ratio (treatment group) 1.33 (95%CI, 0.73 to 2.43) ➢ Hazard ratio (disease duration) 0.83 (95%CI, 0.71 to 1.00) ➢ In comparison to the general French population standardized mortality ratios were not significantly different from 1 in the whole sample of PD patients [1.21 (95%CI, 0.71 to 1.95)] ➢ L-dopa group: [0.98 (95%CI, 0.42 to 1.93)] ➢ L-dopa/Br group [1.53 (95%CI, 0.70 to2.92)] ➢ There was no significant differences between the two groups for causes of death		
Source of Funding	None stated		
Additional comments	➢ Randomisation methods listed ➢ Intention-to-treat analysis ➢ 2 patients lost to follow-up in first 6 months ➢ Small sample size		

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	➢ Dosages reported in previous paper published in 1994
Citation	
NCC CC ID (Ref Man)	2414

Evidence Table **TxNP2** Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Lees, A. J., Katzenschlager, R., Head, J., & Ben Shlomo, Y. 2001, "Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial.[see comment]", *Neurology*, vol. 57, no. 9, pp. 1687-1694.
Study type	Randomised open trial
Evidence level	1+
Study Objective	To report the results of a ten-year follow-up of bromocriptine, L-dopa and L-dopa/selegiline treated PD patients
Number of patients	N=782 de novo PD patients N=249 levodopa alone group N=271 levodopa/selegiline N=262 bromocriptine Location: United Kingdom Sites: 93
Patient characteristics	Inclusion criteria: All patients fulfilled the criteria for a clinical diagnosis of PD Untreated patients required dopaminergic treatment were included Patients with co morbid conditions could be included Patients on anticholinergics and amantadine were included Exclusion criteria: Patients who were known to have failed to respond to dopaminergic drugs Patients with incapacitating cognitive impairment Characteristics: Baseline characteristics of three treatment groups were similar in age, sex, duration of PD, disability

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<table>
<tr><td></td><td>scores</td></tr>
<tr><td>Intervention</td><td>Bromocriptine alone (arm 3)</td></tr>
<tr><td>Comparison</td><td>Levodopa and decarboxylase inhibitor (arm 1); Levodopa/decarboxylase inhibitor & selegiline (arm 2)</td></tr>
<tr><td>Length of follow-up</td><td>10 years</td></tr>
<tr><td>Outcome measures</td><td>Mortality and disability</td></tr>
<tr><td>Effect size</td><td>
➢ 49 patients (16 arm1, 16 arm2, 17 arm3) had diagnosis revised during course of trial
Mortality
➢ Average follow-up 9.2 years
➢ Standardized mortality ratio (SMR) for patients in the study compared to the general population of United Kingdom was 1.78 (95%CI, 1.62 to 1.96)
➢ Statistical significance of difference among 3 arms in first 5 years of study; p=0.27
➢ Hazard ratio of bromocriptine versus levodopa was 1.15 (95%CI, 0.90 to 1.47)
➢ After adjustment for age, sex, duration of disease before randomisation, hazard ratio 1.12
➢ Hazard ratio for arms 2 vs. 3: 1.06 (95%CI, 0.84 to 1.34)
➢ Hazard ratio for arms 2 vs. 1: 1.22 (95%CI, 0.95 to 1.55)
➢ Hazard ratio (mortality attributed to PD arm 3 vs. arm 1) was 1.63 (95%CI, 1.0 to 2.7)

Disability
Table: difference (95%CI) in mean Webster disability scores
<table>
<tr><td>Time in trials</td><td>Arm 3 vs. 1</td><td>Arm 3 vs. 2</td><td>Arm 1 vs. 2</td></tr>
<tr><td>Year 1, n=670</td><td>0.9 (0.3 to 1.5)</td><td>1.3 (0.6 to 1.9)</td><td>0.3 (-0.3 to 1.0)</td></tr>
<tr><td>Year 3, n=688</td><td>1.3 (0.4 to 2.2)</td><td>1.4 (0.6 to 2.3)</td><td>0.2 (-0.7 to 1.1)</td></tr>
<tr><td>Year 5, n=573</td><td>1.0 (-0.2 to 2.1)</td><td>1.4 (0.3 to 2.5)</td><td>0.4 (-0.7 to 1.6)</td></tr>
<tr><td>Year 9, n=270</td><td>0.2 (-1.5 to 1.5)</td><td>1.0 (0.6 to 2.5)</td><td>0.8 (-0.8 to 2.4)</td></tr>
</table>
➢ Adjusted for baseline disability score. A positive difference indicates worse average disability in arm 1.
➢ Difference in disability between arm 1 and 3 diminishes after 5th year of follow-up
➢ The ‘final’ disability scores based on the average of the most recent two ratings before death or the end of 1999- adjusted difference of 0.8 (95%CI 0.3 to 1.9) between arm 1 and 3
➢ Similar findings obtained from an analysis of Northwestern University disability scale
➢ On average patients in bromocriptine arm returned to baseline disability after 3 years, 1 year before levodopa group (arm 1)
➢ Significantly lower incidence of dyskinesia in the group initially randomised to bromocriptine than
</td></tr>
</table>

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	levodopa (arm 1) (rate ratio: 0.73 (95%CI 0.57 to 0.93) ➢ Incidence rate for dystonia was slightly lower in the bromocriptine group (rate ratio: 0.84, 95%CI 0.65 to 1.09, p=0.17) ➢ Slightly lower incidence of on/off fluctuations in the group initially randomised to bromocriptine (difference was not significant; 0.90 (95%CI 0.72 to 1.13)
Source of Funding	Non-profit organization and pharmaceutical company
Additional comments	➢ Randomisation was carried out by independent coordinator methods listed ➢ Intention-to-treat analysis ➢ No blinding of investigators –possible bias in result interpretation ➢ If patents did not improve they could be re-randomised to another group ➢ Additional antiparkinsonian drugs were allowed during the trial ➢ Comparability of results from different sites not stated ➢ Trial took place between 1985 to 1990- where selegiline arm was terminated
Citation	
NCC CC ID (Ref Man)	2309

Evidence Table **TxNP2** Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Przuntek, H., Welzel, D., Blumner, E., Danielczyk, W., Letzel, H., Kaiser, H. J., Kraus, P. H., Riederer, P., Schwarzmann, D., & Wolf, H. 1992, "Bromocriptine lessens the incidence of mortality in L-dopa-treated parkinsonian patients: prado-study discontinued.[see comment]", *European Journal of Clinical Pharmacology*, vol. 43, no. 4, pp. 357-363.
Study type	Randomised trial, open
Evidence level	1+
Study Objective	To report the mortality results of patients treated with L-dopa compared to L-dopa/Bromocriptine
Number of patients	N=587 early Parkinson's disease patients N=302 L-dopa group N=285 L-dopa and bromocriptine group (L-dopa/Br)

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<table>
<tr><td></td><td>Location: Germany and Hungary sites: 101 practicing neurologists treated and recruited</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
De novo PD patients
<table>
<tr><th>Characteristic</th><th>L-dopa (n=302) (%)</th><th>L-dopa/Br (n=285) (%)</th></tr>
<tr><td>Sex male</td><td>51.0</td><td>56.5</td></tr>
<tr><td>Pre-treated with L-dopa/benserazide</td><td>31.5</td><td>30.5</td></tr>
<tr><td>Duration of disease at study onset (months)</td><td>20</td><td>21</td></tr>
<tr><td>Duration of L-dopa pre-treatment months</td><td>2.53</td><td>2.70</td></tr>
<tr><td>Age (y) male</td><td>62.5</td><td>63.0</td></tr>
<tr><td>Age (y) female</td><td>65</td><td>67</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>250 mg L-dopa/benserazide/ 10 mg Bromocriptine- the second 3 months of the study consisted of a gradual substitution of bromocriptine for L-dopa over 3 months in one treatment groups</td></tr>
<tr><td>Comparison</td><td>375 mg L-dopa/benserazide was the median dose on which both groups started for the first 3 months of the study</td></tr>
<tr><td>Length of follow-up</td><td>54 months (4.5 years)</td></tr>
<tr><td>Outcome measures</td><td>Treatment outcomes measures of this study are reported in the systematic review ID 42 only neuroprotective measures are listed here: mortality</td></tr>
<tr><td>Effect size</td><td>➢ Following an interim analysis in 1991- the trial was terminated due to an increased number of deaths in the L-dopa monotherapy group
➢ 18 vs. 8 deaths had been reported in the L-dopa vs. L-dopa/Br groups
➢ Statistical analysis showed a crude p value (double-sided) of 0.07
➢ Adjusted for age and sex (p=0.02)
➢ The risk ratio of L-dopa monotherapy compared to combination therapy was 2.7, a reduction of 63%
➢ For ethical reasons the study was terminated
➢ The median observation on target medication was 38.4 months in the L-dopa only group and 40.1 in the L-dopa/Br group
➢ Causes of death mainly due to cardiovascular complications

Side effects
➢ Mainly: gastro-intestinal complaints, nausea, palpitation, sleep disturbances (which interfered with study medication and patient compliance)
➢ Drop-out/discontinuation occurred in 152/302 L-dopa group and 121/285 L-dopa/Br group</td></tr>
</table>

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Source of Funding	Not stated
Additional comments	➢ Randomisation methods not stated ➢ No blinding of investigators- potential bias in interpretation ➢ Death was not considered a main endpoint in the protocol ➢ Power estimates given ➢ Comparability of results between sites not addressed
Citation	
NCC CC ID (Ref Man)	2518

Evidence Table
TxNP2
Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?

Bibliographic reference	Rinne UK, Bracco F, Chouza C, Dupont E, Gershanik O, Masso JFM *et al*. Early treatment of Parkinson's disease with Cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. *Drugs* 1998; **55**:23-3TxCM 20.
Study type	RCT, multi-centre, double-blind, parallel group, 3 – to 5- year trial
Evidence level	1+
Study objective	To assess whether initial therapy with cabergoline alone or in combination with levodopa prevents or delays the occurrence of long term motor complications in patients with early Parkinson's disease.
Number of patients	N=412 early idiopathic Parkinson's disease (PD) patients N=208 cabergoline N=204 levodopa
Patient characteristics	Patients with Hoehn and Yahr stages 1 to 3 who had functional disability severe enough to warrant pharmacological treatment. Exclusion criteria: prior treatment with levodopa, selegiline, or dopamine agonists (amantadine and anticholinergics were allowed- but discontinued 4 weeks before study commenced)

	Cabergoline	Levodopa (LD)
Male gender (%)	45.7	51.5
Mean age (years) at inclusion	60.5	62.6
Mean UPDRS motor score	27.5	29.1

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Intervention	Cabergoline (titration phase 24 weeks) initial dose 0.25 mg/d. Doses were escalated at 2- to 4-week intervals up to the optimum dose for each patient or a maximum of 4 mg/d cabergoline or 600mg/d (4 doses) LD. Treatment was continued at this dose for 3 to 5 years. Open-label LD could be added.
Comparison	Levodopa (w/ carbidopa) (LD) 100mg/d in 2 doses (titration 24 weeks). Doses were escalated at 2- to 4-week intervals up to the optimum dose for each patient or a maximum of 600mg/d (4 doses) LD. Treatment was continued at this dose for 3 to 5 years. Open label LD could be added.
Length of follow-up	3 to 5 years
Outcome measures	Primary end-point: onset of motor complications (confirmed at 2 subsequent visits), disability using Unified Parkinson's Disease Rating Scale (UPDRS), Clinical Global Impression (CGI) scale, tolerability using adverse events and withdrawal rates
Effect size	➢ Both groups were homogenous regarding sex, age at inclusion, age at onset of PD, severity of PD (mean Hoehn and Yahr stage) and initial symptoms of Parkinson's disease (tremor was the most common) ➢ Median duration of treatment was 1348 and 1344 days respectively at median doses of 3mg/d cabergoline and 500mg/d levodopa ➢ 35% of patients on cabergoline did not require additional LD therapy compared with 52% of those on LD treatment ➢ Mean cumulative exposure to LD in cabergoline and LD treatment groups was 303g and 637g per respectively patient Motor complications ➢ The study end-point was reached in 22% of patients treated with cabergoline ➢ (N=47, 4 on monotherapy, 43 receiving additional LD therapy) ➢ The study end-point was reached in 34% of LD patients ➢ (N=70, 17 on stable LD dose and 53 receiving additional LD) ➢ Daily wearing-off was the most common motor complication, followed by nocturnal akinesia, early morning akinesia and peak-dose dyskinesias ➢ The majority of patients in both treatment groups had just one motor complication- severity was generally mild or moderate ➢ Significant difference ($p<0.02$) between 2 groups- risk of developing motor complications being always lower for cabergoline treated patients ➢ When the Cox model was applied to the analysis- introducing as covariates levodopa addition, baseline UPDRS factor III and age of patients at entry ➢ The relative risk of developing motor complications with cabergoline was more than 50% lower

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	than with levodopa ➢ Cabergoline-treated patients requiring levodopa were at the same risk of developing motor complications as those on stable levodopa dose ➢ The mean cumulative LD exposure at the onset of motor complications was 194g in cabergoline-treated patients and 421g in levodopa treated patients ➢ The analysis repeated according to the Cox model on the 2 main categories of motor complications revealed a borderline significant difference between treatments for end-of-dose failures and a highly significant difference for dyskinesias ➢ Mean percentage decreases vs. baseline in UPDRS factor III scores in cabergoline and LD recipients: UPDRS factor III scores decreased throughout the first year of treatment then as a consequence of disease progression a gradual increase in UPDRS factor II scores occurred ➢ After 4 years LD patients showed an average 30% improvement in motor disability while in patients on cabergoline there was a 22 to 23% improvement vs. baseline ➢ Cabergoline and LD-treated patients who did not require additional LD therapy were similar in the extent of improvement in motor disability ➢ The 2 treatment groups were similar with regard to UPDRS factor II scores for activities of daily living which decreased significantly in the first year of treatment ➢ Level of improvement gradually decreased thereafter Adverse events ➢ Overall incidence similar in cabergoline and LD (83 vs. 82%) ➢ Serious adverse events tended to occur more frequently in cabergoline group (31 vs. 25%) ➢ Most common: Gastrointestinal disturbances (ie nausea and vomiting), dizziness, hypotension, sleep disorders, depression, agitation/anxiety, oedema, headache/migraine ➢ Gastrointestinal disturbances, dizziness, hypotension, and peripheral oedema occurred more often in cabergoline group Mortality ➢ Mortality rates in cabergoline vs. LD was 4.3% vs. 1.9% Withdrawal rate ➢ Cabergoline vs. LD (16 vs. 13%)
Source of Funding	Not stated
Additional comments	➢ Enrolment between October 1989 to July 1992 at 30 centres in 8 countries in Europe and South America ➢ No methods of randomisation or allocation concealment ➢ Not intention-to-treat analysis

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	➢ No between centre analysis
Citation	
NCC CC ID (Ref Man)	19605

Evidence Table **TxNP2** Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Rakshi, J. S., Pavese, N., Uema, T., Ito, K., Morrish, P. K., Bailey, D. L., & Brooks, D. J. 2002, "A comparison of the progression of early Parkinson's disease in patients started on ropinirole or L-dopa: an 18F-dopa PET study", *Journal of Neural Transmission*, vol. 109, no. 12, pp. 1433-1443.
Study type	RCT, double-blind
Evidence level	1-
Study Objective	To study the relative rates of progression of early Parkinson's disease
Number of patients	N=45 early Parkinson's disease (PD) patients Location; UK and France Sites: 11 regional centres
Patient characteristics	➢ Mean age 61 ± 9.8 years ➢ Mean symptom duration 26 ± 16 months ➢ Mean Hoehn and Yahr score was 1.8 ± 0.5 ➢ Mean motor subscale of Unified Parkinson's disease Rating scale (UPDRS) was 13 ± 6.5 ➢ All patients except one fulfilled the UK PD brain bank criteria for clinical diagnosis of idiopathic PD ➢ Patients treated with low-to moderate doses of L-dopa (LD) or Dopamine agonists were eligible
Intervention	Patients randomised in a 2:1 ratio to ropinirole or LD monotherapy Ropinirole dosages were individually titrated
Comparison	LD dosages were individually titrated
Length of follow-up	2 years
Outcome measures	^{18}F-dopa PET scan (at least 12h after stopping their medication on the morning of scan) and UPDRS
Effect size	➢ 17 patients had 2 (baseline and 2 years) 2-D scans and 20 patients had two 3-D scans PET Scan

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	➢ No significant difference in mean putamen Ki (influx rate constant) values between treatment groups at baseline ➢ At 2 years follow-up 51% of the 37 patients remained on monotherapy (no supplemental LD) ➢ Mean % decrease in putamen Ki values over 2 years were 13% ropinirole and 18% LD ➢ No significant differences between treatment groups ➢ Statistically analysis (ANOVA) with scanner type 2D and 3D as a covariant did not show any effect of this variable on percentage loss of dopaminergic function at 2 years UPDRS ➢ Mean subscale motor UPDRS at baseline and 2 years was non-significant ➢ The mean increase in disability as assessed by UPDRS motor score in practically-defined ''off'' state 12 hours withdrawn from medication was greater in ropinirole (11.4 $\pm$ 1.4) thank LD (8.2 $\pm$ 2.7), $p<0.01$ Power Data from the study suggests that 80 patients in each cohort would have been required to show 25% difference between intention-to-treat group ($p<0.05$) to provide 80% power Numbers in this study only sufficient to demonstrate a 50% disease-mollifying effect Smaller differences in rate of progression between ropinirole and LD cohorts would not achieve significance
Source of Funding	Primary author supported by grant from SmithKline Beecham U.K.
Additional comments	➢ Discontinued treatment of LD and dopamine agonists at least 2 weeks prior to screening ➢ Concomitant selegiline was not allowed ➢ Dosage of each medication was titrated to individual response ➢ Maximum daily doses permitted was 24 mg ropinirole and 1200 mg LD ➢ If there was lack of therapeutic effect supplemental, open label LD could be added ➢ 6 patients withdrew from the study before their second scan (reasons listed) ➢ 2 of the patients had to be excluded from final analysis because of PET scan results (reasons listed) ➢ Intention-to-treat analysis ➢ Small sample size ➢ No standard initial dose, no average dosages listed ➢ Comparable results among sites not stated

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	➢ Randomisation methods and allocation concealment methods not stated
Citation	
NCC CC ID (Ref Man)	2535

TxNP3 – section 6.3

Evidence Table
TxNP3

Bibliographic reference	Shults, C. W., Haas, R. H., & Beal, M. F. 1999, "A possible role of coenzyme Q_{10} in the etiology and treatment of Parkinson's disease", *Biofactors*, vol. 9, no. 2-4, pp. 267-272.
Study type	Randomised, parallel-group, placebo-controlled, double-blind, dosage-ranging trial
Evidence level	1++
Number of patients	N=80 early Parkinson's disease (PD) Location: USA Sites: 10
Patient characteristics	Inclusion criteria: presence of all 3 cardinal features of PD (resting tremor, bradykinesia, and rigidity), which had to be asymmetrical. The diagnosis must have been made within the previous 5 years in men or in women 30 years or older. Exclusion criteria: list of 20 items (see paper) A notable exclusion includes: disability sufficient to require treatment with dopaminergic drugs (as determined by enrolling investigator).

Baseline characteristics (SD)	Placebo group (n=16)	Coenzyme Q_{10} dosage groups			P value
		300 mg/day (n=21)	600 mg/day (n=20)	1200 mg/day (n=23)	
Male, No. (%)	12 (75)	21 (57)	14 (70)	14 (61)	0.64
Age, years	63.1 (12.1)	60.9 (10.8)	61.9 (11.7)	59.9 (11.2)	0.84
Total UPDRS score	24.1 (6.4)	23.9 (9.8)	23.0 (11.1)	22.7 (10.7)	0.96

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	UPDRS mental score	0.88 (1.15)	0.71 (0.72)	1.10 (1.12)	0.70 (0.97)	0.53
	UPDRS motor score	17.8 (6.6)	17.1 (7.1)	16.7 (8.8)	16.7 (7.5)	0.97
	UPDRS ADL score	5.4 (2.5)	6.1 (3.5)	5.2 (3.4)	5.3 (3.7)	0.80
	Hoehn &Yahr score	1.9 (0.4)	1.8 (0.5)	1.8 (0.4)	1.9 (0.4)	0.80
Intervention	Each patient was randomly assigned to receive Coenzyme Q_{10} at dosages of 300, 600, or 1200 mg/day or matching placebo. Medication was taken 4x per day.					
Comparison	Placebo					
Length of follow-up	16 months (or until investigator determined that patient needed levodopa treatment)					
Outcome measures	Change in UPDRS score from screening, baseline, and 1,4,8,12, and 16 months					
Effect size						

Adjusted Mean change from baseline to final visit (95% CI)	**Placebo group** (n=16)	**Coenzyme Q_{10} dosage groups**			**P value**
		300 mg/day (n=21)	**600 mg/day** (n=20)	**1200 mg/day** (n=23)	
Total UPDRS score	11.99 (7.99 to 5.99)	8.81 (5.42 to 12.20)	10.82 (7.39 to 14.26)	6.69 (3.49 to 9.89)	.09
UPDRS mental score	0.90 (0.42 to 1.37)	0.54 (0.14 to 0.95)	0.35 (-0.06 to 0.77)	0.33 (-0.05 to 0.72)	.06
UPDRS motor score	6.54 (3.56 to 9.51)	5.88 (3.38 to 8.39)	6.47 (3.93 to 9.01)	4.61 (2.24 to 6.97)	.35
UPDRS ADL score	4.74 (3.10 to 6.38)	2.54 (1.14 to 3.94)	4.02 (2.60 to 5.44)	1.62 (0.30 to 2.93)	.02
Hoehn &Yahr score	0.02 (-0.13 to 0.18)	0.16 (0.03 to 0.29)	0.15 (0.01 to 0.28)	0.13 (0.01 to 0.26)	.39
Schwab & England score For ADL (examiner)	-7.98 (-10.58 to –5.37)	-4.89 (-7.08 to –2.70)	-7.03 (-9.26 to -4.79)	-3.55 (-5.63 to –1.48)	.04
Schwab & England score For ADL (subject)	-7.06 (-10.64 to –5.37)	-4.53 (-7.54 to –1.51)	-7.50 (-10.57 to –4.43)	-5.38 (-8.24 to –2.53)	.81

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	<table><tr><td>Timed tapping score</td><td>-13.17 (-21.82 to – 4.51)</td><td>-5.06 (-12.26 to 2.13)</td><td>-8.99 (-16.30 to –1.68)</td><td>-10.32 (-17.23 to –3.42)</td><td>.97</td></tr></table> ➢ ➢ The difference in total UPDRS between 1200 mg/day and placebo 5.30 (95% CI 0.21 to 10.39) ➢ A secondary analysis compared each of the treatment groups to placebo and the difference was significant in the 1200mg/d (p=0.04), but not for the 300 mg/d (p=0.22) or 600 mg/d (p=0.66) ➢ The discrepancy in the reduction on the Schwab & England scale, as assessed by the examiner but not the patient, was explained by the discordance of one patient who was assigned the 1200 mg/day treatment group and the examiner ➢ Co-enzyme Q_{10} was well tolerated- no dosage reductions were needed in any treatment group ➢ % Of subjects reporting adverse events: 300mg/day (90%), 600 mg/day (60%), 1200mg/day (91%), and placebo group (81%), p=0.51 ➢ Most adverse events reported were mild ➢ No significant trend in dosage was found in the number of subjects experiencing an adverse event ➢ Analysis of the data for weight, sitting and standing blood pressure, and heart rate did not show any significant differences among treatment groups.
Source of funding	National Institutes of Health, Bethesda, MD
Additional comments	➢ Aim: ''to determine whether a range of dosages of coenzyme Q_{10} is safe and well tolerated and could slow the functional decline in PD'' ➢ Computer-generated randomisation plan ➢ 3 subjects dropped-out ➢ Double-blind including enrolling investigators, enrolling coordinators, other personnel involved in care of patients as well as the acquisition and analysis of data.
NCC CC ID (Ref Man)	801

Evidence Table **TxNP3** Is Co-enzyme Q10 vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Muller, T., Buttner, T., Gholipour, A. F., & Kuhn, W. 2003, "Coenzyme Q_{10} supplementation provides mild symptomatic benefit in patients with Parkinson's disease", *Neuroscience Letters*, vol. 341, no. 3,

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<table>
<tr><td></td><td>pp. 201-204.</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial, parallel group, placebo controlled, double-blind trial</td></tr>
<tr><td>Evidence level</td><td>1+</td></tr>
<tr><td>Number of patients</td><td>N=28 Parkinson’s disease patients

Location: Germany Sites: One</td></tr>
<tr><td>Patient characteristics</td><td>
<table>
<tr><th></th><th>PD group: CoQ_{10}</th><th>PD group: placebo</th></tr>
<tr><td>Age, years (SD)</td><td>66.21 (9.33)</td><td>64.36 (7.69)</td></tr>
<tr><td>Male: female</td><td>7: 7</td><td>7:7</td></tr>
</table>
There were no significant differences regarding age, FMT scores, and scored PD symptoms.
All patients were statin-free with non-fluctuating symptoms.
Exclusion criteria: dementia, electrophysiological or neuroradiological evidence of additional CNS pathology exceeding PD, previous exposure to neuroleptics or any drugs affecting the dopaminergic system, tx with digitalis, retinopathy or colour blindness.
</td></tr>
<tr><td>Intervention</td><td>Randomly assigned participating patients to one of the groups (via numbered containers). Participants started their intake of 180mg (b.i.d) CoQ10 or identically looking placebo capsules (b.i.d) after initial scoring of UPDRS and FMT performance.</td></tr>
<tr><td>Comparison</td><td>Placebo control group</td></tr>
<tr><td>Length of follow-up</td><td>4 weeks</td></tr>
<tr><td>Outcome measures</td><td>UPDRS, UPDRS III (motor score) [PD symptoms] and FMT (Farnsworth-Munsell 100 Hue Test total error score) [visual function]</td></tr>
<tr><td>Effect size</td><td>

Mild significant reduction in UPDRS total and FMT score in CoQ10 treated group
No improvement in motor symptoms
FMT score also decreased in placebo treated group, UPDRS scores did not change significantly

<table>
<tr><th></th><th>Test</th><th>Initial
(Mean ± SD; min-max)</th><th>End
(Mean ± SD; min-max)</th><th>Difference
(Mean ± SD; min-max)</th><th>P value</th></tr>
<tr><td rowspan="3">CoQ_{10}</td><td>UPDRS</td><td>23.29 ± 20.36; 2-73</td><td>21.00 ± 18.66; 2-70</td><td>2.29 ± 2.92;0-8</td><td>.012</td></tr>
<tr><td>UPDRS III</td><td>8.21 ± 7.37; 1-27</td><td>7.93 ± 7.22; 1-27</td><td>0.29 ± 0.61; -1-1</td><td>.10</td></tr>
<tr><td>FMT</td><td>159.29±69.98; 66-291</td><td>110.71±59.28; 1-216</td><td>48.57 ± 27.12; 7-120</td><td>.00002</td></tr>
<tr><td>Placebo</td><td>UPDRS</td><td>17.36 ± 10.97; 2-45</td><td>16.14 ± 10.61; 2-45</td><td>1.21 ± 2.64;0-10</td><td>.11</td></tr>
</table>
</td></tr>
</table>

		UPDRS III	7.29 ± 5.24; 1-21	6.64 ± 5.31; 1-21	0.64 ± 1.28;0-4	.08
		FMT	118.79±58.54; 76-295	97.64±52.45; 48-229	21.14 ± 19.87; -5-66	.002
	➢ The comparison between groups showed that the Coenzyme Q_{10} group significantly improved more on the FMT test than the placebo group (p=0.008) ➢ There were no significant differences in UPDRS total score (p=0.35) or motor score (p=0.71) ➢ There was no impact of covariants on the results ➢ No adverse effects were reported.					
Source of Funding	None stated					
Additional comments	➢ Aim: to assess the response of additional oral daily Coenzyme Q_{10} application lasting 4 weeks on PD symptoms and FMT error scores in comparison with placebo ➢ Disease duration or severity not stated ➢ UPDRS raters were blinded to FMT results ➢ Small population ➢ Short follow-up					
Citation						
NCC CC ID (Ref Man)	799					

TxNP4 – section 6.2

Evidence Table **TxNP4** Are specific vitamins vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Koller, W., Olanow, C. W., Rodnitzky, R., Fink, J. S., Growdon, J. H., Paulson, G., Kurlan, R., Friedman, J. H., Gancher, S., Nutt, J., Rajput, A. H., Bennett, J. B., Wooten, G. F., LeWitt, P., Goetz, C., Tanner, C., Shannon, K., Suchowersky, O., & Brin, M. F. 1993, "Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease", *New England Journal of Medicine*, vol. 328, no. 3, pp. 176-183.
Study type	RCT, double blind, placebo controlled
Evidence level	1++
Number of patients	N=800 Parkinson's disease (PD) patients (DATATOP study patients)

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	Location: United States and Canada Sites: 28 (23 US and 5 Canada)
Patient characteristics	Untreated PD patients (stage I or II) Disease duration less than 5 years
Intervention	3 treatment groups: 1. Tocopherol (2000 IU per day) and deprenyl placebo 2. Deprenyl (10mg per day) and tocopherol placebo 3. Deprenyl (10 mg per day) and tocopherol (2000 IU per day) The subjects took 1000 IU capsules of tocopherol or identical-appearing placebo capsules and 5 mg tablets of deprenyl or identical-appearing tablets of placebo twice daily with morning and evening meals.
Comparison	Tocopherol placebo and deprenyl placebo
Length of follow-up	The subjects were re-evaluated 1 and 3 months after randomisation and approximately every 3 months thereafter for 24 months follow-up
Outcome measures	• Primary end-point: the onset of disability prompting the clinical decision to begin administering levodopa • Secondary outcome measures: Unified Parkinson's disease Rating Scale (UPDRS) (including motor, mental, and activities of daily living components), and the Hamilton Depression Scale
Effect size	➢ Only the data for the tocopherol groups and placebo groups will be assessed here (deprenyl vs.placebo will be addressed in another clinical question) **Tocopherol** ➢ 53.9% of tocopherol & placebo reached the endpoint vs. 56.8% of placebo only group subjects ➢ 7.9% of tocopherol subjects withdrew before reaching the end point vs. 7.0% of placebo subjects ➢ 38% of tocopherol subjects remained in the trial without reaching the end point vs. 36% placebo group ➢ No adverse symptoms were reported in the tocopherol group ➢ Laboratory abnormalities include: abnormal aspartate aminotransferase p=0.005 tocopherol (greater than 36U per litre in men and 34U per litre in women); and alanine aminotransferase p=0.001 tocopherol (greater than 43 U per litre in men and 43 U per litre in women) ➢ Compliance ranged from 97.9 to 99.5% for both tocopherol and deprenyl groups ➢ Regardless of deprenyl administration the probability of reaching end-point was not reduced (hazard ratio 0.91, 95%CI, 0.74 to 1.12; p=0.35) ➢ The hazard ratios for tocopherol remained homogenous throughout the maximal follow-up period (24

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months)

- Tocopherol alone did not significantly reduce the risk of reaching end-point, as compared with double placebo (hazard ratio, 0.92; 95% CI, 0.70 to 1.22; p=0.57)
- There was no interaction between deprenyl and tocopherol, p=0.97

- 367 (45.9%) patients who did not reach end-point were withdrawn from experimental treatments and evaluated approximately one and two months later
- During the two months after treatment was withdrawn 4 patients reached the end-point
- 52 subjects were given deprenyl
- No evidence among the treatment groups in rate of early deprenyl administration (p=0.12)

Secondary outcomes:

- There was no significant change in UPDRS variables for the tocopherol treatment groups

- 6 months (mo) refers to patients who completed at least 6 mo evaluation regardless of whether they reached the end-point (the rate of decline in these patients was calculated from base-line to last evaluation during treatment) (mean follow-up for this group was 16 ± 6 mo from randomisation)
- 24 mo refers to patients who did not reach the end-point and who did not require the early initiation of deprenyl by the end of the 2- mo period after the withdrawal of treatments (the mean follow-up for this group was 21± 4 mo from randomisation)

Table xxx: Average rate of decline in UPDRS variables

UPDRS	Placebo	Tocopherol & placebo	Deprenyl & placebo	Deprenyl and tocopherol	P value
Total 6 mo	14.02 ± 12.32 (175)	15.16 ± 16.12 (178)	7.00±10.76 (190)	7.28±11.11 (182)	<0.001
24 mo	5.74 ± 5.64 (57)	5.57 ± 5.98 (63)	3.63 ± 4.32 (89)	3.60 ± 5.35 (96)	<0.001
Mental 6 mo	0.69 ± 1.72 (176)	0.71 ± 2.03 (178)	0.12 ± 1.20 (191)	0.04 ± 1.10 (182)	<0.001

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	24 mo	0.02 ± 0.94 (57)	0.02 ± 0.74 (63)	+0.07 ± 0.75 (89)ϕ	+0.03 ± 0.76 (96) φ	0.599
	Motor 6 mo	8.91± 8.41 (175)	9.80 ± 10.81 (178)	4.90 ± 7.61 (190)	4.87 ± 8.01 (182)	<0.001
	24 mo	3.62 ± 3.74 (57)	3.92 ±4.47 (63)	2.66 ± 3.22 (89)	2.51 ± 3.86 (96)	0.002
	ADL 6 mo	4.40 ± 4.34 (176)	4.65 ± 5.81 (178)	2.01 ± 3.94 (190)	2.38 ± 3.69 (182)	<0.001
	24 mo	2.10 ± 2.28 (57)	1.62 ± 2.02 (63)	1.04 ± 1.95 (89)	1.13 ± 2.16 (96)	0.002
	➢ P values indicate the main effect of deprenyl; rating ± standard deviation (number of subjects) ➢ φ Represents an improvement in score (instead of declining) No evidence of any beneficial effect of α-tocopherol (2000 IU per day) in either slowing functional decline or ameliorating the clinical features of Parkinson's disease					
Source of Funding	Public Health service grant from the national institute of neurological disorders and stroke… and others (no pharmaceutical companies list)					
Additional comments	➢ Aim: to investigate the effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease ➢ Extension of original DATATOP study by 14 ± 6 months ➢ Enrolment period: September 3rd, 1987 to November 15, 1988 ➢ Intention-to-treat analysis ➢ Methodology of randomisation and allocation concealment taken from original DATATOP study ➢ Treatment groups did not differ significantly in the variables measured at baseline, including age, sex, rating on UPDRS and Hamilton Depression Scale, any previous levodopa treatment, time from onset of illness to randomisation, level of education, and employment status.					
Citation						
NCC CC ID (Ref Man)	148					

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Evidence Table **TxNP4** Are specific vitamins vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Shults, C. W. 1993, "Effect of selegiline (deprenyl) on the progression of disability in early Parkinson's disease. Parkinson Study Group", *Acta Neurologica Scandinavica.Supplementum*, vol. 146, pp. 36-42.
Study type	RCT, double blind, placebo controlled
Evidence level	1++
Number of patients	N=800 Parkinson's disease (PD) patients (DATATOP study patients) Location: United States and Canada Sites: 28 (23 US and 5 Canada)
Patient characteristics	Untreated PD patients (stage I or II) Disease duration less than 5 years Exclusion criteria: use of any medications for PD or other agents active on the nervous system that might confound interpretation of the data, previous use of selegiline or tocopherol (at dose exceeding 2000 IU per day) for one month, resting tremor (tremor score $\geq$ 3), secondary or atypical parkinsonism, previous stereotactic brain surgery, dementia or depression
Intervention	3 treatment groups: 4. Tocopherol (2000 IU per day) and selegiline placebo 5. Selegiline (10mg per day) and tocopherol placebo 6. Selegiline (10 mg per day) and tocopherol (2000 IU per day) The subjects took 1000 IU capsules of tocopherol or identical-appearing placebo capsules and 5 mg tablets of selegiline or identical-appearing tablets of placebo twice daily with morning and evening meals.
Comparison	Selegiline and tocopherol placebo
Length of follow-up	After randomisation, the subjects were re-evaluated at 1 month, at 3 months, and then at 3 month intervals (90 $\pm$ 10 days) until 2 years after randomisation
Outcome measures	• Primary end-point: the onset of disability prompting the clinical decision to begin administering levodopa • Secondary outcome measures: UPDRS, Hoehn and Yahr scale, Schwab and England Activities of Daily Living Scale, and neuropsychological testing. The Hamilton depression scale was administered at baseline, at 1 and 3 months and at 6-month intervals thereafter.
Effect size	➢ In the group B who did take selegiline 97 subjects reached end-point

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	➢ In group A who did not take selegiline 176 subjects reached end-point ➢ Difference for reaching end-point was significant $p<10^{-8}$ ➢ Hazard ratio of group B compared to group A was 0.43 (95% CI 0.33 to 0.55) ➢ Treatment with selegiline reduced likelihood of reaching end-point by 57% ➢ There was no significant differences in baseline secondary outcome values between groups ➢ Significant differences at 1 month (mo) and 3 mo evaluations in favour of selegiline group ➢ Hoehn and Yahr, 1 and 3 mo not significant ➢ Schwab/England scale 1 mo non-significant, 3 mo (p=0.0064) ➢ Total UPDRS scores 1 mo and 3 mo (p<0.0001) ➢ Motor UPDRS 1 mo (p=0.0004) 3 mo (p<0.0001) ➢ ADL UPDRS 1 mo (p=0.0033) 3 mo (p<0.0001) ➢ Hamilton Scale 1 mo non significant, 3 mo (p=0.0028) ➢ The mean changes between the evaluation at end point and the final evaluation, which occurred one month after end-point, were not significant between groups A and B.
Source of Funding	Not stated
Additional comments	➢ Aim: to determine the effects of selegiline on the progression of disability in early Parkinson's disease ➢ Enrolment between September 3, 1987 and November 15, 1988 ➢ After a patient had reached the end-point, the experimental treatment was withdrawn in a blinded fashion and 30 days later the subject received a final evaluation
Citation	
NCC CC ID (Ref Man)	805

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Evidence Table **TxNP4** Are specific vitamins vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Kieburtz, K., McDermott, M., Como, P., Growdon, J., Brady, J., Carter, J., Huber, S., Kanigan, B., Landow, E., Rudolph, A., Saint-Cyr, J., Stern, Y., Tennis, M., Thelen, J., & Shoulson, I. 1994, "The effect of deprenyl and tocopherol on cognitive performance in early untreated Parkinson's disease", *Neurology*, vol. 44, no. 9, pp. 1756-1759.
Study type	RCT, double blind, placebo controlled
Evidence level	1+
Number of patients	N=800 Parkinson's disease (PD) patients (DATATOP study patients) Location: United States and Canada Sites: 28 (23 US and 5 Canada)
Patient characteristics	Untreated PD patients (stage I or II) Disease duration less than 5 years 530 men (mean age 61.5 $\pm$ 9.4 years) 269 women (mean age 60.4 $\pm$ 9.8) Exclusion criteria: use of any medications for PD or other agents active on the nervous system that might confound interpretation of the data, previous use of selegiline or tocopherol (at dose exceeding 2000 IU per day) for one month, resting tremor (tremor score $\geq$ 3), secondary or atypical parkinsonism, previous stereotactic brain surgery, dementia or depression.
Intervention	3 treatment groups: 7. Tocopherol (2000 IU per day) and selegiline placebo 8. Selegiline (10mg per day) and tocopherol placebo 9. Selegiline (10 mg per day) and tocopherol (2000 IU per day) The patients took 1000 IU capsules of tocopherol or identical-appearing placebo capsules and 5 mg tablets of selegiline or identical-appearing tablets of placebo twice daily with morning and evening meals.
Comparison	Selegiline and tocopherol placebo
Length of follow-up	14 $\pm$ 6 months
Outcome measures	• Primary end-point: the onset of disability prompting the clinical decision to begin administering levodopa

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	• Secondary measures: Digit Span, Selective Reminding Test, Odd Man Out test, Spot the Dot Task, the Controlled Word Association Task (verbal fluency), and mini-mental state examination (MMSE).
Effect size	➢ The four treatment groups were similar at baseline with respect to cognitive measures, demographic and motor measurements ➢ None of the tests demonstrated a clinically significant annualised rate of decline over the period of observation ➢ There was no significant effects for tocopherol or deprenyl on the annualised rates of change of any cognitive measure after adjustment for multiple comparisons ➢ There was a trend for deprenyl to slow annualised rates of change for the Symbol Digit test ($p<0.01$).
Source of Funding	National Institute of Neurological Disorders and Stroke and University grants (see paper)
Additional comments	➢ Aim: To determine if cognitive performance would decline appreciably during the early stages of PD, and if the experimental interventions would slow this decline or whether this decline was associated with motor deterioration ➢ Blinding of investigators to treatment group for data analysis not stated ➢ Methodology of randomisation and patient allocation taken from original study.
Citation	
NCC CC ID (Ref Man)	281

TxMN1 – section 7.2.4

Evidence Table **TxMN1** What is the effectiveness of MAO-B vs. placebo or levodopa in the treatment of early Parkinson's disease?	
Bibliographic reference	Ives, N., Stowe, R. L., Marro, J., Counsell, C., Macleod, A., & Clarke, C. E. Monoamine oxidase type B inhibitors in early Parkinsons's disease: A meta analysis of 17 randomised trials involving 3525 patients. 2004.

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Study type	Meta-analysis: 17 randomised trials
Evidence level	1++
Study objective	To quantify more reliably the benefits and risks of monoamine oxidase type B inhibitors (MAOBI) in early Parkinson's disease.
Number of patients	N=3525 early Parkinson's disease patients
Patient characteristics	Early disease patients: patients who had no history of motor complications and were untreated or had received limited (generally less than 12 months) exposure to anti-parkinsonian medication
Intervention	Trials- selegiline (13), lazabemide (3), rasagiline (1)
Comparison	Placebo or levodopa
Length of follow-up	6 weeks to 10 years
Outcome measures	Clinical disability rating scales, need for levodopa therapy, motor complications, side-effects and patient withdrawal (mortality covered in TxNP1)
Effect size	**Clinical disability rating scales** ➢ Data was only available from 6 trials of selegiline ➢ UPDRS scores at 3 months were: • Total score: 2.7 (95%CI 1.4 to 4.1, p=0.00009); • Motor score: 1.8 (95%CI 0.8 to 2.7, p=0.0004) and • Activities of daily Living scores: 0.9 points (0.5 to 1.4, p=0.00007) • All better with selegiline than controls ➢ The large DATATOP study accounted for over 65% of the patients analysed and over 79% of patients in the MAOBI v placebo comparison ➢ Combined results from the other two studies of MAOBI v placebo were consistent with those from the DATATOP and significant independently (p=0.004) **Need for levodopa therapy** ➢ 8 trials reported data on need for levodopa (MAOBI v placebo) ➢ Median follow-up of 13 months (range 3 months-5 years) ➢ Highly significant reduction in need for levodopa in patients randomised to a MAOBI compared to placebo (0.57, 95%CI 0.48 to 0.67, p<0.00001) ➢ 2 trials reported on levodopa dose (selegiline+ levodopa v levodopa) ➢ Dose of levodopa required for adequate symptom control was 67mg (14 to 119; p=0.01) lower in

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	selegiline arm **Motor complications** ➢ Data on motor complications was available from 5 trials ➢ There was a 25% reduction in motor fluctuations randomised to MAOBI (0.75, 95%CI 0.59 to 0.95, p=0.02) ➢ There was no difference in the incidence of dyskinesia between MAOBI and non-MAOBI groups (0.97, 95%CI 0.75 to 1.26, p=0.8) ➢ There was no evidence of heterogeneity between trials or the three treatment comparisons for either outcome **Side effects and patient withdrawal** ➢ More side-effects reported in patients randomised to a MAOBI (1.36, 95%CI 1.002 to 1.80, p=0.04) ➢ No sub-analysis of specific side effects as not enough data was reported in trials ➢ More MAOBI patients withdrew due to adverse events than non-MAOBI patients (2.16, 95%CI 1.44 to 3.23, p=0.0002) ➢ There was some evidence of heterogeneity between trials (p=0.03) but not between treatment comparisons (p=0.09) ➢ Heterogeneity was explained by atypical results in UK=PDRG study which reported significantly more drop-outs due to adverse events in open-label selegiline plus levodopa group than levodopa alone group (14% v 3%) ➢ An analysis of drop-out due to adverse events for placebo-controlled trials (excluding 2 of the above trials) showed no difference between MAOBI and non-MAOBI patients (1.52, 95%CI 0.87 to 2.68, p=0.1) ➢ With no evidence of heterogeneity between trials (p=0.2) or the two treatment comparisons (p=0.9) ➢ There was no difference between thr two groups (MAOBI versus non-MAOBI) in overall number of patients withdrawing from trials (18% vs. 19%: 1.06, 95%CI 0.87 to 1.28, p=0.6)
Source of funding	Government funding
Additional comments	➢ Robust search strategy ➢ Systematic review of literature from 1966 to December 2003 ➢ Inclusion criteria for trials listed

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	➢ Two investigators independently scored the methodological quality of the included studies ➢ Tests for heterogeneity were used ➢ All trials double-blind (15/17 double blind) ➢ Not all studies intention-to-treat analysis ➢ Trials included for these outcome measure reported here: Lees et al (1995), Kirollos et al (1996), Olanow (1995), Caraceni et al (2001), Tetrud et al (1989), Larsen et al (1999), Pruntek (1999), Myllyla et al (1992), Myllyla et al (1995), Myllyla et al (1997)
NCC CC ID (Ref Man)	2739

Evidence Table **TxNP1** Is MAO-B vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease? **TxMN1** What is the effectiveness of MAO-B vs. placebo or levodopa in the treatment of early Parkinson's disease?	
Bibliographic reference	Macleod AD, Counsell CE, Ives N, Stowe R. Monoamine oxidase B inhibitors for early Parkinson's disease. The Cochrane Database of Systematic Reviews 2005, Issue 3.
Study type	Cochrane review meta-analysis: 10 randomised trials
Evidence level	1++
Study objective	To assess the evidence from randomised controlled trials for the effectiveness and safety of long-term use of MAO-B inhibitors in early PD
Number of patients	N=2422 early Parkinson's disease patients
Patient characteristics	Early disease patients: patients were starting parkinsonian treatment for the first time (or had started treatment in the last 12 months) and where the majority of patients were classified as Hoehn-Yahr stage II or less. Trial including a significant proportion of patients with motor fluctuations (greater than 10%) were excluded.
Intervention	9 trials- selegiline, 1- lazabemide
Comparison	Placebo or levodopa
Length of follow-up	1 to 9.2 years, mean follow-up 5.8 years (studies with < 1 year of follow-up were excluded)

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Outcome measures	Deaths at the end of follow-up, changes in UPDRS motor scores and ADL scores from baseline, levadopa requirements, development of motor fluctuations, dyskinesias, adverse events and withdrawals.
Effect size	Mortality ➢ All the studies reported data on deaths at the end of follow-up ➢ There was a non-significant increase in deaths amongst patients treated with MAO-B inhibitors compared with those given control (OR 1.15; 95%CI 0.92 to 1.44, p=0.21) with no significant heterogeneity. The result remained non-significant when the unadjusted data (not adjusted for differing lengths of follow-up in each group) from the UK-PDRG (RR) 1998 study were used. Mean change in UPDRS motor score from baseline to one year on treatment ➢ Data from 5 studies was available for analysis. ➢ All the studies favoured treatment with MAO-B inhibitors. The weighted mean difference (WMD) was –3.81 (95%CI –5.36 to –2.27). This shows that the mean decline in the motor impairment score at one year was nearly 4 points (out of a total scale of 108 points) less in participants treated with MAO-B inhibitors than those treated with control. ➢ Although this result is highly statistically significant (p<0.00001) its clinical significance is unclear. ➢ There was significant heterogeneity amongst the studies in this analysis however this was entirely attributable to the PSG 1996 study which used lazabemide. The results suggest that lazabemide (WMD –1.35; 95%CI –3.09 to 0.39) has a significantly weaker effect than selegiline (WMD –4.55; 95%CI –5.62 to –3.47, p=0.002). Mean change in UPDRS ADS score from baseline to one year on treatment ➢ Data from 5 studies was available for analysis. ➢ All the studies favoured treatment with MAO-B inhibitors. The WMD was –1.5 (95%CI –2.53 to –0.48, p=0.004) that is the scores were about one and a half points better (out of a total score of 52 points) after one year in patients treated with MAO-B inhibitors. ➢ There was an apparent difference in effect between the studies using selegiline (WMD –2.23; 95%CI –2.84 to –1.61) and the study that used lazabemide (WMD –0.47; 95%CI –1.31 to 0.37). This accounted for the substantial heterogeneity in this analysis. Subgroup analysis showed a highly significant difference between the two types of MAO-B inhibitor used (p=0.0006). Mean change in UPDRS total score from baseline to the end of washout ➢ Data from 3 studies was available for analysis.

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	➢ The mean duration of follow-up for this analysis was 1.1 years and the length of the washout was between 2 weeks and 2 months. ➢ Meta analysis yielded a WMD was –3.15 (95%CI –5.48 to –0.82, p=0.008) that is the increase in score severity from baseline to the end of washout was about three points less in the treatment group. Heterogeneity was low. Levodopa requirements ➢ Data from 3 studies was available for analysis as they assessed this outcome at a comparable follow-up period of one year. ➢ The mean duration of follow-up for this analysis was 1.1 years and the length of the washout was between 2 weeks and 2 months. ➢ The combined OR was 0.53 (95%CI 0.36 to 0.79), significantly in favour of MAO-B inhibitors (p=0.01) with no significant heterogeneity ➢ The California 1089 study reported these data at 3 years by which time only one patient (in the seefiline arm) did not require levodopa. In the other two studies all the patients were receiving levodopa at the end of 4 years of follow-up (Finland 1997; Swedish PSG 1998). Motor fluctuations ➢ Data from 5 studies was available for analysis. ➢ The mean weighted duration of follow-up for this analysis was 3.4 years. ➢ The overall effect was significantly in favour of MAO-B inhibitors (OR 0.75; 95% CI 0.59 to 0.94. p=0.01) with no heterogeneity. However, this results was very dependent on the adjusted results of the UK-PDRG study (adjusted for different durations of follow-up in each group) and if the unadjusted results are used the overall result becomes non-significant. ➢ Results were not reported for 336 patients in these five studies. A modified worst-case analysis was performed which also made the results non-significant (OR 1.02, 0.53 to 1.95). The authors therefore judged that the motor fluctuation result was not robust in sensitivity analyses. Dyskinesias ➢ Data from 4 studies was available for analysis. ➢ The mean duration of follow-up was 3.5 years. ➢ No difference between intervention and control was found (OR 0.98; 95% CI 0.76 to 1.26). Re-

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	analysis using the raw data from the UK- PDRG trial did not alter the results (OR 0.99). Patients with adverse events ➢ Data from 4 studies reported the number of patients with significant adverse events. ➢ There was a non-significant trend for more adverse events with MAO-B inhibitors (OR 1.38; 95%CI 0.92 to 2.06, p=0.12). ➢ Five studies reported data on nausea. More patients in the MAO-B inhibitor group reported nausea but the overall difference was not significant (OR 1.64; 95%CI 0.85 to 3.17). ➢ None of the 4 studies which reported data on blood pressure found lower mean blood pressures in patients in the MAO-B arms (thus no evidence to support postural hypotension concerns). Withdrawals ➢ Six studies reported the number of withdrawals due to adverse events at the end of follow-up ➢ There were significantly more withdrawals with MAO-B inhibitors (OR 2.36; 95% CI 1.32 to 4.20, p=0.004) and with no significant heterogeneity. ➢ All 10 trials reported data on total number of withdrawals by end of follow up. There was no significant difference in the number of withdrawals between the MAO-B inhibitor and control arms (OR 0.93; 95%CI 0.74 to 1.16).
Source of funding	The Health Foundation UK (support).
Additional comments	➢ Robust search strategy ➢ Systematic review of literature from 1966 to August 2004 ➢ Inclusion criteria for trials listed ➢ All data were extracted by two reviewers and cross-checked. ➢ Tests for heterogeneity were used ➢ 9/10 trials double-blind (the UK-PDRG 2001 study was unblinded) ➢ Not all studies intention-to-treat analysis ➢ The authors conclude, “MAO-B inhibitors do not appear to delay disease progression but may have a beneficial effect on motor fluctuations. There was no statistically significant effect on deaths although the confidence interval does not exclude a small increase with MAO-B inhibitors. At present we do not feel these drugs can be recommended for routine use in the treatment of early Parkinson’s disease but further randomised controlled trials should be carried out to clarify, in particular, their effect on deaths and motor complications”. ➢ Trials included: California 1989, DATATOP 1993, Finland 1997, Norway Denmark 1999, PSG 1996, SELEDO 1999, Swedish PSG 1998, UK 1996, UK-PDRG (RR) 1998, UK-PDRG 2001 and

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	US 1995.
NCC CC ID (Ref Man)	19938

Evidence Table **TxMN1** What is the effectiveness of MAO-B vs. placebo or levodopa in the treatment of early Parkinson's disease?	
Bibliographic reference	Presthus J, Berstad J, Lien K. Selegiline (1-deprenyl) and low-dose levodopa treatment of Parkinson's disease. A double-blind crossover trial. *Acta Neurologica Scandinavica.* 1987;**76**:200-3.
Study type	Double-blind, placebo-controlled, cross-over study
Evidence level	1++
Study objective	To determine if selegiline is of value in addition to levodopa in the treatment of patient with early PD.
Number of patients	N=15 levodopa-naïve parkinsonian patients Location: Norway Sites: 1
Patient characteristics	All suffered from idiopathic Parkinson's disease (PD) All previously untreated with either levodopa or dopaminergic agonists Exclusion criteria: concomitant disease (i.e. diabetes, diseases of gastrointestinal tract and of thyroid, insufficiency of the liver, the kidneys or the heart), dementia or inability to cooperate, pervious psychotic periods, and previous use of neuroleptic or antidepressant medications. Mean disease duration 3.5 (range 1.05-1.5) years Mean age 65 (range 44-77) years 12 males, 3 females
Intervention	200 mg/d Madopar (levodopa 50 mg + benserazide 12. 5mg 4x daily) and 10mg selegiline (5mg 2x)
Comparison	200 mg/d Madopar and placebo
Length of follow-up	2 treatment periods of 6 weeks including a 2 week wash-out period inbetween treatments
Outcome measures	Webster rating scale, sensimotoric test, adverse events
Effect size	**Patient perceptions** ➢ 6 patients reported better therapeutic effect of Madopar + selegiline than of Madopar + placebo

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	➢ 2 reported possible improvement of selegiline ➢ 2 reported no difference ➢ 4 preferred placebo **Webster rating scale (total scores)** ➢ Madopar + selegiline caused a reduction of 29% and Madopar + placebo a reduction of 27% ➢ Differences in effects observed was not significant between treatments ➢ There was no period effect ➢ Carry-over effect: no significant differences between the initial values of the treatment periods ➢ The estimated differences between treatment groups was 0.143 (95%CI –5.85 to 6.14) **Sensimotoric test** ➢ No significance in treatment effect ➢ Significant period effect (p<0.01) ➢ Carry-over effect: significantly lower value for the second period (p<0.01) **Side effects** ➢ Patients presented minimal or no side effects ➢ No differences were noted between treatment periods ➢
Source of funding	Pharmaceutical company
Additional comments	➢ Before the trial patients went through a one-week wash-out period ➢ Randomisation of treatments was performed by a statistician ➢ Randomisation methods and allocation concealment methods not stated ➢ One patient withdrew, reasons stated ➢ Small sample size ➢ Short trial duration ➢ Not intention-to-treat analysis
NCC CC ID (Ref Man)	2761

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Evidence Table **TxMN1** What is the effectiveness of MAO-B vs. placebo or levodopa in the treatment of early Parkinson's disease?	
Bibliographic reference	Stern MB, Marek KL, Friedman J, Hauser RA, LeWitt PA, Tarsy D *et al*. Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. *Movement Disorders* 2004;**19**:916-23.
Study type	Randomised, double-blind, multi-centre, placebo-controlled study
Evidence level	1++
Study objective	To evaluate the safety, tolerability, and preliminary efficacy of rasagiline monotherapy in early Parkinson's disease (PD) patients not receiving levodopa.
Number of patients	N=56 PD patients N=15 rasagiline 1mg/d N=14 rasagiline 2mg/d N=14 rasagiline 4 mg/d N=13 placebo Location: USA sites: nine
Patient characteristics	Patients were eligible for enrolment if they were between the ages of 40 and 75 years and had a diagnosis of idiopathic PD, and had a Hoehn and Yahr disease severity of less than stage III. The treatment groups were well balanced for demographics. The mean age was 61.5 years, 68% (38/56) were male, 91% (51/56) were Caucasian. The distribution of baseline characteristics was similar from centre to centre.
Intervention	Orally administered once-a-day monotherapy 1,2 or 4 mg. The drug was titrated up during the first 3 weeks, and this was followed by a 7-week maintenance phase.
Comparison	Placebo
Length of follow-up	10-week trial duration and a post-treatment follow-up visit 6 weeks after the end of treatment period.
Outcome measures	UPDRS, Clinical Global Impression of Change Scale (CGIC), Hoehn and Yahr stage, Schwab and England Activities of Daily Living (ADL) scale, or Beck Depression Inventory, adverse events, withdrawal rates
Effect size	Efficacy:

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	➢ Mean changes in total UPDRS scores in rasagiline and placebo groups between baseline and weeks 1 to 10: ➢ Total UPDRS score during 10-week period ($p<0.05$) for rasagiline 2mg but not for 1mg and 4mg groups compared to placebo ➢ At week 10 the mean (± SE) change from baseline in total UPDRS score was –1.8 (±1.3) in rasagiline 1mg (9.9% improvement), -3.6 (±1.7) in rasagiline 2 mg (17.1% improvement), -3.6 (±1.2) in the rasagiline 4mg group (17.8% improvement) and –0.5 (±0.8) in placebo (2.8% improvement) ➢ A responder analysis showed that 28% of patients (12/43) receiving rasagiline had an improvement in total UPDRS score of more than 30% compared with none of the patients receiving placebo ($p<0.05$) ➢ No evidence of drug effect was noted with respect to the CGIC scale, Hoehn and Yahr stage, Schwab and England ADL scale, or BDI Adverse events ➢ No serious events were reported ➢ Frequency and types of events reported were similar between groups ➢ No statistically significant differences were found between the incidence of adverse events by body system in each treatment arm and placebo, between the incidence of most commonly reported adverse events in rasagiline and placebo groups, or between adverse events commonly associated with dopaminergic medications in rasagiline groups and placebo ➢ The most commonly reported adverse events in rasagiline-treated patients were pain, headache, and dizziness ➢ Rasagiline treatment was not associated with hypertension Withdrawals ➢ One patients in rasagiline 1mg/d group discontinued treatment 15 days after starting study medication due to non-serious adverse event (visual hallucinations and dizziness) ➢ The other 55 patients received the full course of treatment and had good compliance
Source of funding	Pharmaceutical
Additional comments	➢ First patient was screened February 1995 and last patient was screened September 1996 ➢ Methods of randomisation and allocation concealment stated ➢ Intention-to-treat analysis ➢ Centre comparability analysed ➢ Power calculation performed suggested 120 patients per group needed for 80% power

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	➢ Target sample size of 55 patients was selected without consideration of statistical power for assessing anti-PD efficacy ➢ No formal statistical analyses were defined in protocol to assess safety, tolerability and efficacy ➢ Post-hoc comparisons were performed after unblinding to assess change in efficacy measures (eg UPDRS)
NCC CC ID (Ref Man)	19854

TxMN2 – section 7.2.3

Evidence Table
TxMN2
Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?

Bibliographic reference	Kieburtz K. Safety and efficacy of pramipexole in early Parkinson disease: A randomized dose-ranging study. Journal of the American Medical Association 1997;278:125-30.
Study type	Placebo-controlled dose-response RCT
Study objective	Comparison of Dopamine-Antagonist (Pramipexole) with Placebo in terms of UPDRS Score and Dose-Response
Evidence level	1++
Number of patients	N= 264 Parkinson's disease (PD) patients N=213 dopamine-agonist (pramipexole) N=51 placebo Location: USA/Canada Sites: 20
Patient characteristics	Inclusion Criteria: Patients >30 years old with idiopathic PD of less than 7 years duration and H&Y score 1 to 3 with no current or previous use or indication for levadopa or dopamine-antagonists. Concurrent treatment with selegiline, anticholinergics or amantadine was permitted. Exclusion criteria: atypical parkinsonian syndromes, dementia or serious concurrent diseases such as heart disease or cancer. **Baseline Data:**

	Pramipexole	Placebo
Age, years (SD)	60.3 to 62.8	60.4 (12.0)

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<table>
<tr><td></td><td>
<table>
<tr><td>% Male</td><td>62.0 to 69.1</td><td>62.7</td></tr>
<tr><td>Prior Levadopa use, %</td><td>20.4 to 30.9</td><td>27.5</td></tr>
<tr><td>Baseline UPDRS Score (SD)</td><td>27.3 to 32.9</td><td>28.7 (12.3)</td></tr>
<tr><td>Baseline H&Y stage (SD)</td><td>1.8 to 1.9</td><td>1.8 (0.5)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Dopamine-Antagonist (Pramipexole): pramipexole titrated over 4 weeks to either 1.5mg/day, 3.0mg/day, 4.5mg/day, 6.0mg/day</td></tr>
<tr><td>Comparison</td><td>Placebo: matching placebo with parallel titration</td></tr>
<tr><td>Length of follow-up</td><td>10 weeks</td></tr>
<tr><td>Outcome measures</td><td>UPDRS Score (change from baseline compared to placebo), Dose-Response (slope of dose-response regression line)</td></tr>
<tr><td>Effect size</td><td>Efficacy:
<table>
<tr><th>Variable</th><th>Value</th><th>95% CI</th><th>p (ANOVA)</th></tr>
<tr><td>UPDRS Score (1.5mg/day)</td><td>-5.24</td><td>-8.95 to -1.54</td><td><0.001</td></tr>
<tr><td>UPDRS Score (3.0mg/day)</td><td>-5.08</td><td>-8.86 to -1.29</td><td><0.001</td></tr>
<tr><td>UPDRS Score (4.5mg/day)</td><td>-5.86</td><td>-9.59 to -2.13</td><td><0.001</td></tr>
<tr><td>UPDRS Score (6.0mg/day)</td><td>-5.24</td><td>-8.96 to -1.53</td><td><0.001</td></tr>
<tr><td>Dose-Response</td><td>-0.82</td><td>-1.28 to -0.37</td><td><0.001</td></tr>
</table>
Adverse events:
➢ There was a "trend" towards more adverse events in the higher-dose groups
➢ There were significantly more moderate-severe adverse events in the 6.0mg Pramipexole group compared to the placebo group (67.3% versus 37.3%; nominal p=0.002)</td></tr>
<tr><td>Source of funding</td><td>Pharmacia and Upjohn, USA</td></tr>
<tr><td>Additional comments</td><td>➢ Although the dose-response relationship is significant, it is not indicated whether the placebo groups was included in the dose-response analysis. Because the effectiveness of each group appears comparable (suggesting no dose-response relationship at the levels considered), and the dose-response curve is significant, this suggests that the significant of the dose-response curve is entirely due to the inclusion of the placebo results in the dose-response analysis
➢ Methods of randomisation and allocation concealment stated
➢ Power calculations provided</td></tr>
<tr><td>NCC CC ID (Ref Man)</td><td>1501</td></tr>
</table>

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Evidence Table
TXMN2
Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?

Bibliographic reference	Barone P, Bravi D, Bermejo-Pareja F, Marconi R, Kulisevsky J, Malagu S *et al*. Pergolide monotherapy in the treatment of early PD: a randomized, controlled study. Pergolide Monotherapy Study Group. *Neurology* 1999;**53**:573-9.
Study type	A multi-centre double-blind RCT of pergolide versus placebo of 3 months duration in patients with early Parkinson's disease.
Study objective	To assess the efficacy and safety of pergolide monotherapy in patients with early Parkinson's disease.
Evidence level	
Number of patients	N= 105 Parkinson's disease patients N= 53 pergolide group N= 52 placebo group Location: Europe Sites: 19 sites
Patient characteristics	Inclusion criteria: Patients were eligible for the study if they fulfilled the UK Parkinson's Disease Society Brain Bank Criteria for a clinical diagnosis of Parkinson's disease, with a disease stage of 1 to 3 on the modified Hoehn & Yahr Staging Scale, and a score greater than 14 points on the motor examination section (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS). In addition patients entering the trial were required to have normal cognitive function as indicated by a score of 25 points on the Mini-Mental State Examination (MMSE). The maximum period allowed between clinical diagnosis of Parkinson's disease and study entry was 3 years. Exclusion criteria: No concomitant treatment with any antiparkinsonian agent other than the study drug was allowed. Any previous therapy with selegiline must have been discontinued at least 8 weeks before inclusion, whereas anticholinergics, dopamine agonists and amantadine were discontinued at least 4 weeks before study entry. Any history of lack of response to previous levodopa treatment precluded entry into the study. Patients were also excluded if they were affected by depression as revealed by a score greater than 2 points on the UPDRS part I, item 3.

Demographic characteristics at study entry		
Characteristic	Pergolide (N=53)	Placebo (N=52)
Mean age +/- SD, y	63.1 +/-8.6	61.4 +/- 9.9
Men /women, %	56.6/43.4	69.2/30.8

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	Hoehn & Yahr stage, median	2	2
	UPDRS part III, motor score, mean +/- SD	24.4 +/-8.6	25.3 +/-7.5
	UPDRS overall score, mean +/- SD	34.4 +/-11.5	35.8 +/-10.6
	Schwab & England, median*	2	2
	CGI severity, mean +/- SD$	3.2 +/-0.7	3.3 +/-0.7
	*Schwab & England scale measuring current level of independence: 100% independent =1, 90%=2 etc to 10% =10 $ CGI severity score: normal=1 to most extremely ill =7.		
Intervention	Pergolide: During the initial therapy period comprising the fixed dosage titration regimen, daily doses pf pergolide started at 0.05mg/day and escalated to 0.75mg/day (0.25mg thrice daily). To reduce the risk of unblinding patients or adverse events, concomitant therapy with domperidone (20mg thrice daily) was mandatory during the 3-week dose titration period. Only patients tolerating the fixed-dose titration at the end of 3 weeks were eligible to continue. During the second period (9 weeks) drug dose was flexible in the range 0.75 to 3.0mg/day and was based on the clinical judgment of the clinician to optimise the clinical status of each individual patient. A fixed drug dose was maintained during the lst 2 weeks of the period and final assessment of efficacy was made at the end of 9 weeks of flexible therapy. Thereafter patients detitrated their medication over 1 to 2 weeks.		
Comparison	Placebo: Study drug kits were prepared to ensure the placebo and pergolide products were indistinguishable.		
Length of follow-up	The study period lasted for 3 months.		
Outcome measures	The primary outcome measure was a response criterion, based on change from baseline in UPDRS part III score to evaluate symptomatic relief. Responders were defined as having at least a 30% reduction in UPDRSS part III score to evaluate symptomatic relief. Responders were defined as having at least a 30% reduction in UPDRS part III score between baseline and the patients last visit. Secondary measures were changes from baseline to end point in UPDRS overall, UPDRS parts II and III, CGI improvement (at end point), modified Hoehn & Yahr Staging Scale score and Schwab & England ADL score.		
Effect size	➢ Forty-eight of 53 pergolide-treated patients (90.5%) completed the fixed-titration regimen reaching a daily dose of 0.75mg. Forty-three patients in the pergolide treated group (81%) completed the trial. The mean (+/- SD) daily dose of pergolide was 2.06 +/- 0.76mg at the end of		

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	the 9-week flexible dosing period. In the placebo group 46 patients (88%) completed the trial. ➢ Patients fulfilling the primary efficacy criteria (less than or equal to a 30% decrease of UPDRS part III, motor examination score from baseline) were 30 of 53 (56.6%) in the pergolide-treated group (p<0.001). The estimate for treatment difference in percentages was 39.3% (95%CI 22.5 to 56.1%). ➢ The UPDRS subscores improved significantly in the pergolide-treated group over the 12 week treatment period (p<0.001). The mean decrease in the change in UPDRS overall score was 9.8 in the pergolide group and 1.8 in the placebo group with an estimate for the treatment difference of -8.2 (95%CI –11.6 to –4.8). ➢ There was a significant difference between the treatment groups in UPDRS part II score: the mean change in the pergolide group was –2.3 and was 0.1 in the placebo group (p<0.001). ➢ A significant difference (p<0.001) was found between the treatment groups also in the change in UPDRS part III score from baseline to end point: the mean change in the pergolide group was -7.5 and in the placebo group was -1.7, with an estimate for the treatment difference of –5.9 (95%CI –8.4 to –3.4). ➢ A significantly greater improvement in Schwab & England ADL score was observed in pergolide-treated patients compared with placebo-treated patients (p<0.001). In the pergolide group the mean change in rating was –0.4, representing a slight improvement in independence. In the placebo group the mean change was +0.2 indicating a slight worsening. Similarly analysis of CGI improvement scores showed a significant difference between the two groups (p<0.001) with a total of 48.2% of pergolide treated patients versus 5.8% of placebo-treated patients rated as "very much improved" or "much improved". ➢ Overall, 65 patients reported at least one adverse event: 34 (64%) in the pergolide group and 31 (60%) in the placebo group. This was not a significant difference (p=0.632). Anorexia (p=0.043), nausea (p=0.001), vomiting (p=0.0023) and dizziness (p=0.029) occurred significantly more in the pergolide patients compared with placebo. The most common adverse effects in the pergolide group were nausea (32.1%), somnolence (15.1%) and dizziness (13.2%). ➢ The overall rate of early discontinuation was similar in both groups: 10 patients in the pergolide group and 6 in the placebo group. All adverse events leading to discontinuation were rated as mild or moderate. ➢ No clinically significant abnormalities in vital signs and lab tests were associated with pergolide treatment.
Source of funding	The study was supported by Eli Lilly and Company.

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Additional comments	➢ Methods of randomisation and allocation concealment stated ➢ Intention-to-treat analysis ➢ Centre comparability and country comparability tested ➢ Power calculations stated
NCC CC ID (Ref Man)	1937

Evidence Table **Q TXMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	C. H. Adler, K. D. Sethi, R. A. Hauser, T. L. Davis, J. P. Hammerstad, J. Bertoni, R. L. Taylor, J. Sanchez-Ramos, and C. F. O'Brien. Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group.[erratum appears in Neurology 1997 Nov;49(5):1484]. *Neurology* 49 (2):393-399, 1997.
Study type	A multi-centre double-blind RCT of Ropinirole versus placebo of 6 months duration in patients with early Parkinson's disease.
Study objective	Comparison of the effect of Ropinirole with placebo in improving Parkinson's disease symptoms, including motor function, and its safety and tolerability in the study population.
Evidence level	1+
Number of patients	N= 241 Parkinson's disease patients N= 116 ropinirole group N= 125 placebo group Location: USA Sites: 25 sites
Patient characteristics	Inclusion Criteria: Patients with motor symptoms sufficiently severe to warrant the introduction of dopaminergic therapy but had not received levadopa or any dopaminergic agonist for more than 6 weeks prior to study entry. All other antiparkinsonian therapies, except selegiline were discontinued 4 weeks prior to study entry. Patients on selegiline were required to receive a stable dose 4 weeks prior to study entry and for the duration of the study. Those not receiving selegiline prior to study entry were prohibited from receiving it during the study. Exclusion criteria: Treatment with vasodilators, anti-arrhythmics, digoxin, calcium channel blockers,

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<table>
<tr><td></td><td>angiotensin-converting enzyme inhibitors, other antihypertensive agents (excluding diuretics), previous treatment with ropinirole, history of severe systemic disease, major psychosis, dementia, history of severe dizziness or fainting, diastolic blood pressure equal or over 110mm Hg, recent history of alcoholism or drug dependence.
<table>
<tr><th>Characteristics</th><th>Ropinirole
No selegiline
N=58</th><th>Ropinirole
Selegiline
N=58</th><th>Placebo
No selegiline
N=64</th><th>Placebo
Selegiline
N=61</th></tr>
<tr><td>Age, years, Mean (SD)</td><td>64.9 (9.8)</td><td>59.1 (10.6)</td><td>65.9 (10.3)</td><td>61.6 (10.6)</td></tr>
<tr><td>Male, N (%)</td><td>34 (58.6)</td><td>36 (62.1)</td><td>35 (54.7)</td><td>45 (73.8)</td></tr>
<tr><td>Female, N (%)</td><td>24 (41.4)</td><td>22 (37.9)</td><td>29 (45.3)</td><td>16 (26.2)</td></tr>
<tr><td>Hoehn and Yahr Stage I and I.5, N (%)</td><td>14 (24.1)</td><td>18 (31)</td><td>19 (29.7)</td><td>18 (29.5)</td></tr>
<tr><td>H and Y Stage II and II.5, N (%)</td><td>35 (60.4)</td><td>35 (60.3)</td><td>35 (54.7)</td><td>38 (62.3)</td></tr>
<tr><td>H and Y Stage III, N (%)</td><td>9 (15.5)</td><td>5 (8.6)</td><td>10 (15.6)</td><td>5 (8.2)</td></tr>
<tr><td>Duration of disease, months, Mean (SD)</td><td>18.8 (19.7)</td><td>30.4 (19.7)</td><td>18.2 (17.8)</td><td>27.5 (19.8)</td></tr>
<tr><td>UPDRS motor score, Mean (SD)</td><td>19.1 (8.2)</td><td>16.7 (9.2)</td><td>17.6 (7.7)</td><td>17.7 (8.6)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Ropinirole: 0.25 mg t.i.d titrated upward at weekly intervals until optimal therapeutic response was achieved, where patients remained for the duration of the study. All patients were titrated up to a minimum dose of 1.5mg t.i.d, with a maximum dose of 8mg t.i.d. An 80% compliance with study medication was required. Additional symptomatic therapy was permitted if patients were first titrated to the highest tolerated dose of study medication. Additional symptomatic therapy consisted of open-label carbidopa/levodopa while continuing to receive blinded study medication for the remainder of the trial. No other symptomatic therapy was permitted.</td></tr>
<tr><td>Comparison</td><td>Placebo: 0.25 mg t.i.d titrated upward at weekly intervals until optimal therapeutic response was achieved, where patients remained for the duration of the study. All patients were titrated up to a minimum dose of 1.5mg t.i.d, with a maximum dose of 8mg t.i.d. An 80% compliance with study medication was required. Additional symptomatic therapy was permitted if patients were first titrated to the highest tolerated dose of study medication. Additional symptomatic therapy consisted of open-label carbidopa/ levodopa while continuing to receive blinded study medication for the remainder of the trial.</td></tr>
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<table>
<tr><td></td><td>No other symptomatic therapy was permitted.</td></tr>
<tr><td>Length of follow-up</td><td>The study period lasted for 6 months.</td></tr>
<tr><td>Outcome measures</td><td>Improvement in Motor Function (UPDRS Motor Examination), Percentage of Patients with at least 30% reduction in UPDRS Motor Score, Percentage Patients Scoring 1 or 2 on the CGI Global Improvement Item, Percentage Patients with Insufficient Symptomatic Benefit, Adverse Experiences, Dropout Rate.</td></tr>
<tr><td>Effect size</td><td>
<table>
<tr><th></th><th>Ropinirole N=116</th><th>Placebo N=125</th><th>Significance</th><th>Comment</th></tr>
<tr><td>UPDRS Motor Examination, Mean ± SD</td><td>17.9± 8.8 at baseline to 13.4 ±9.5 at 6 months</td><td>17.7 ± 9.5 at baseline to 17.9 ± 10.5 at 6 months</td><td>p<0.001
24% Improvement in Motor Improvement score in Ropinirole compared with placebo.</td><td>Weighted regression analysis

Results were similar in patients receiving selegiline compared with those not on selegiline.</td></tr>
<tr><td>At least 30% reduction in UPDRS Motor Score</td><td>47% of patients</td><td>20% of patients</td><td>OR 4.45 (95%CI 2.26 to 8.78)
Significantly greater percentage in favour of Ropinirole compared with placebo.</td><td>56% of patients on Ropinirole vs 14% on placebo in selegiline stratum (P=0.008).

38% of patients on Ropinirole vs 25% on placebo in non-selegiline</td></tr>
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</table>

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				stratum (NS).
CGI Global Improvement at study end-point.	33% of patients rated as 'very much improved' or 'much improved' on this item.	12% of patients rated as 'very much improved' or 'much improved' on this item.	OR 4.06 (95% CI 2.0 to 8.22) Significantly greater percentage in favour of Ropinirole compared with placebo.	No significant interaction between selegiline strata and treatment.
Insufficient Symptomatic Benefit.	11% of patients required Levadopa for additional symptomatic relief at the end of the 6-month treatment period.	29% of patients required Levadopa for additional symptomatic relief at the end of the 6-month treatment period.	OR 0.30 (95% CI 0.14 to 0.61). Significant treatment difference in favour of Ropinirole compared with placebo.	No significant interaction between selegiline strata and treatment.
Adverse Experiences	111 (96%) patients with one or more reported AE's	113 (90%) patients with one or more reported AE's	Not reported.	
Dropout Due to AE's	27 (23%)	13 (10%)	Not reported	
Total Dropout Rate	37 (32%)	20 (16%)	p= 0.004	Fisher's exact test
Daily dose at end-point for ITT population, mean ± SD	15.7 ± 8.3 mg 15.5 ± 8.3 mg selegiline vs 15.8 ± 8.4 mg	19.7 ± 7.1 mg 20.0 ± 6.5 mg selegiline vs 19.2 ± 7.6 mg	Not reported	Maximum DD allowed = 24mg/day

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	non-selegiline patients	non-selegiline patients		

Notes:

- Selegiline and Non-Selegiline Strata: Duration of disease was shorter in the non-selegiline group at baseline.
- Baseline Demographic Variables: Comparable between the two groups, including the distribution of patients receiving selegiline.
- UPDRS Motor Examination: A regression approach was used for statistical analysis of improvement in motor score, based on the assumption that treatment effect was proportional to baseline score. The model was weighted by the square of the baseline score to ensure that patients with more severe disease (with higher baseline scores) contributed more to the analysis that those with less severe disease (i.e. lower baseline scores).

Source of funding	The study was supported by a grant from SmithKline Beecham Pharmaceuticals.
Additional comments	➢ Prior to randomisation, patients were entered into a 7-day placebo run-in to assess treatment compliance, and those that were at least 80% compliant were allowed to continue in the study. ➢ Patients stratified according to the concomitant use of selegiline were randomised in a 1:1 ratio to receive ropinirole or placebo, but methods of randomisation and allocation concealment were not reported. ➢ Patient follow-up appointments were scheduled weekly for the first month, every other week for 2 months, and monthly thereafter for the duration of the study. ➢ Methods of blinding used in the study were not reported. ➢ Number of dropouts was significantly greater in ropinirole compared to placebo over the six-month study period. ➢ More participants in the ropinirole group withdrew from the study due to AE's than in the placebo group. ➢ Intention-to-treat analysis ➢ No power calculations provided
NCC CC ID (Ref Man)	1902

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Evidence Table
Q TXMN2
Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?

Bibliographic reference	Hubble JP, Koller WC, Cutler NR, Sramek JJ, Friedman J, Goetz C et al. Pramipexole in patients with early Parkinson's disease. Clin Neuropharmacol 1995;18:338-47.
Study type	Parallel RCT (4 sites) with intra-group comparisons
Study objective	Comparison of Dopamine-Antagonist (Pramipexole) with Placebo in terms of UPDRS Factor II Score, UPDRS Factor III Score, Adverse Events
Evidence level	1+
Number of patients	**Treatment Group** / **N**: Dopamine-Antagonist (Pramipexole) 28; Placebo 27; **Total:** 55 Location: USA Sites: 4
Patient characteristics	Inclusion Criteria: Early (H&Y stages 1 to 3) idiopathic PD without evidence of atypical parkinsonian syndromes, clinically significant cardiovascular or cerebrovascular diseases or other unstable medical conditions Subjects received selegiline (5mg bid) throughout the study period. An anticholinergic agent was also permitted, but not other antiparkinsonian medications were permitted. **Baseline Data:**

	Pramipexole	Placebo
Age, years (SD)	63.5 (12.3)	63.0 (8.8)
% Male	71.4	55.6
PD Duration, years (SD)	2.1 (2.5)	2.4 (2.4)

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<table>
<tr><td></td><td>
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<tr><td>UPDRS Part II baseline score</td><td>10.94</td><td>10.46</td></tr>
<tr><td>UPDRS Part III baseline score</td><td>26.47</td><td>27.43</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Dopamine-Antagonist (Pramipexole): titrated over 6 weeks to a maximum of 1.5 mg t.i.d or the maximum tolerated dose</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow-up</td><td>10 weeks (6 weeks titration</td></tr>
<tr><td>Outcome measures</td><td>UPDRS Factor II Score (change from baseline during maintenance treatment), UPDRS Factor III Score (change from baseline during maintenance treatment), Adverse Events, Orthostatic Hypotension</td></tr>
<tr><td>Effect size</td><td>
<table>
<tr><th></th><th>Pramipexole</th><th>Placebo</th><th>p</th></tr>
<tr><td>UPDRS Factor II Score</td><td>4.84</td><td>2.29</td><td>0.005</td></tr>
<tr><td>UPDRS Factor III Score</td><td>11.96</td><td>8.15</td><td>0.08</td></tr>
<tr><td>Adverse Events</td><td>100%</td><td>100%</td><td>NS</td></tr>
</table>
Notes:
➢ Orthostatic Hypotension: No patient required treatment for orthostatic hypotension or associated symptoms. Differences in incidence of orthostatic hypotension were not significant between the two groups except during one visit (p=0.04).
</td></tr>
<tr><td>Source of funding</td><td>Boehringer Ingelheim Pharmaceuticals, USA.</td></tr>
<tr><td>Additional comments</td><td>➢ Methods of randomisation and allocation concealment not stated
➢ Power calculations not provided
➢ No intention-to-treat analysis
➢ Centre interaction was analysed</td></tr>
<tr><td>NCC CC ID (Ref Man)</td><td>19643</td></tr>
</table>

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Evidence Table **Q TXMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	Shannon KM, Bennett JPJ, Friedman JH. Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. *Neurology* 1997;**49**:724-8.
Study type	A multi-centre double-blind RCT of pramipexole versus placebo in patients with early Parkinson's disease.
Study objective	To assess the efficacy and tolerability of pramipexole in patients with mild to moderate Parkinson's disease who were not receiving levodopa.
Evidence level	1+
Number of patients	N= 335 Parkinson's disease patients N= 164 pramipexole group N= 171 placebo group Location: USA Sites: 18 sites
Patient characteristics	Inclusion criteria: Patients over the age of 25 years with idiopathic Parkinson's disease in Hoehn and Yahr (HY) stages I (unilateral symptoms) to III (bilateral symptoms with impairment of balance) who were not taking levodopa. Up to 180 days of prior levodopa exposure were allowed, although patients had to be levodopa-free for 60 days prior to study entry. Selegiline use was allowed so long as the dose had been stable for 30 days and did not exceed 10mg/d. Randomization to each centre was stratified by selegiline use. Exclusion criteria: Prior or current treatment with direct-acting dopamine agonists. Other restricted medications included dopamine receptor antagonists, catecholamine depleters, amantadine (within 21 days of study entry), amphetamine derivatives and alphamethyldopa. Patients were excluded if they had signs suggestive of atypical or secondary parkinsonism, dementia, psychosis, recent surgery or electroconvulsive therapy, supine systolic blood pressure less than 100mmHg, a greater than 20mm Hg orthostatic drop in systolic blood pressure, or any significant or unstable medical illness. Of the patients entering the trial, 203 (61%) were men and 132 (39%) were women. Their mean age was 62.7 years and mean duration of disease was 1.8 years. About two-thirds in each group were taking selegiline. No further details given of baseline characteristics.
Intervention	Pramipexole: The dose was titrated over a period up to 7 weeks from 0.375mg to a maximum of 4.5mg

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	daily in three divided doses. Patients entered the maintenance phase of the study once they achieved a dose of 4.5mg daily in three divided. Patients entered the maintenance phase of the study once they achieved a dose of 4.5mg daily or once dose-limiting toxicity developed or the investigator determined there had been no further response to two successive dose increases. During the 6 month maintenance phase, they remained on the maximum dose of premipexole achieved during the ascending dose phase. At the end of the maintenance interval the patients entered a 1-week dose reduction phase.
Comparison	Placebo: Identical-appearing placebo administered as for pramipexole.
Length of follow-up	7-week titration phase followed by a 6 months maintenance phase.
Outcome measures	Changes in UPDRS parts II (ADL) and III (motor) scores between baseline and the end of the maintenance period. Change from baseline was defined as the follow-up score minus the baseline score. Secondary outcome variables included changes from baseline in the individual components of the UPFRS, HY stage, and number of days until failure (defined as unsatisfactory benefit or progression of disease to a point requiring additional therapy, such as levodopa).
Effect size	➢ Eighty percent of placebo and 83% of pramiprexole-treated patients completed the study, with 74% of those completing the study reaching the target dose of 4.5mg daily. The mean maintenance dose was 3.8mg. ➢ At the end of the maintenance interval, the UPDRS ADL and motor subscales had decreased significantly compared with baseline in the pramipexole group (mean ADL at baseline 8.2 versus end maintenance 6.4; mean motor at baseline 18.8 versus end maintenance 20.1) and were at about the baseline level in the placebo group (mean ADL at baseline 8.3 versus end maintenance 8.7; mean motor at baseline 18.8 versus end maintenance 20.1) ($p<0.0001$). ➢ Benefit was significant at all other maintenance visits as well (patients were evaluated biweekly during the first 3 months of maintenance and monthly during the last 3 months) ($p \leq 0.0001$). Throughout the maintenance period, the magnitude of benefit ranged from 22 to 29% for ADL and 25 to 31% for motor scores. ➢ Analysis of individual items of the UPDRS showed no preferential effects on any specific aspect of the PD symptom complex (analysis not provided). ➢ Analysis of patient sub-groups including co-treatment with selegiline showed no differences in

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medication benefit related to baseline variables (analysis not provided).

- During the course of the study, potential adverse events were reported in 95% of pramipexole-treated and 91% of placebo treated patients. Of all reported adverse events only nausea, insomnia, constipation, somnolence and visual hallucinations occurred significantly more frequently in the pramipexole-treated patients compared with placebo patients

Most common adverse events (percentage of patients affected)			
	Pramipexole group (%)	Placebo group (%)	Significant P Value
Nausea	39.0	20.5	0.0002
Insomnia	25.6	12.9	0.0034
Constipation	17.7	6.4	0.0021
Somnolence	18.3	8.8	0.015
Fatigue	14.6	8.8	
Orthostatic blood pressure change >20mmHg systolic	9.8	5.6	
Hallucinations Visual Auditory	 9.7 1.8	 2.3 0.0	 0.0048
Peripheral oedema	7.9	3.5	
Asthenia	6.1	2.3	
Vomiting	1.8	4.7	

- Adverse events led to discontinuation of the study medication in 18 pramipexole and 8 placebo treated patients. Most pramipexole-treated patients had multiple reasons for discontinuation, the most common of which were gastrointestinal complaints (10 patients), hallucinations (7 patients)

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	and sleepiness or fatigue (5 patients). ➢ Overall, pramipexole was not associated with significant changes in blood pressure, pulse, EC, or any hematologic or serum chemistry test.
Source of funding	The study was supported by Pharmacia & Upjohn
Additional comments	➢ No information supplied regarding processes used in terms of randomisation, concealment and blinding ➢ Full baseline characteristics of patients not provided ➢ Power calculations provided ➢ Intention-to-treat analysis ➢ No centre comparability
NCC CC ID (Ref Man)	19764

Evidence Table **Q TXMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	D. J. Brooks, R. J. Abbott, A. J. Lees, E. Martignoni, D. V. Philcox, O. Rascol, R. A. Roos, and H. J. Sagar. A placebo-controlled evaluation of ropinirole, a novel D2 agonist, as sole dopaminergic therapy in Parkinson's disease. *Clinical Neuropharmacology* 21 (2):101-107, 1998.
Study type	A multi-centre double-blind RCT of Ropinirole versus placebo of 12 weeks duration in patients with early Parkinson's disease.
Study objective	Comparison of the effect of Ropinirole with placebo in improving Parkinson's disease symptoms, including motor function, and its safety and tolerability in the study population.
Evidence level	1+
Number of patients	N= 63 Parkinson's disease patients N= 41 ropinirole group N= 22 placebo group

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<table>
<tr><td></td><td>Location: UK and Europe (eight sites), South Africa (one site) Sites: 9 sites</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion Criteria: Patients with idiopathic Parkinson's disease (H & Y stages I-IV) who required dopaminergic therapy, and in addition had bradykinesia, and tremor/rigidity were included. Eligible candidates could be previously untreated, on levadopa or dopamine agonists for no longer than 6 months prior to the study, or receiving anticholinergics, amantadine, or selegiline at a stable dose prior to study entry.
Exclusion criteria: Patients outside the age range of 30-80 years, of childbearing potential, or with clinically significant abnormalities on medical history, physical examination or diagnostic testing were excluded. Patients with any symptomatic orthostatic hypotension were ineligible. Therapy with levadopa, dopamine agonists, vasodilators, antiarrythmics, beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, or other antihypertensive agents (except diuretics) were discontinued at least 2 weeks before initial study entry screening. Treatment with domperidone, metoclopramide, or sulpiride was not permitted during the study period.

<table>
<tr><td>Characteristics</td><td>Ropinirole N=41</td><td>Placebo N=22</td></tr>
<tr><td>Age, years, means (range)</td><td>59 (38-74)</td><td>57 (36-72)</td></tr>
<tr><td>Male</td><td>44%</td><td>64%</td></tr>
<tr><td>Female</td><td>56%</td><td>36%</td></tr>
<tr><td>Hoehn and Yahr Stage I and II</td><td>34 (82.9%)</td><td>14 (63.6%)</td></tr>
<tr><td>Hoehn and Yahr Stage III and IV</td><td>7 (17.1%)</td><td>8 (36.4)</td></tr>
<tr><td>Mean Duration of Illness, (range, months)</td><td>28 (4-109)</td><td>26 (5-77)</td></tr>
<tr><td>Mean Height (range, cm)</td><td>167 (150-179)</td><td>169 (150-191)</td></tr>
<tr><td>Mean Weight (range, kg)</td><td>69 (38-102)</td><td>72 (46-98)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Ropinirole: 0.5 mg b.i.d; titrated upward at weekly intervals in increments of 0.5 mg or 1.0 mg b.i.d. to a maximum dose of 5.0 mg b.i.d. Administered twice daily with meals, with first dose between 7 and 9 am and the second 8 hours later. Dosage was adjusted at the discretion of the investigator in response to unacceptable dopaminergic side-effects.</td></tr>
<tr><td>Comparison</td><td>Placebo: Provided as white tablets. No information on dosing or times when medication was administered was reported.</td></tr>
<tr><td>Length of follow-up</td><td>Clinic visits were scheduled for the beginning of each new dosing period, and took place on a weekly basis up to week 4, and thereafter once a fortnight from weeks 5 to 12 of the study period.</td></tr>
<tr><td>Outcome measures</td><td>Progression of disease (UPDRS Total Score), UPDRS Motor Score, Therapeutic Response (Clinician's Global Evaluation Score and Finger Tap Test), Adverse Events, Dropout Rate.</td></tr>
</table>

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Effect size

	Ropinirole N=41	**Placebo N=22**	**Significance**	**Comment**
Disease Progression (UPDRS total score) at end-point	Not reported	Not reported	No significant differences between the treatment groups for UPDRS sub-scores assessing mental abilities, activities of daily living, and H & Y sections.	
UPDRS Motor Score, Mean percentage improvement at endpoint compared to baseline values, ITT	43.4	21	p= 0.018 (95%CI –40.8% to –4.0) Statistically significant difference favours ropinirole.	ANOVA
30% plus reduction in UPDRS Motor Score from baseline to endpoint, percentage patients	71	41	p= 0.021 Significantly superior response in favour of ropinirole.	
Therapeutic Response (CGE score)	Not reported	Not reported	p= 0.008 Statistically significant difference in	Mann-Whitney test

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				favour of ropinirole.	
	Improvement in Therapeutic Response from baseline to endpoint (CGE score)	71% of patients showed marked or mild/ moderate improvement in symptoms	41% of patients showed marked or mild/ moderate improvement in symptoms	p=0.021 Statistically significant difference in favour of ropinirole.	
	Finger Tap Test, mean percentage change from baseline to endpoint	20.9	17.5	Not significant	
	Total Adverse Events, % patients	85.4	68.2	Not significant	
	Nausea, Number of patients (%)	28 (68.3)	2 (9.1)	p<0.001	Chi-squared test
	Somnolence, Number of patients (%)	23 (29.3)	0	p=0.005	Fisher's exact test
	Dizziness, Number of patients (%)	14 (34.1)	2 (9.1)	p=0.0326	Chi-squared test
	Dropout Rate, Number of patients (%)	5 (12.2)	3 (13.6)	Not reported	
	Dropout Rate due to AE's, Number of patients (%)	3 (7.3)	1 (4.5)	Not reported	
	Notes: ➢ Baseline characteristics: No 'marked' differences between the two groups with regard to demographic and clinical characteristics, although the gender proportions for the two groups differed. Four patients in the ropinirole group had taken levadopa prior to the study.				
Source of funding	Not reported				
Additional comments	➢ Methods of blinding used in the study were not reported. ➢ Method of randomisation used in the study was not reported.				

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	➢ Methods of dosing of placebo tablets were not reported. ➢ All patients who were randomly allocated to the study groups and had data from at least one post-dose assessment were included in the ITT. ➢ Efficacy data from the last available visit during the treatment period were carried forward (LOCF) and an endpoint analysis was performed using either ANOVA, chi-squared, or Fisher's exact tests to detect differences between treatment groups, with a value of $p<0.05$ regarded as significant. ➢ More participants in the ropinirole group withdrew from the study due to AE's than in the placebo group, but the numbers of withdrawals in both groups were low. ➢ The study period of only 12 weeks may be insufficient to determine the longer-term efficacy and safety profile of ropinirole, given the potential for its long-term use in patients with early stage Parkinson's Disease. ➢ Small sample size with no power calculations provdided
NCC CC ID (Ref Man)	1977

TxMN2 – section 7.3.2

Evidence Table **TxMN2** What is the effectiveness of dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled early Parkinson's disease?	
Bibliographic reference	Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., & Lang, A. E. 2000, "A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group.[see comment]", *New England Journal of Medicine*, vol. 342, no. 20, pp. 1484-1491.
Study type	RCT, double-blind
Evidence level	1++
Number of patients	N=268 early Parkinson's disease patients

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<table>
<tr><td></td><td>N=179 ropinirole
N=89 levodopa

Location: Europe, Israel, and Canada sites: 30 centres</td></tr>
<tr><td>Patient characteristics</td><td>➢ Clinical diagnosis of Parkinson’s disease
<table>
<tr><th>Characteristics</th><th>Ropinirole</th><th>Levodopa</th></tr>
<tr><td>Age (SD), years</td><td>63 (9)</td><td>63 (9)</td></tr>
<tr><td>Male %</td><td>63.1</td><td>58.4</td></tr>
<tr><td>Selegiline treatment at start of study No. (%)</td><td>81 (45.3)</td><td>39 (43.8)</td></tr>
<tr><td>Prior levodopa treatment for ≤ 6 weeks No. (%)</td><td>26 (14.5)</td><td>7 (7.9)</td></tr>
<tr><td>Duration of disease, months (SD)</td><td>30 (34)</td><td>29 (27)</td></tr>
<tr><td>Hoehn and Yahr stage no. (%)</td><td></td><td></td></tr>
<tr><td>1</td><td>23 (12.8)</td><td>20 (22.5)</td></tr>
<tr><td>1.5</td><td>27 (15.1)</td><td>8 (9.0)</td></tr>
<tr><td>2</td><td>66 (36.9)</td><td>33 (37.1)</td></tr>
<tr><td>2.5</td><td>46 (25.7)</td><td>19 (21.3)</td></tr>
<tr><td>3</td><td>17 (9.5)</td><td>9 (10.1)</td></tr>
<tr><td>UPDRS score- baseline score for ADL (SD)</td><td>8.0 (5.0)</td><td>8.0 (4.6)</td></tr>
<tr><td>UPDRS score- baseline score for motor score (SD)</td><td>21.5 (10.5)</td><td>21.7 (11.3)</td></tr>
</table>
➢</td></tr>
<tr><td>Intervention</td><td>Ropinirole initiated at 0.75 mg/day (0.25 mg 3 times per day) (max dose24 mg/d)</td></tr>
<tr><td>Comparison</td><td>Levodopa-benserazide initiated at 50mg once daily plus placebo twice daily (max dose 1200mg)</td></tr>
<tr><td>Length of follow-up</td><td>5 years</td></tr>
<tr><td>Outcome measures</td><td>Dyskinesia (score of 1 or more on item 32 of UPDRS scale)</td></tr>
<tr><td>Effect size</td><td>➢ Assessments were performed at weekly intervals for the first month, every two weeks for the next two months, then every month up to six months and every two months thereafter
➢ Dose of the medication was adjusted weekly if required with 13 possible increasing dose levels

➢ Reduced risk of dyskinesia for ropinirole group (regardless of levodopa supplementation) hazard ratio 2.82; 95%CI, 1.78 to 4.44, p<0.001) dyskinesia developed in 20% of the ropinirole group compared to 45% in the levodopa group
➢ Before the addition of levodopa supplementation 5% of the ropinirole group and 36% of the levodopa group had dyskinesia</td></tr>
</table>

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	➢ Risk of disabling dyskinesia was significantly lower in ropinirole group, regardless of levodopa supplementation: Hazard ratio for remaining free of disabling dyskinesia in ropinirole group compared to levodopa group 3.02, 95% CI, 1.52 to 6.02; p=0.002 ➢ 8% of ropinirole group and 23% of the levodopa group had disabling dyskinesia ➢ No significant difference in mean scores for activities of daily living throughout study between the two treatment groups (p=0.08) (slight worsening in ropinirole group) ➢ The differences in mean motor scores during the study were significant in favour of the levodopa group (adjusted treatment difference 4.48 points; 95% CI 1.25 to 7.72, p=0.008) ➢ Length of time until 25% of the patients remaining in the study first had an increase in the wearing-off effects was 199 weeks in the ropinirole group and 145 weeks in the levodopa group ➢ The length of time until 25% of the patients remaining in the study first had an increase in freezing while walking was 166 weeks in the ropinirole group and 207 weeks in the levodopa group ➢ 8% of the ropinirole group withdrew from the study early because of lack of efficacy as compared with 6% in levodopa group ➢ Aggravated parkinsonism was responsible for withdrawal of 3% of patients in both groups Adverse events ➢ There was no significant difference in the incidence of neuropsychiatric adverse events between the two groups (p=0.18) ➢ The incidence of hallucinations was higher in the ropinirole group (17%) compared to the levodopa group (6%) ➢ Adverse events caused early withdrawal in 27% of the ropinirole group and 33% of the levodopa group ➢ Two most common adverse side effects were nausea (ropinirole 3% and levodopa 6%) and hallucinations (ropinirole 4% and levodopa 2%) ➢ No other individual adverse events cause greater than 4% or more patients in either group to withdraw ➢ 5/179 (3%) ropinirole patients and 2/89 (2%) levodopa patients dies during the study ➢ No deaths were directly attributed to the medications
Source of Funding	SmithKline Beecham Pharmaceuticals
Additional comments	➢ Aim: to compare the incidence of dyskinesia in patients with early Parkinson's disease in patients who were treated with ropinirole or levodopa ➢ Prior short-term treatment with levodopa or dopamine agonist was limited to a maximum of 6 weeks and had to be discontinued 2 weeks prior to study

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	➢ If symptoms were not adequately controlled by the assigned medication than levodopa could be supplemented in an open-label fashion ➢ Details of randomisation and allocation concealment provided ➢ Patients underwent a single blind placebo run-in period of 7 days to demonstrate 80% compliance with taking study medication ➢ Intention-to-treat analysis ➢ Whether the results were comparable between the 30 sites is not reported
Citation	
NCC CC ID (Ref Man)	2540

Evidence Table **Q TxMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	Holloway RG, Shoulson I, Fahn S, Kieburtz K, Lang A, Marek K *et al*. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Archives of Neurology* 2004;**61**:1044-53.
Study type	4-year follow-up, multi-centre, randomised, double-blind parallel group trial
Evidence level	1++
Study objective	To compare initial treatment with pramipexole vs levodopa in early Parkinson's disease (PD), followed by levodopa supplementation with respect to the development of dopaminergic motor complications, other adverse events, and functional and quality-of-life outcomes.
Number of patients	N=301 patients with early (PD) N=151 patients assigned to pramipexole N=150 assigned to carbidopa/levadopa Location: USA and Canada Sites: 22
Patient characteristics	Patients with early PD who required dopaminergic therapy to treat emerging disability were enrolled between October 1996 and August 1997 and observed until August 2001. ➢ Inclusion criteria: adults ages >30 years who had IPD for less than 7 yrs and required dopaminergic antiparkinsonian therapy at time of enrolment. The 2 groups were similar at baseline in terms of demographic and clinical variables. ➢ Baseline characteristics of patients who completed the trial:

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		PPX (n=83)	LD (n=100)
	Age, years (SD)	61.1 (9.6)	60.8 (9.8)
	No. (%) of male patients	50 (60.2)	68 (68.0)
	Years since diagnosis	1.4 (1.3)	1.8 (1.7)
	No. (%) of patients with prior levodopa use	20 (24.1)	15 (15.0)
	No. (%) of patients with prior selegiline use	14 (16.9)	21 (21.0)
	No. (%) of patients with prior amantadine use	12 (14.5)	15 (15.0)
	No. (%) of patients with prior anticholinergic use	5 (6.0)	6 (6.0)
	Parkinson's disease Quality-of-life Scale	28.2 (9.9)	29.3 (12.2)
	EuroQol visual analogue scale	76.3 (14.3)	79.2 (11.5)
Intervention	0.5 mg 3x daily pramipexole (levodopa placebo). (Dosage was escalated during the first 10 weeks for patients with ongoing disability, thereafter investigators were permitted to add open-label levodopa or other anti-PD medications to treat ongoing or emerging disability)		
Comparison	25/100 mg 3x daily carbidopa/levodopa (pramipexole placebo) (same as above)		
Length of follow-up	Extended follow-up of two years		
Outcome measures	Wearing-off, dyskinesias, on-off fluctuations, and freezing; changed in UPDRS and quality of life scales, adverse events and withdrawal rates		
Effect size	Dosage ➢ 109 (72%) in PPX group required open-label LD compared with 89 (59%) in LD group (hazard ratio, 1.64; 95%CI 1.22 to 2.21; p=0.001) ➢ The mean total daily LD dosage in PPX subjects was 434 ± 498 mg/d (supplemental only) compared with 702 ± 461 mg/d (experimental: 427 ± 112 mg plus supplemental: 274 ± 442 mg) in LD group ➢ Subjects allocated to PPX took an average 2.78 ± 1.1 mg/d by the end of the trial Motor complications ➢ 52% of patients assigned PPX reached primary end point of developing dyskinesias, wearing off, or on-off fluctuations compared with 74% of levodopa group (hazard ratio: 0.48, 95%CI 0.35 to 0.66; p<0.001) ➢ Reduced risk was observed for those subjects assigned to PPX for wearing-off (hazard ratio: 0.68, 95%CI 0.49 to 0.93, p=0.02), dyskinesias (hazard ratio: 0.37, 95%CI 0.25 to 0.56, p<0.001) but not for on-off fluctuations (hazard ratio 064, 95%CI 0.26 to 1.59, p=0.34) ➢ Increased risk of freezing in PPX group v levodopa: (hazard ratio 1.7, 95%CI 1.11 to 2.59, p=0.01) ➢ There was no difference between groups for off-period dystonia (p=0.10)		

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- In the PPX group the majority of complications occurred after initiating open-label levodopa therapy
- Whereas the majority of levodopa group complications occurred prior to open-label supplementation
- The development of dopaminergic complications by treatment group was not significantly influenced by age, sex, years since onset of disease, dosage level, or baseline UPDRS score

Severity of dyskinesias

- At month 48- 12 (13%) of 91 subjects in PPX group indicated presence of dyskinesias and 4 of 12 indicated that dyskinesias were mildly disabling
- In LD group 32 (32%) of 101 subjects indicated the presence of dyskinesias; 6 indicated that dyskinesias were mildly disabling, and 1 that dyskinesias were moderately disabling
- The remainder in both groups indicated no disability form their dyskinesias: 8 in PPX and 25 in LD
- Similar patterns of dyskinesia frequency and disability were seen at month 42 and 45

UPDRS

- The mean improvements in total, motor and ADL UPDRS scores were greater in LD group than PPX
- Mean changes from baseline to month 48

	PPX	LD	Treatment effect (95%CI)	P value
Total UPDRS	-3.2 (17.3)	2.0 (15.4)	-5.9 (-9.6 to –2.1)	0.003
Motor	-1.3 (13.3)	3.4 (12.3)	-4.9 (-7.8 to –1.9)	0.001
ADL	-1.7 (5.4)	-0.5 (4.7)	-1.4 (-2.5 to –0.2)	0.02
Mental	-0.3 (1.6)	-0.8 (1.6)	0.3 (-0.1 to 0.7)	0.10

Quality-of-life

- Total scores on PDQUALIF and EuroQol VAS improved in both groups by approximately 2 units during the first 6 months and then worsened across time at a decay rate of approximately one unit per year
- At 48 months the mean changes were not significant between groups for either score

Adverse events

- More patients in PPX experienced oedema ($p<0.001$, somnolence ($p=0.005$), and cellulites ($p=0.01$)
- Oedema (including peripheral oedema, localised oedema, generalised oedema, facial oedema, tongue oedema, periorbital oedema, and lymphedema) was significant ($p<0.001$) as was peripheral

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	oedema separately (p<0.001) ➢ Urinary frequency (p=0.01) and hernia (p=0.002) were more common in LD group ➢ Somnolence was most commonly developed during the escalation phase in the PPX group as compared with the oedema and cellulites, which tended to occur later in the trial Withdrawals ➢ Of 301 randomised- 68 (45%) of 151 randomised to pramipexole withdrew compared to 50 (33%) of 150 in levodopa group ➢ In PPX group: 11 withdrew because of somnolence, 5 because of oedema, 1 because of both ➢ In LD group: 1 withdrew because of somnolence and none because of oedema ➢ Other reasons for study withdrawal were similar between groups ➢ There were 5 deaths (3 in LD group and 2 in PPX group) all judged to be not related to study drug ➢ Two subjects (one in each group) were lost to follow-up- both occurred after month 38 visit
Source of Funding	Pharmaceutical, non-profit and university
Additional comments	➢ Intention-to-treat analysis ➢ Comparability between sites assessed ➢ Patients were randomised in 1:1 ratio, using computer-generated randomisation plan that included stratification by investigator and blocking ➢ Allocation concealment methods described
Citation	
NCC CC ID (Ref Man)	19842

Evidence Table **Q TXMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	Riopelle RJ, Gawel MJ, Libman I, King DB, McLean DR, Paulseth R *et al*. A double-blind study of bromocriptine and L-dopa in de novo Parkinson's disease. Short-term results. *European Neurology* 1988;**28**:11-4.
Study type	Multicentre double-blind randomised controlled trial
Study objective	Comparison of bromocriptine and L-dopa (as Sinemet) as de novo therapy in Parkinson's disease
Evidence level	1+

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<table>
<tr><td>Number of patients</td><td>N= 81 Parkinson’s disease patients
N= 42 bromocriptine group (Br)
N= 39 L-dopa group (LD)

Location: Canada Sites: 7 sites</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion Criteria: Patients with idiopathic Parkinson’s disease who had not been exposed previously to antiparkinsonism therapy (other than anticholinergics).
<table>
<tr><th>Characteristics</th><th>Br (N=42)</th><th>LD (N=39)</th></tr>
<tr><td>Age, years, Mean(SD)</td><td>66.5 +/- 1.36</td><td>66.2 +/- 1.97</td></tr>
<tr><td>Sex: female/male</td><td>13/29</td><td>19/20</td></tr>
<tr><td>Clinical stage at entry (not ITT)
I
II
III
IV
V</td><td>

4
10
19
5
0</td><td>

11
8
17
2
1</td></tr>
<tr><td>Mean clinical stage</td><td>2.66 +/- 1.2</td><td>2.33 +/- 10</td></tr>
<tr><td>Previous concomitant anticholinergics</td><td>13</td><td>7</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>For the first 3 weeks of treatment, the daily dose of bromocriptine was 5mg. A titration phase lasted a maximum of 15 weeks during which medication dosage was incremented following assessment every 3 weeks until stable improvement or a maximum of 30mg per day of bromocriptine was achieved. Stable improvement was defined as a lack of further improvement when the dose was increased for two consecutive titration visits. This was followed by a maintenance period of 6 weeks duration during which time the dose was held constant.</td></tr>
<tr><td>Comparison</td><td>For the first 3 weeks of treatment, the daily dose of L-dopa was 50mg. A titration phase lasted a maximum of 15 weeks during which medication dosage was incremented following assessment every 3 weeks until stable improvement or a maximum of 300/75 mg per day of Sinemet was achieved. Stable improvement was defined as a lack of further improvement when the dose was increased for two consecutive titration visits. This was followed by a maintenance period of 6 weeks duration during which time the dose was held constant.</td></tr>
<tr><td>Length of follow-up</td><td>23 weeks</td></tr>
<tr><td>Outcome measures</td><td>Clinical status was assessed by Hoehn and Yahr, the Columbia University Scale and the Northwestern</td></tr>
</table>

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<table>
<tr><td></td><td>University Disability Scale (NUDS). Side effects of medications were reported at every visit. At the end of the maintenance period, the patients were classified as responders or nonresponders based upon clinical response at the tolerated or maximal dose of medication.</td></tr>
<tr><td>Effect size</td><td>

Four patients on bromocriptine dropped out of the study. These patients left the study before the dose was incremented to 10mg per day at the end of the first 3 weeks of the 15 week titration phase.
At the end of the 23 weeks, the bromocriptine group patients were taking a dose of 26 +/- 1.2mg (mean +/- SEM), with the 32 responders taking 25 +/- 1.4mg. The 39 L-dopa group patients were taking a dose of 262.8 +/- 10mg of L-dopa with the 31 responders taking 261.3 +/- 11.5mg.
Intragroup improvements from baseline are shown in the table below. Week 0 versus week 23 was significant at if p was </= 0.0001 unless indicated.

<table>
<tr><td>Intragroup improvement, %</td><td>Bromocriptine</td><td>L-dopa</td></tr>
<tr><td>Hochn and Yahr clinical stage</td><td>20</td><td>16</td></tr>
<tr><td>Columbia University Scale</td><td></td><td></td></tr>
<tr><td>Cardinal signs
Tremor
Rigidity
Bradykinesia</td><td>
59
66
49</td><td>
63
57
47</td></tr>
<tr><td>Motor and posture
Arising
Posture
Postural stability
Gait</td><td>
65
56
61
57</td><td>
47 (p</= 0.001)
48
54
45</td></tr>
</table>
</td></tr>
</table>

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	<table><tr><td>Overall improvement</td><td>61</td><td>55</td></tr><tr><td>NUDS</td><td>38</td><td>37</td></tr></table> ➢ No significant differences were found between the two groups for clinical stage overall assessments with the Colombia University Scale and NUDS or cardinal signs as scored using the Colombia University Scale. ➢ For the 77 patients completing the 23 weeks of the study, dyskinesias and fluctuations in disbility were absent, side effects were tolerable and laboratory assessments did not necessitate discontinuation.
Source of funding	The study was supported by Sandoz (Canada),
Additional comments	➢ No ITT analysis. ➢ No details given of methods for randomisation, concealment and blinding (although it is reported that identical capsules were used), leaving a total of 79 patients completing the trial.
NCC CC ID (Ref Man)	1048

Evidence Table **Q TXMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	Rinne UK, Bracco F, Chouza C, Dupont E, Gershanik O, Masso JFM et al. Early treatment of Parkinson's disease with Cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. Drugs 1998;55:23-3TxCM 20.
Study type	Randomised double-blind levadopa-controlled multi-centre RCT
Study objective	Comparison of Dopamine-Antagonist (Cabergoline) with Levadopa in terms of Prevalence of Motor Complications, Risk of Motor Complications, Risk of Motor Complications (all)
Evidence level	1++
Number of patients	N= 412 Parkionson's disease patients

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<table>
<tr><td></td><td>N= 208 dopamine-agonist group
N= 204 levodopa group

Location: Europe and South America Sites: 8 sites</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion Criteria: patients with recently diagnosed PD (H&Y stage 1-3) with functional disability justifying pharmacological intervention.
Exclusion criteria: patients previously treated with levadopa, dopamine antagonists or selegiline.
Any use of amantadine or anticholinergics was discontinued 4 weeks before the study began
<table>
<tr><td>Characteristics</td><td>Cabergoline</td><td>Levadopa</td></tr>
<tr><td>Age, years (SD) at inclusion</td><td>60.5 (9.2)</td><td>62.6 (9.1)</td></tr>
<tr><td>Age, years (SD) at PD onset</td><td>58.6 (9.5)</td><td>60.6 (9.3)</td></tr>
<tr><td>% Male</td><td>45.7</td><td>51.5</td></tr>
<tr><td>Mean Hoehn and Yahr Stage (SD)</td><td>1.9 (0.6)</td><td>2.0 (0.5)</td></tr>
<tr><td>Mean UPDRS motor score (SD)</td><td>27.5 (14.6)</td><td>29.1 (14.1)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Dopamine-Antagonist (Cabergoline): 3mg/day titrated over 24-week period, with additional levadopa when required.</td></tr>
<tr><td>Comparison</td><td>Levadopa: 500mg/day titrated over 24-week period, with additional levadopa when required.</td></tr>
<tr><td>Length of follow-up</td><td>Median treatment period of 1,348 days (treatment) and 1,344 days (control)</td></tr>
<tr><td>Outcome measures</td><td>Prevalence of Motor Complications, Risk of Motor Complications, Risk of Motor Complications (all), Cumulative Levadopa at Endpoint, UPDRS Factor II/III, Adverse Events, Withdrawal Rate</td></tr>
<tr><td>Effect size</td><td>
<table>
<tr><th></th><th>Cabergoline</th><th>Levadopa</th><th>Significance</th><th>Comment</th></tr>
<tr><td>Prevalence of Motor Complications</td><td>47</td><td>70</td><td>Not reported</td><td></td></tr>
<tr><td>Risk of Motor Complications</td><td>Not reported</td><td>Not reported</td><td>p<0.02 (in favour of Cabergoline)</td><td>log-rank test</td></tr>
<tr><td>Risk of Dyskinesias</td><td>Not reported</td><td>Not reported</td><td>"borderline significance"</td><td>direction of effect not reported</td></tr>
<tr><td>Risk of End-of-dose Failures</td><td>Not reported</td><td>Not reported</td><td>"highly significant"</td><td>direction of effect not</td></tr>
</table></td></tr>
</table>

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					reported
	Adverse Events (all)	83%	82%	Not reported	
	Adverse Events (major)	31%	25%	Not reported	
	Withdrawal Rate	16%	13%	Not reported	
	Cumulative Levadopa at Endpoint	194g	421g	Not reported	
	UPDRS Factor III	22 to 23%	30%	Not reported	

Notes:

- Risk of Motor Complications: Patients in the Cabergoline group who required additional Levadopa were at the "same risk" of developing motor complications as those patients in the Levadopa group
- UPDRS Factor III: Score decreased in both groups in the first year, after which a gradual increase occurred.
- UPDRS Factor II: The two groups were similar in terms of UPDRS Factor II, which decreased in the first year of treatment and rose thereafter.

Source of funding	Not reported
Additional comments	➢ Methods of randomisation and allocation concealment reported in subsequent publication ID19850 ➢ Power calculations provided in subsequent publication ID 19850 ➢ Intention-to-treat analysis not stated ➢ It is unclear how missing data due to withdrawal was addressed in the survival analysis. ➢ Data on the endpoint survival analysis was only given graphically. Estimates of effect for the risk of developing motor complications are 0.6 for levadopa and 0.35 for cabergoline.
NCC CC ID (Ref Man)	19605

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Evidence Table **TxMN2** Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Hely, M. A., Morris, J. G., Traficante, R., Reid, W. G., O'Sullivan, D. J., & Williamson, P. M. 1999, "The sydney multicentre study of Parkinson's disease: progression and mortality at 10 years", *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 67, no. 3, pp. 300-307.
Study type	Randomised, levodopa-controlled, double-blind
Evidence level	1+
Study objective	To compare mortality in the study's cohort of patients on either bromocriptine or levodopa therapy, to see if bromocriptine lessens mortality.
Number of patients	N=126 Parkinson's disease patients Location: Australia Sites: multi-centre
Patient characteristics	➢ Patients were recruited with Hoehn and Yahr stage I to III ➢ 70 men and 56 women ➢ (More detail in original study published of the first 5 years- included in systematic review ID24)
Intervention	Low dose bromocriptine (≤ 30g/day)
Comparison	Low dose levodopa-carbidopa (≤600/150 mg/day)
Length of follow-up	10-13 years
Outcome measures	Mortality, Hoehn and Yahr stages, adverse events
Effect size	➢ 4 patients were lost to follow-up (n=122) ➢ Of the 10 patients who did not complete first 6 months of the study (phase I), 8 were accounted for at 10 years by telephone or personal examination ➢ 50 (38%) of patients (34 men, 16 women) died during the first 10 years ➢ 63 (48%) had died by the last follow-up (maximum 13 years) ➢ The standardized mortality ratio (SMR) for the whole cohort was 1.58 (95%CI, 1.21 to 2.02) indicating a higher rate of death than the age-matched population (p<0.001) Bromocriptine ➢ At 10 years there were 29/63 (46%) deaths in the bromocriptine-treatment group patients ➢ At max. 13 years there were 33/63 (52%) deaths in this group ➢ The mean time of taking bromocriptine was 22.4 months ➢ The mean time from ceasing bromocriptine until death was 63.7 months

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	Levodopa ➢ There were 21/67 (31%) deaths in the levodopa-carbidopa treatment group ➢ At max. 13 years there were 30/67 (45%) deaths Progression of modified Columbia Rating Score ➢ Randomisation to bromocriptine or continued use of bromocriptine for 1 year or more did not influence deterioration in Columbia score by 10 or 20 points Progression of Hoehn and Yahr stages ➢ There was no significant difference between the groups for progression through Hoehn and Yahr stages Adverse events (reasons for stopping bromocriptine therapy: ➢ Confusion (11), postural hypotension (6), lack of efficacy (2), peripheral oedema, Raynaud's phenomenon, and abnormal liver function (1 each).
Source of Funding	Initial study (first 5 years) was funding Pharmaceutical company. Continuation of study (present study) follow-up was funded was administered by a non-profit organization and local hospital.
Additional comments	➢ 10 year follow-up of study included in systematic review which included 5-year follow-up ➢ Few patients remained on bromocriptine alone for more than 2years ➢ Patients recruited between 1984 and 1987 ➢ Patients considered to have atypical parkinsonism before 5 years were excluded from analysis ➢ Only two patients were on bromocriptine monotherapy when they died, the other patients were receiving levodopa-carbidopa alone or in combination with bromocriptine ➢ Author's conclusions: they were unable to show any protective effect from bromocriptine on longevity or disease progression in new patients with Parkinson's disease ➢ No detail on randomisation methods (probably included 5 year study) ➢ Allocation concealment and blinding of investigators not detailed (probably included 5-year publication) ➢ Intention-to-treat poorly addressed ➢ Comparability of results from different sites not addressed
Citation	
NCC CC ID (Ref Man)	2184

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Evidence Table
TxMN2
Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?

Bibliographic reference	Hely MA, Morris JG, Reid WG, O'Sullivan DJ, Williamson PM, Rail D *et al*. The Sydney Multicentre Study of Parkinson's disease: a randomised, prospective five year study comparing low dose bromocriptine with low dose levodopa-carbidopa. *Journal of Neurology, Neurosurgery & Psychiatry* 1994;**57**:903-10.
Study type	Randomised, double-blind, parallel group study
Evidence level	1+
Study objective	To present data on response to low dose treatment and frequency of motor side effects during 5 years follow-up.
Number of patients	N=126 untreated PD patients N= 62 bromocriptine (Br) patients N=64 levodopa (LD) patients Location: sites:
Patient characteristics	Patients aged 37 to 79 were recruited. There were 70 men and 56 women. There were no statistically significant differences between the two treatment groups.

	Br (n=62)	LD (n=64)
Age at entry, yr, mean (SD)	62 (9.8)	62 (9.8)
Duration of disease before trial (mo), mean (SD)	22 (18.0)	25 (22.8)
Modified Columbia Score, mean (SD)	18.3 (9.0)	15.3 (6.8)
Modified NUDS score, mean (SD)	4.4 (3.4)	3.3 (2.2)
Dementia, no (%))	12 (19)	7 (11)
Gait disorder, no (%)	11 (18)	5 (8)

Intervention	Bromocriptine (≤ 30 mg/d). The mean dose was 32 mg/d (range 7.35 to 60)
Comparison	Levodopa/carbidopa (≤ 600/150 mg/d)
Length of follow-up	5 years
Outcome measures	Columbia score, Northwestern University Disability Score (NUDS), dyskinesia, dystonia, end-of-dose failure, exclusions and withdrawals
Effect size	➢ The median time on bromocriptine as monotherapy was 12.1 mo (95%CI 8.5 to 17.7 months)- whereas the median time on LD alone was 52.3 mo (95%CI 46.6 to ….)

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	➢ No patient was able to remain on bromocriptine monotherapy alone for 5 years Columbia score ➢ The actual numbers of patients who improved or deteriorated shows a similar trend for each treatment group: LD was significantly better than BR at one year (p=0.009) ➢ At 5 years the Br+LD group were improved and had less deterioration than LD group (p=0.047) NUDS scores ➢ Followed similar pattern to changes in modified Columbia score for each of the groups Dyskinesia ➢ 52 patients developed dyskinesia by 5 years ➢ 35 were from LD group and 17 from Br group ➢ Difference between the groups as randomised was significant at 5 years (p=0.002) Dystonia ➢ There were 31 patients with foot dystonia: 10 randomised to Br of whom 9 received LD before dystonia developed and 21 randomised to LD (p<0.05)- overall dystonia was more of a problem in patients randomised to LD (mean 411 mg/d)- even allowing for subsequent introduction of higher doses of LD (mean 633 mg/d) to patients on BR (p=0.005) End-of-dose failure ➢ 23/62 (37%) from Br group (20/27) after addition of LD and 26/64 (41%) patients from LD group developed end-of-dose failure at 5 years ➢ 42/49 (86%) was graded as mild ➢ Only one patient developed on-off phenomenon Exclusions/ withdrawals ➢ 149 patients were recruited into the study ➢ Ten patients were excluded after the initial assessment period for atypical PD ➢ 3 further patients were excluded later on for atypical PD ➢ Ten patients failed to complete the dose titration phase ➢ Lack of efficacy was the main reason for patients failing to remain on Br alone ➢ Other reasons for withdrawal from Br: confusion and hallucinations (10), postural hypotension (4), and nausea (4) ➢ These side effects generally occurred within the first year of treatment ➢ LD was substituted for Br in these patients- forming a BR to LD group ➢ 7/10 who became confused on Br also became confused on low dose LD- of these 7 satisfied the criteria for dementia ➢ main reasons for code-breaking in LD group was dyskinesia and dystonia occurrence

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	➢ low dose LD proved ineffective in 8 patients who had rapidly progressive disease (mean 475 mg/d, range 300-600 mg/d) ➢ a further 6 LD patients experienced confusion and hallucinations and 4 LD patients had nausea
Source of Funding	Pharmaceutical
Additional comments	➢ Recruitment, diagnosis, stratification, randomisation, dose titration and code-breaking reported in previous publication ➢ No power calculations, methods of randomisation or allocation concealment reported here ➢ Not intention-to-treat analysis
Citation	
NCC CC ID (Ref Man)	2185

Evidence Table **TxMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	Herskovits E, Yorio A, Leston J. Long term bromocriptine treatment in de novo parkinsonian patients. *Medicina* 1988;**48**:345-50.
Study type	Randomised, single blind, parallel study
Study objective	To compare long-term results using different schemes of therapy in previously untreated parkinsonian patients: bromocriptine, levodopa/carbidopa and bromocriptine plus levodopa/carbidopa
Evidence level	**+**
Number of patients	N=86 Parkinson's disease (PD) patients N= 31 bromocriptine patients (Br) N=29 levodopa patients (LD) N=26 bromocriptine/levodopa patients (Br/LD) combination Location: Argentina Sites: single
Patient characteristics	Patients aged 40 to 83 years (mean 67.5). There were 52 females and 34 males. Patients had been recently diagnosed and they had not received any prior anti-PD medication. Patients with significant cardiovascular, pulmonary, hepatic or renal impairment were excluded. The three groups were

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	homogenous for clinical signs, stage and disability levels.
Intervention	Br and Br/LD given at optimal dose (defined as minimal dose that produces satisfactory clinical response with the least adverse events). Br was initiated at a dose of 1.25mg and increased by doses of 1.25mg.
Comparison	LD given at optimal dose. Levodopa/carbidopa was started at 125/12.5 mg and then increased 125/12.5.
Length of follow-up	18-45 months (mean 31 months)
Outcome measures	Medication, doses, efficacy measures (Hoehn and Yahr and Webster Scores), adverse events and withdrawal rates
Effect size	Medication ➢ Br group- all patients initially responded to treatment but therapeutic effect decreased by 50% (14 patients) from 7th month onwards ➢ These patients had to undergo combined therapy in order to maintain improvement ➢ The mean starting time for LD treatment in BR group was 16.3 ± 6.4 months ranging from 7-28 mo Dose ➢ The mean dose of Br for patients was in whom no additional LD was required was 12.6 ± 3.2 mg ➢ The dose of Br for patients requiring LD was similar 12.9± 3.3 mg ➢ The dose of additional LD was 401.8 ± 140.2mg ➢ In groups LD and Br/LD the mean LD dose was higher (LD: 556.1 ± 228 mg, Br/LD: 572.1 ± 226.8) ➢ This may represent a tendency to lower LD dose in the combination group Efficacy ➢ At the beginning of the trial patients in the three groups had similar Hoehn and Yahr stages (II to III) and Webster scores of disability (mild to moderate) ➢ At the end of the trial there was a significant difference both in the clinical stage ($p<0.01$) and level of disability ($p<0.01$) between the initial and last evaluation- which was similar in all 3 groups ➢ The improvement achieved was about 50% in all groups and it was observed in all categories assessed-being similar for the three cardinal signs as well as for the different kinds of disabilities ➢ There were no significant differences in the results between the three treatments ➢ Comparing the effects of BR with and without the addition of levodopa/carbidopa- there were no significant differences between the scores at final visit Adverse events ➢ Br group showed fewer events than LD and Br/LD ➢ In two cases gastric intolerance and allergic nodular vasculitis were important enough to discontinue medication ➢ Dyskinesia appeared in one patient on a low dose- since no increment of the dose was advisable the

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	patient showed less improvement ➢ Nausea and vomiting were transient ➢ At higher doses: confusion, hallucinations, extrasystoles and hypotension were observed ➢ The levodopa groups had more secondary effects and these were usually minimised by reducing the dose Withdrawal rates ➢ 3 patients withdrew due to intolerance, two from Br group and one from LD group ➢ These patients were not included in the final analysis
Source of funding	Not stated
Additional comments	➢ Blinded rater ➢ Lack of patient characteristics ➢ No methods of randomisation or allocation concealment ➢ No power calculations provided ➢ Intention-to-treat analysis not stated
NCC CC ID (Ref Man)	2193

Evidence Table **Q TxMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	J. Kulisevsky, C. Garcia-Sanchez, M. L. Berthier, M. Barbanoj, B. Pascual-Sedano, A. Gironell, and A. Estevez-Gonzalez. Chronic effects of dopaminergic replacement on cognitive function in Parkinson's disease: a two-year follow-up study of previously untreated patients. *Movement Disorders* 15 (4): 613-626, 2000.
Study type	An open label RCT with blind neuropsychologic evaluation
Evidence level	1+
Study objective	Comparison of the effect of Levadopa versus Pergolide in producing sustainable improvement in Parkinson's disease symptoms, including cognitive status and motor function in patients with early-stage Parkinson's disease.
Number of patients	N= 20 Parkinson's disease patients

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<table>
<tr><td></td><td>N= 10 levadopa group
N= 10 pergolide group

Location: Spain Sites: 1 site</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion Criteria: Newly diagnosed patients who fulfilled the London Brain Bank Criteria for idiopathic Parkinson's Disease and who had never received antiparkinsonian medication. This included subjects with low mood possibly associated with Parkinson's disease, but without meeting DSM-IV diagnostic criteria for major depression or dysthymia.
Exclusion criteria: Patients with a Mini Mental State Examination score of less than 24, history of major psychiatric disorders, psychoactive medication, alcoholism, stroke, neurosurgical operation, or any other condition known to impair mental status other than PD.
<table>
<tr><th>Characteristics, mean ± SD</th><th>Pergolide N=10</th><th>Levadopa N=10</th></tr>
<tr><td>Age, years</td><td>63.7 ± 10.5</td><td>67.3 ± 7.5</td></tr>
<tr><td>Male</td><td>4</td><td>3</td></tr>
<tr><td>Female</td><td>6</td><td>7</td></tr>
<tr><td>Education, years</td><td>6.7 ± 6.4</td><td>5.2 ± 4.1</td></tr>
<tr><td>Duration of Illness Prior to Treatment, months</td><td>14.1 ± 7.3</td><td>14.4 ± 6.2</td></tr>
<tr><td>Hoehn and Yahr</td><td>1.5 ± 0.6</td><td>1.8 ± 0.5</td></tr>
<tr><td>Predominant Symptom (tremor/akinetic rigid)</td><td>8/2</td><td>8/2</td></tr>
<tr><td>Side of Maximal Involvement (right/left)</td><td>4/6</td><td>5/5</td></tr>
<tr><td>Beck Depression Inventory</td><td>10.1 ± 7.9</td><td>8.5 ± 5.9</td></tr>
</table>
* Fisher's exact test</td></tr>
<tr><td>Intervention</td><td>Pergolide (PG): Dosage was progressively increased every 3 days up to 1.5 mg/day for all patients, with patients receiving 3 daily doses of the medication. Thereafter doses were titrated on an individual basis by an examiner blinded to the treatment regimen who recommended a dosage modification to a non-blinded examiner.

Pergolide plus levodopa (PG/LD): Patients received pergolide as monotherapy until the day after the 6-month neuropsychological evaluation when levadopa was added.</td></tr>
<tr><td>Comparison</td><td>Levodopa: Dosage was progressively increased every 3 days up to 300mg/day for all patients, with patients receiving 3 daily doses of the medication. Patients received levadopa monotherapy for the entire length of the study.</td></tr>
<tr><td>Length of follow-up</td><td>Patients received a BDI and a comprehensive neuropsychological study at 3, 6, 12, 18, and 24 months after treatment initiation. Safety assessments were performed at all programmed monthly visits.</td></tr>
<tr><td>Outcome measures</td><td>Disease Progression (UPDRS Total Score), UPDRS Motor Score, Motor Speed (Simple Reaction Time</td></tr>
</table>

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	and Finger Tap Test), Attention and Short-Term Memory (Span Performance), Verbal Learning (RAVLT), Visuospatial and Visuoconstructive abilities and Long-Term Visual Memory (RCFT), Frontal Tasks (Letter Fluency, Category Fluency, Luria Rhythm, Luria Motor, Arithmetic), Adverse Events.
Effect size	➢ Disease Progression (UPDRS Total Score): Addition of levadopa in the pergolide group after the 6-month examination did not detract from both groups obtaining a comparable symptomatic benefit. ➢ Motor Speed (Simple Reaction Time and Finger Tapping): No significant differences in time, treatment or treatment-by-time in motor speed tests between baseline and study endpoint. The addition of levadopa to the pergolide group after 6 months produced no significant changes. ➢ Attention and Short-Term Memory (Span Performance): No significant differences in time, treatment or treatment-by-time in patients' span performance for digits (Digit-Span) or visual designs (BVRT) between baseline and study endpoint. The addition of levadopa to the pergolide group after 6 months produced no significant changes. ➢ Verbal Learning (RAVLT): No treatment or treatment-by-time differences were observed. The addition of levadopa to the pergolide group after 6 months produced no significant changes. ➢ Visuospatial and Visuoconstructive abilities and Long-Term Visual Memory (RCFT): All measures of the RCFT decreased at the 18 and 24 month evaluations with improvement on visuospatial and visuoconstructive abilities (copy) becoming non-significant with respect to baseline. When comparing performance on the visuoconstructive ability test at 12 versus 6 months, this had declined in patients in the levadopa only group, whereas the introduction of levadopa in the pergolide group was associated with additional improvement. ➢ Frontal Tasks (Letter and Category fluency): Both letter and category fluency improvement became non-significant with respect to baseline at the study endpoint evaluation, with a t test comparison revealing a significant worsening at the 24 month versus the 18 month evaluation. ➢ Frontal Tasks (Stroop's Paradigm): No significant time, treatment, or treatment-by-time differences were reported from baseline to study endpoint. ➢ Frontal Tasks (Luria Rhythm and Motor tests, Arithmetic): While Luria Motor and Arithmetic tests revealed significant differences in performance for both groups between baseline and study endpoint, performance on the Luria Rhythm test became non-significant with respect to baseline at the 18 and 24 month evaluations, with a statistically significant worsening in performance at 24 months. Patients in the pergolide group showed improvement in arithmetic performance after the addition of levadopa at 6 months compared to the levadopa monotherapy group, which exhibited a decline in performance after 6 months. ➢ Dropout: All 20 patients included in the study completed the planned assessments for the first 12

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	months, while one patient was lost to follow-up at 18 months.
Source of Funding	The study was partially supported by a grant from Fundacio la Marato de TV3.
Additional comments	➢ The study was open-label with respect to patients' knowledge of treatment received. ➢ A board-certified neuropsychologist blind to the treatment regimen administered all neuropsychological tests. ➢ Method of randomisation used in the study was not reported. ➢ The authors claim that although small, the sample is 'probably' representative of Parkinson's disease patients ➢ Lack of power calculations
Citation	2287
NCC CC ID (Ref Man)	

Evidence Table **TxMN2** Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Lees, A. J., Katzenschlager, R., Head, J., & Ben Shlomo, Y. 2001, "Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial.[see comment]", *Neurology*, vol. 57, no. 9, pp. 1687-1694.
Study type	Randomised open trial
Evidence level	1+
Study Objective	To report the results of a ten-year follow-up of bromocriptine, L-dopa and L-dopa/selegiline treated PD patients
Number of patients	N=782 de novo PD patients N=249 levodopa alone group N=271 levodopa/selegiline N=262 bromocriptine Location: United Kingdom Sites: 93
Patient characteristics	Inclusion criteria:

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<table>
<tr><td></td><td>All patients fulfilled the criteria for a clinical diagnosis of PD
Untreated patients required dopaminergic treatment were included
Patients with co morbid conditions could be included
Patients on anticholinergics and amantadine were included
<u>Exclusion criteria</u>:
Patients who were known to have failed to respond to dopaminergic drugs
Patients with incapacitating cognitive impairment
<u>Characteristics</u>:
Baseline characteristics of three treatment groups were similar in age, sex, duration of PD, disability scores</td></tr>
<tr><td>Intervention</td><td>Bromocriptine alone (arm 3)</td></tr>
<tr><td>Comparison</td><td>Levodopa and decarboxylase inhibitor (arm 1); Levodopa/decarboxylase inhibitor & selegiline (arm 2)</td></tr>
<tr><td>Length of follow-up</td><td>10 years</td></tr>
<tr><td>Outcome measures</td><td>Mortality and disability</td></tr>
<tr><td>Effect size</td><td>➢ 49 patients (16 arm1, 16 arm2, 17 arm3) had diagnosis revised during course of trial
Mortality
➢ Average follow-up 9.2 years
➢ Standardized mortality ratio (SMR) for patients in the study compared to the general population of United Kingdom was 1.78 (95%CI, 1.62 to 1.96)
➢ Statistical significance of difference among 3 arms in first 5 years of study; p=0.27
➢ Hazard ratio of bromocriptine versus levodopa was 1.15 (95%CI, 0.90 to 1.47)
➢ After adjustment for age, sex, duration of disease before randomisation, hazard ratio 1.12
➢ Hazard ratio for arms 2 vs. 3: 1.06 (95%CI, 0.84 to 1.34)
➢ Hazard ratio for arms 2 vs. 1: 1.22 (95%CI, 0.95 to 1.55)
➢ Hazard ratio (mortality attributed to PD arm 3 vs. arm 1) was 1.63 (95%CI, 1.0 to 2.7)

Disability
Table: difference (95%CI) in mean Webster disability scores
<table>
<tr><td>Time in trials</td><td>Arm 3 vs. 1</td><td>Arm 3 vs. 2</td><td>Arm 1 vs. 2</td></tr>
<tr><td>Year 1, n=670</td><td>0.9 (0.3 to 1.5)</td><td>1.3 (0.6 to 1.9)</td><td>0.3 (-0.3 to 1.0)</td></tr>
<tr><td>Year 3, n=688</td><td>1.3 (0.4 to 2.2)</td><td>1.4 (0.6 to 2.3)</td><td>0.2 (-0.7 to 1.1)</td></tr>
<tr><td>Year 5, n=573</td><td>1.0 (-0.2 to 2.1)</td><td>1.4 (0.3 to 2.5)</td><td>0.4 (-0.7 to 1.6)</td></tr>
<tr><td>Year 9, n=270</td><td>0.2 (-1.5 to 1.5)</td><td>1.0 (0.6 to 2.5)</td><td>0.8 (-0.8 to 2.4)</td></tr>
</table></td></tr>
</table>

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	➢ Adjusted for baseline disability score. A positive difference indicates worse average disability in arm 1. ➢ Difference in disability between arm 1 and 3 diminishes after 5th year of follow-up ➢ The 'final' disability scores based on the average of the most recent two ratings before death or the end of 1999- adjusted difference of 0.8 (95%CI 0.3 to 1.9) between arm 1 and 3 ➢ Similar findings obtained from an analysis of Northwestern University disability scale ➢ On average patients in bromocriptine arm returned to baseline disability after 3 years, 1 year before levodopa group (arm 1) ➢ Significantly lower incidence of dyskinesia in the group initially randomised to bromocriptine than levodopa (arm 1) (rate ratio: 0.73 (95%CI 0.57 to 0.93) ➢ Incidence rate for dystonia was slightly lower in the bromocriptine group (rate ratio: 0.84, 95%CI 0.65 to 1.09, p=0.17) ➢ Slightly lower incidence of on/off fluctuations in the group initially randomised to bromocriptine (difference was not significant; 0.90 (95%CI 0.72 to 1.13)
Source of Funding	Non-profit organization and pharmaceutical company
Additional comments	➢ Randomisation was carried out by independent coordinator methods listed ➢ Intention-to-treat analysis ➢ No blinding of investigators –possible bias in result interpretation ➢ If patents did not improve they could be re-randomised to another group ➢ Additional antiparkinsonian drugs were allowed during the trial ➢ Comparability of results from different sites not stated ➢ Trial took place between 1985 to 1990- where selegiline arm was terminated
Citation	
NCC CC ID (Ref Man)	2309

Evidence Table **TxMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	Weiner WJ, Factor SA, Sanchez-Ramos JR, Singer C, Sheldon C, Cornelius L *et al*. Early combination therapy (bromocriptine and levodopa) does not prevent motor fluctuations in Parkinson's disease.[see comment]. *Neurology* 1993;**43**:21-7.

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<table>
<tr><td>Study type</td><td>Double-blind, randomised, parallel group study</td></tr>
<tr><td>Study objective</td><td>To compare the effects of early combination therapy, LD monotherapy, and Br monotherapy on PD patients previously untreated with dopaminergic medications, with particular attention to late complications and efficacy.</td></tr>
<tr><td>Evidence level</td><td>+</td></tr>
<tr><td>Number of patients</td><td>N=25 PD patients
N=8 bromocriptine monotherapy (Br)
N=10 levodopa monotherapy (LD)
N=7 levodopa plus bromocriptine combination therapy (Br/LD)

Location: USA Sites</td></tr>
<tr><td>Patient characteristics</td><td>None of the patients had been previously treated with bromocriptine or levodopa. 12 were receiving anticholinergic medications, and 5 were receiving amantadine. These medications were continued if necessary.
<table>
<tr><th></th><th>Br</th><th>LD</th><th>BR/LD</th></tr>
<tr><td>Mean age</td><td>60.3</td><td>65.7</td><td>57.6</td></tr>
<tr><td>Mean duration of PD (mo)</td><td>34</td><td>11.6</td><td>13.9</td></tr>
<tr><td>Hoehn and Yahr stage</td><td>2.0</td><td>2.1</td><td>2.4</td></tr>
<tr><td>Mean duration in study</td><td>43.7</td><td>38.4</td><td>40.9</td></tr>
<tr><td>Motor fluctuations n, (%)</td><td>1 (17)</td><td>3 (33)</td><td>5 (71)</td></tr>
<tr><td>Dystonia</td><td>2 (33) *</td><td>9 (100)</td><td>5 (71)</td></tr>
<tr><td>Chorea</td><td>1 (17)</td><td>5 (56)</td><td>4 (57)</td></tr>
<tr><td>Freezing</td><td>5 (83)</td><td>2 (22)</td><td>4 (57)</td></tr>
</table>
* Statistically significant difference (p<0.02)
No significant differences for age or PD baseline measures. A longer disease duration in Br group because one patient had PD for 105 months. Other patients in this group had a range similar to the other two groups (difference was not significant).</td></tr>
<tr><td>Intervention</td><td>Br initiated at 1.25 mg per day and could be advanced to 30 mg per day
Br/LD: patients started on 2.5 mg Br- the next dose was the addition of carbidopa/levodopa 25/100 which occurred after 2 weeks. Gradually increased to max Br dose of 18 mg and carbidopa/levodopa dose of 300/1200</td></tr>
<tr><td>Comparison</td><td>LD: carbidopa/levodopa initiated at 12.5/50 and could be increased to a max dose of 300/1200</td></tr>
</table>

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Length of follow-up	Study duration of 4 years
Outcome measures	Doses, Motor scores, activities of daily living, complications scores, adverse events, withdrawal rates
Effect size	Doses ➢ Br dose ranged from 6.25 to 30 mg- with a mean of 18 mg per day at the end of the study ➢ LD monotherapy dose ranged from 150-700 mg, with a mean of 417 mg per day at end of study ➢ Br/LD group the LD dose ranged from 200 to 800 mg (mean, 386 mg per day) and the Br dose ranged from 9 to 20 mg (mean, 14 mg per day) ➢ Comparison of LD doses in LD monotherapy and combination group were not significantly different ➢ Comparison of Br doses also did not show significant difference Motor examination (modified Columbia rating scale) ➢ Br group score decreased maximally by one month- improvement not significant compared to baseline ➢ Motor scores then became progressively worse despite increasing doses and exceeded baseline scores after 15 mo ➢ At no time did Br monotherapy result in significant improvement of motor examination scores ➢ LD group achieved statistically significant improvement at 3 months ($p<0.03$) and peak improvement at 6 months ($p<0.0001$) ➢ Motor examination score remained below baseline throughout study ➢ Br/LD group reached peak improvement in motor examination score at 3 months- but degree of improvement never reached significance compared with baseline ➢ Three groups tended to parallel each other: Br group had worst motor examinations score and LD group the best with Br/LD inbetween ➢ No significant difference was found between the 3 groups at any time Activities of daily living ➢ All 3 groups reached maximal improvement at 6 months ➢ The degree of improvement within each group was significant ($p<0.02$ for Br, $p=0.007$ for group LD, $p=0.05$ for Br/LD) ➢ There were no differences between the groups throughout the study- with the exception of scoring at 48 months (LD group had lowest score $p<0.03$) Complications scores ➢ No difference was seen between the three groups for motor fluctuations, dystonia, freezing and chorea ➢ During the last year LD group had the lowest complication scores and Br/LD group the highest

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	➢ There was a trend towards earlier onset of complications in the combination group Adverse events ➢ Uncommon in study- only one patient in each group experienced hallucinations at some point during the course of the study Withdrawals ➢ 3 patients dropped-out early and were not included in final evaluation ➢ One Br patient never returned after baseline visit ➢ Another Br patient dropped-out at 4 mo because of orthostatic hypotension ➢ LD patient dropped-out after being diagnosed with progressive supranuclear palsy within 1st year of trial ➢ Duration of therapy for Br patients (mo): 36, 39, 42, 2x 45, 48 ➢ One patient stopped therapy prior to end because of loss of efficacy (45 mo) ➢ Duration of therapy for LD patients (mo): 15, 2x 36, 39, 2x 45, 3x 48 ➢ One patient dropped out because of liver enzymes (at 15 mo) ➢ None of these patients dropped out due to lack of efficacy ➢ Duration of therapy for Br/LD patients (mo): 21, 30, 42, 4x 48 ➢ One patient dropped out because of lack of efficacy (21 mo) and one because of hospitalization secondary to depression (30 mo) ➢ Duration of therapy in the 3 groups was not significantly different
Source of funding	Pharmaceutical, non-profit, University grant
Additional comments	➢ Methods of randomisation and allocation concealment not stated ➢ Small sample size- lack of power calculations ➢ Not intention-to-treat analysis ➢ Activities of daily living outcome?? Validated scale??
NCC CC ID (Ref Man)	2718

Evidence Table **Q TxMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	Olanow CW, Hauser RA, Gauger L, Malapira T, Koller W, Hubble J *et al*. The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Annals.of Neurology* 1995;**38**:771-7.

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Study type	Randomised, double blind, placebo-controlled trial
Evidence level	1++
Study objective	To evaluate the effect of deprenyl and levodopa/carbidopa on the progression of signs and symptoms in patients with mild Parkinson's disease (PD).
Number of patients	N=101 untreated PD patients N=25 deprenyl and sinemet (group I) **N=24 placebo and sinemet (group II)** N=27 deprenyl and bromocriptine (group III) **N=25 placebo and bromocriptine (group IV)** Location: USA and UK sites: two centres
Patient characteristics	Patients with PD, Hoehn and Yahr stage I to III, were selected from movement disorder clinics. All had at least two of resting tremor, bradykinesia, or cogwheel rigidity. Patients were on no medication at the time of baseline evaluation. There were 32 women and 69 men, the mean age was 66.2 $\pm$ 1.1 years, and the average disease duration at the time of enrolment was 3.0 $\pm$ 0.3 years. No statistically significant difference in baseline characteristics.
Intervention	Bromocriptine 5 mg (dosage could be titrated upward or downward during the course of the study). Patients on bromocriptine could receive supplemental doses of sinemet once a total daily bromocriptine dose of 20mg had been achieved.
Comparison	Carbidopa/levodopa 25/100 (dosage could be titrated upward or downward during the course of the study).
Length of follow-up	12 month treatment duration- treatment withdrawal of 7 days prior to final visit
Outcome measures	UPDRS scores, adverse events and withdrawal rates
Effect size	Group II v group IV (bromocriptine v sinemet) ➢ An analysis was performed which compared 41 patients randomised to sinemet (with or without deprenyl) and the 41 patients randomised to bromocriptine (with or without deprenyl) ➢ No statistically significant differences in baseline parameters ➢ Mean change in total UPDRS between baseline and final visit was 1.7 $\pm$ 1.6 in sinemet-treated patients and 4.5 $\pm$ 1.2 in bromocriptine patients- not significant (p=0.32) ➢ Following washout- patients in all 4 groups experienced a statistically significant deterioration in UPDRS scores- not significant differences observed between groups Adverse events ➢ No significant adverse events were encountered during the study

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	➢ No statistically significant differences in the incidence of side effects between any treatment groups Withdrawal rates ➢ 19 patients did not complete the study ➢ 5 from group I, 3 from group II, 5 from group III and 6 from group IV ➢ The demographics of these patients were similar to the whole study population ➢ Reasons for drop-out included: development of confusion (2), lack of efficacy (3), death (1), unrelated medical problems (3), refusal of washout (1), and loss to follow-up (5) ➢ There were no significant differences in reasons for drop-outs between groups ➢ 4 additional patients did not have a final visit following washout ➢ 82 patients who had baseline and final visits were included in the analysis
Source of Funding	Non-profit and pharmacetical
Additional comments	➢ Methods of randomisation stated ➢ Adequate allocation concealment reporting ➢ Power calculation provided ➢ Not intention-to-treat
Citation	
NCC CC ID (Ref Man)	2746

Evidence Table

TxMN2

What is the effectiveness of MAO-B vs. dopamine agonists in the treatment of early Parkinson's disease?

Bibliographic reference	Caraceni T,.Musicco M. Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomized multicenter study. *Parkinsonism & Related Disorders.* 2001;**7**:107-14.
Study type	Randomised open trial
Evidence level	1+
Study objective	To compare the occurrence of motor fluctuations and dyskinesias in previously untreated patients assigned to receive levodopa, a dopamine agonist or deprenyl

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<table>
<tr><td>Number of patients</td><td>N=473 Parkinson’s disease patients
N= 156 levodopa
N=162 dopamine agonist
N=155 deprenyl

Location: Italy sites: 35 neurological departments</td></tr>
<tr><td>Patient characteristics</td><td>
<table>
<tr><th></th><th>Levodopa</th><th>Dopamine agonist</th><th>Deprenyl</th></tr>
<tr><td>Mean age (years)</td><td>63.4</td><td>63.0</td><td>63.4</td></tr>
<tr><td>Sex (men: women) (%)</td><td>52.6: 47.4</td><td>48.2: 51.8</td><td>55.5: 44.5</td></tr>
<tr><td>Mean months from first diagnosis</td><td>4.6</td><td>3.6</td><td>5.0</td></tr>
<tr><td>Mean months from disease onset</td><td>16.21</td><td>17.7</td><td>16.0</td></tr>
</table>
➢ Diagnosis of PD was made on clinical criteria, when hypokinesia was associated with tremor, rigidity, or both for at least 6 months
➢ Exclusion criteria: interval from diagnosis greater than 2 years, dementia, secondary parkinsonism, and parkinsonian syndromes, taking drugs that could give rise to extrapyramidal signs, and previous treatment for more than 4 months with any of the studied drugs</td></tr>
<tr><td>Intervention</td><td>➢ Maximum dose was 10 mg for deprenyl</td></tr>
<tr><td>Comparison</td><td>➢ Maximum doses were 750 mg for levodopa plus dopa decarboxylase, 60 mg for bromocriptine, and 6 mg for lisuride</td></tr>
<tr><td>Length of follow-up</td><td>5 years</td></tr>
<tr><td>Outcome measures</td><td>Occurrence of motor fluctuations (wearing off and early morning akinesia) and dyskinesias</td></tr>
<tr><td>Effect size</td><td>➢ The drug doses were increased slowly over 2-4 weeks until clinical efficacy was reached or adverse effects occurred
➢ If deprenyl or dopamine agonists were or subsequently became ineffective levodopa was added
➢ In cases of non-tolerance the assigned drug was substituted for another by neurologist
➢ Patients were seen every 2 months (for first 6 months), then every 6 months
➢ Since no significant difference in the occurrence of principle outcomes was observed between patients assigned to bromocriptine and lisuride a single group of patient assigned to dopamine agonists was considered in the analysis
➢ No differences in the occurrences of the end-points among centres and in particular no significant interaction between treatment and centre was observed</td></tr>
</table>

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	Motor fluctuations: ➢ More frequent among patients assigned to levodopa (29.7%) than patients assigned to dopamine agonists (16.7%) or deprenyl (18.7%) ➢ Mean time to motor fluctuations: levodopa: 26 months (SE 2.3), dopamine agonists: 23 (3.2) and deprenyl: 29 (3.2) ➢ Risk of developing motor fluctuations was significantly reduced in patients taking deprenyl or dopamine agonists compared to levodopa ➢ In patients assigned to a dopamine agonist or deprenyl, motor fluctuations occurred more frequently when levodopa was added to or substituted for the initial monotherapy Dyskinesia: ➢ Occurred less frequently in the dopamine agonist (14.8%) and deprenyl (20.7%) groups that in the levodopa group (27.1%) ➢ Dyskinesia occurred in patients assigned to levodopa after a mean period of 26 months (2.3), in dopamine agonist patients in 18 months (2.9) and deprenyl 21 months (2.6) ➢ In patients assigned to dopamine (not deprenyl) the risk of dyskinesia was significanrlt lower than patients assigned to levodopa ➢ Patients originally assigned to dopamine agonist or deprenyl- risk of dyskinesia was increased when levodopa was added to or substituted for original treatment ➢ No significant difference in % of patients whose motor signs deteriorated between 3 groups **Adverse events** ➢ 6% of patients stopped taking levodopa during the follow-up period, 32.7% stopped taking dopamine agonists and 19.4% stopped taking deprenyl ➢ Most patients withdrew from dopamine agonists because of: nausea/vomiting or postural hypotension (or both) (43/53 patients) ➢ Probability of ceasing treatment in patients assigned to deprenyl was 3x higher than patients assigned to levodopa ➢ Most of the withdrawals occurred in the first 6 months of treatment and were due to patient's or physician's determination of inefficacy ➢ Combination therapy was started in 12.9% of levodopa patients, 40.7% of dopamine agonist

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	patients and 63.9% of deprenyl patients ➢ The initiation of levodopa therapy was delayed for a median of 30 months in dopamine agonist group and 15 months in deprenyl group ➢ No significant in mortality was found between the three groups followed-up from 1997
Source of funding	Pharmaceutical and government funding
Additional comments	➢ Rationale of open-trial: financial resources for trial were insufficient to overcome organisational complexities connected with double-blind study ➢ Methods of randomisation and allocation concealment listed ➢ Intention-to-treat analysis ➢ Power of 80% a sample of 500 patients necessary
NCC CC ID (Ref Man)	324

TxMN2 – section 7.3.3

Evidence Table **TxMN2** What is the effectiveness of dopamine agonists vs. placebo or levodopa in the treatment of functionally disabled early Parkinson's disease?	
Bibliographic reference	Herskovits E, Yorio A, Leston J. Long term bromocriptine treatment in de novo parkinsonian patients. *Medicina* 1988;**48**:345-50.
Study type	Randomised, single blind, parallel study
Evidence level	+
Study objective	To compare long-term results using different schemes of therapy in previously untreated parkinsonian patients: bromocriptine alone, levodopa/carbidopa alone, bromocriptine plus levodopa/carbidopa
Number of patients	N=86 Parkinson's disease (PD) patients N=31 bromocriptine (Br) N=29 levodopa/carbidopa (LD) N=26 levodopa/carbidopa plus bromocriptine (Br/LD) Location: Argentina Sites: single centre

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Patient characteristics	Patients were aged between 40 to 83 years (mean 67.5) with idiopathic PD. There were 52 females and 34 males. Patients selected for the study had recently been diagnosed with and had not received any prior PD medication. Patients with significant cardiovascular, pulmonary, hepatic or renal impairment were excluded. The three groups were homogenous for clinical signs, stage and disability levels.
Intervention	Br or Br/LD: optimal dose was defined as the minimal dose that produces a satisfactory clinical response (not necessarily 100% of clinical clearing) with the least adverse events. Drugs were started at lowest dose and slowly increased until optimal dose was reached, and then maintained. Br was initiated at 1.25 mg and increased by doses of 1.25 mg
Comparison	LD: was started at 125/12.5 mg and then increased by 125/12.5 each time up to a daily optimal dose.
Length of follow-up	18-45 months, average 31
Outcome measures	Dose, efficacy, adverse events, withdrawal rates
Effect size	Dose ➢ At the end of the trial- the mean dose of Br for patients in Br group who did not require LD was 12.6 ± 3.2 mg ➢ The dose of Br for patients who required LD was 12.9 ± 3.3 mg ➢ The dose of additional LD was 401.8 ± 140.2 mg ➢ In LD and Br/LD groups the mean dose of LD was higher (LD group: 556.1 ± 228mg; group Br/LD: 572.1 ± 226.8 mg) ➢ This may represent a tendency to lower dose of levodopa in the combination when initial drug is Br Efficacy ➢ At the beginning of the trial- patients in the three groups were in similar stages (between II and III) and levels of disability (mild to moderate) ➢ At the end of the trial there was a significant difference both in clinical stage ($p<0.01$) and level of disability ($p<0.01$) between initial and last evaluation- which was similar in all 3 groups ➢ This improvement achieved was about 50% in all groups and it was observed in all categories assessed-being similar for the three cardinal signs as well as for the different kinds of disabilities ➢ No significant differences ($p>0.05$) in the results between the 3 treatments ➢ In Br group- comparing the therapeutic effects of Br-with and without the addition of LD there were no significant differences between scores at final visits ($p>0.05$) Adverse events ➢ Br group showed less side effects than other groups ➢ In two cases (gastric intolerance and allergic nodular vasculitis) these were important enough to

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	discontinue medication ➢ Dyskinesia appeared in one patient on a low dose- no increment of dose was advisable- therefore he was one of the patients showing less improvement ➢ Other adverse events: nausea and vomiting were mild and transient ➢ The usual toxic symptoms which appear at higher doses- confusion, hallucinations, extrasystoles and hypotension were not observed ➢ The LD and Br/LD groups had more secondary effects than Br and were those usually seen with LD treatment- they were generally minimised by reducing the dose ➢ In LD group one patient had to change the therapeutic scheme because of gastric intolerance Withdrawal rates ➢ 3 patients required withdrawal due to intolerance: 2 from Br group and one from LD group ➢ 83 patients completed the study and are included in the analysis ➢ Br group: all patients responded to medication initially- therapeutic effect decreased in 50% of cases (n=14) from 7th month onwards- these patients had to receive combined therapy (plus LD) in order to maintain their improvement ➢ Mean starting time for LD treatment was 16.3 $\pm$ 6.4 mo (range 7 to 28 mo)
Source of funding	Not stated
Additional comments	➢ Scoring forms were completed by blinded investigator ➢ No methods of randomisation or allocation concealment ➢ No intention-to-treat analysis ➢ No power calculations ➢ Lack of baseline characteristics and demographics
Citation	
NCC CC ID (Ref Man)	2193

Evidence Table **TxMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	Weiner WJ, Factor SA, Sanchez-Ramos JR, Singer C, Sheldon C, Cornelius L *et al*. Early combination therapy (bromocriptine and levodopa) does not prevent motor fluctuations in Parkinson's disease.[see comment]. *Neurology* 1993;**43**:21-7.

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<table>
<tr><td>Study type</td><td>Double-blind, randomised, parallel group study</td></tr>
<tr><td>Study objective</td><td>To compare the effects of early combination therapy, LD monotherapy, and Br monotherapy on PD patients previously untreated with dopaminergic medications, with particular attention to late complications and efficacy.</td></tr>
<tr><td>Evidence level</td><td>+</td></tr>
<tr><td>Number of patients</td><td>N=25 PD patients
N=8 bromocriptine monotherapy (Br)
N=10 levodopa monotherapy (LD)
N=7 levodopa plus bromocriptine combination therapy (Br/LD)

Location: USA Sites</td></tr>
<tr><td>Patient characteristics</td><td>None of the patients had been previously treated with bromocriptine or levodopa. 12 were receiving anticholinergic medications, and 5 were receiving amantadine. These medications were continued if necessary.
<table>
<tr><th></th><th>Br</th><th>LD</th><th>BR/LD</th></tr>
<tr><td>Mean age</td><td>60.3</td><td>65.7</td><td>57.6</td></tr>
<tr><td>Mean duration of PD (mo)</td><td>34</td><td>11.6</td><td>13.9</td></tr>
<tr><td>Hoehn and Yahr stage</td><td>2.0</td><td>2.1</td><td>2.4</td></tr>
<tr><td>Mean duration in study</td><td>43.7</td><td>38.4</td><td>40.9</td></tr>
<tr><td>Motor fluctuations n, (%)</td><td>1 (17)</td><td>3 (33)</td><td>5 (71)</td></tr>
<tr><td>Dystonia</td><td>2 (33) *</td><td>9 (100)</td><td>5 (71)</td></tr>
<tr><td>Chorea</td><td>1 (17)</td><td>5 (56)</td><td>4 (57)</td></tr>
<tr><td>Freezing</td><td>5 (83)</td><td>2 (22)</td><td>4 (57)</td></tr>
</table>
* Statistically significant difference (p<0.02)
No significant differences for age or PD baseline measures. A longer disease duration in Br group because one patient had PD for 105 months. Other patients in this group had a range similar to the other two groups (difference was not significant).</td></tr>
<tr><td>Intervention</td><td>Br initiated at 1.25 mg per day and could be advanced to 30 mg per day
Br/LD: patients started on 2.5 mg Br- the next dose was the addition of carbidopa/levodopa 25/100 which occurred after 2 weeks. Gradually increased to max Br dose of 18 mg and carbidopa/levodopa dose of 300/1200</td></tr>
<tr><td>Comparison</td><td>LD: carbidopa/levodopa initiated at 12.5/50 and could be increased to a max dose of 300/1200</td></tr>
</table>

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Length of follow-up	Study duration of 4 years
Outcome measures	Doses, Motor scores, activities of daily living, complications scores, adverse events, withdrawal rates
Effect size	Doses ➢ Br dose ranged from 6.25 to 30 mg- with a mean of 18 mg per day at the end of the study ➢ LD monotherapy dose ranged from 150-700 mg, with a mean of 417 mg per day at end of study ➢ Br/LD group the LD dose ranged from 200 to 800 mg (mean, 386 mg per day) and the Br dose ranged from 9 to 20 mg (mean, 14 mg per day) ➢ Comparison of LD doses in LD monotherapy and combination group were not significantly different ➢ Comparison of Br doses also did not show significant difference Motor examination (modified Columbia rating scale) ➢ Br group score decreased maximally by one month- improvement not significant compared to baseline ➢ Motor scores then became progressively worse despite increasing doses and exceeded baseline scores after 15 mo ➢ At no time did Br monotherapy result in significant improvement of motor examination scores ➢ LD group achieved statistically significant improvement at 3 months ($p<0.03$) and peak improvement at 6 months ($p<0.0001$) ➢ Motor examination score remained below baseline throughout study ➢ Br/LD group reached peak improvement in motor examination score at 3 months- but degree of improvement never reached significance compared with baseline ➢ Three groups tended to parallel each other: Br group had worst motor examinations score and LD group the best with Br/LD inbetween ➢ No significant difference was found between the 3 groups at any time Activities of daily living ➢ All 3 groups reached maximal improvement at 6 months ➢ The degree of improvement within each group was significant ($p<0.02$ for Br, $p=0.007$ for group LD, $p=0.05$ for Br/LD) ➢ There were no differences between the groups throughout the study- with the exception of scoring at 48 months (LD group had lowest score $p<0.03$) Complications scores ➢ No difference was seen between the three groups for motor fluctuations, dystonia, freezing and chorea ➢ During the last year LD group had the lowest complication scores and Br/LD group the highest

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	➢ There was a trend towards earlier onset of complications in the combination group Adverse events ➢ Uncommon in study- only one patient in each group experienced hallucinations at some point during the course of the study Withdrawals ➢ 3 patients dropped-out early and were not included in final evaluation ➢ One Br patient never returned after baseline visit ➢ Another Br patient dropped-out at 4 mo because of orthostatic hypotension ➢ LD patient dropped-out after being diagnosed with progressive supranuclear palsy within 1st year of trial ➢ Duration of therapy for Br patients (mo): 36, 39, 42, 2x 45, 48 ➢ One patient stopped therapy prior to end because of loss of efficacy (45 mo) ➢ Duration of therapy for LD patients (mo): 15, 2x 36, 39, 2x 45, 3x 48 ➢ One patient dropped out because of liver enzymes (at 15 mo) ➢ None of these patients dropped out due to lack of efficacy ➢ Duration of therapy for Br/LD patients (mo): 21, 30, 42, 4x 48 ➢ One patient dropped out because of lack of efficacy (21 mo) and one because of hospitalization secondary to depression (30 mo) ➢ Duration of therapy in the 3 groups was not significantly different
Source of funding	Pharmaceutical, non-profit, University grant
Additional comments	➢ Methods of randomisation and allocation concealment not stated ➢ Small sample size- lack of power calculations ➢ Not intention-to-treat analysis ➢ Activities of daily living outcome?? Validated scale??
NCC CC ID (Ref Man)	2718

Evidence Table **Q TxMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	F. Alarcon, N. Cevallos, and A. J. Lees. Does combined levodopa and bromocriptine therapy in

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<table>
<tr><td></td><td>Parkinson's disease prevent late motor complications? European Journal of Neurology 5 (3):255-263, 1998.</td></tr>
<tr><td>Study type</td><td>A randomised open-label study of Levadopa-carbidopa plus Bromocriptine versus Levadopa-carbidopa alone in patients with early Parkinson’s disease.</td></tr>
<tr><td>Study objective</td><td>Comparison of the effect of Levadopa-carbidopa plus Bromocriptine in comparison to Levadopa-carbidopa alone in improving Parkinson’s disease symptoms, including motor function, and its safety and tolerability in the study population.</td></tr>
<tr><td>Evidence level</td><td>+</td></tr>
<tr><td>Number of patients</td><td>N= 78 Parkinson’s disease (PD) patients
N= 40 levadopa-carbidopa plus bromocriptine group
N= 38 levadopa-carbidopa group

Location: Ecuador Sites: 1 site</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion Criteria: Patients with idiopathic PD who had bradykinesia, had not taken Levadopa or dopaminergic agonists before the study, and had at least one of the following symptoms: muscular rigidity, 4-6 HZ rest tremor, postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction. Prospectively all patients had at least two of the following criteria: unilateral onset, rest tremor present, progressive disorder, and persistent asymmetry affecting the side of onset most. Exclusion criteria: see paper for list.
<table>
<tr><th>Characteristics</th><th>Levadopa plus Bromocriptine N=40</th><th>Levadopa N=38</th></tr>
<tr><td>Age, years, mean ± SD</td><td>63.8 ± 8.4</td><td>63.7 ± 10.2</td></tr>
<tr><td>Male, N (%)</td><td>21 (52.5)</td><td>20 (52.6)</td></tr>
<tr><td>Female, N (%)</td><td>19 (47.5)</td><td>18 (47.3)</td></tr>
<tr><td>Hoehn and Yahr Stage, mean ± SD</td><td>2.4 ± 0.8</td><td>2.6± 0.8</td></tr>
<tr><td>Hoehn and Yahr Stage I</td><td>5=12.5</td><td>3=7.8</td></tr>
<tr><td>Hoehn and Yahr Stage II</td><td>17=42.5</td><td>15=39.4</td></tr>
<tr><td>Hoehn and Yahr Stage III</td><td>13=32.5</td><td>14=36.8</td></tr>
<tr><td>Hoehn and Yahr Stage IV</td><td>5=12.5</td><td>6=15.7</td></tr>
<tr><td>Duration of Illness, mean ± SD</td><td>3.8 ± 4*</td><td>4.1 ± 1.7*</td></tr>
<tr><td>Depression, N (%)</td><td>21 (52.5)</td><td>17 (44.7)</td></tr>
<tr><td>UPDRS Motor Score, mean ± SD</td><td>26.7 ± 8.1</td><td>25.4 ± 7.8</td></tr>
</table>
*Statistically significant difference p<0.05(chi-square test)</td></tr>
<tr><td>Intervention</td><td>Levadopa-carbidopa plus Bromocriptine (LD/Br): 125mg/day Levadopa-carbidopa (LD) increased weekly by the same amount until adjusted to achieve maximum ‘on’ time and as little ‘off’ time as possible, with</td></tr>
</table>

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<table>
<tr><td></td><td>a maximum dose of 500mg/day. After the third month 1.25 mg/day of Bromocriptine (Br) was added once, and increased every 2 weeks by the same with a maximum dosage of 15 mg/day.</td></tr>
<tr><td>Comparison</td><td>Levadopa-carbidopa: same as LD dosage above</td></tr>
<tr><td>Length of follow-up</td><td>Trial duration of 3 years</td></tr>
<tr><td>Outcome measures</td><td>Study end-point was defined when motor complications appeared and persisted in the following 3-monthly visits.
Duration of treatment, Hoehn and Yahr scores, Webster scores, UPDRS motor score, activities of daily living (NUDS), nocturnal /early morning akinesia, wearing-off, on-off, Dyskinesias, time of onset of motor fluctuations, adverse events, dropouts.</td></tr>
<tr><td>Effect size</td><td>
<table>
<tr><th>Outcomes, mean ± SD</th><th>Br/LD N=40</th><th>LD N=38</th><th>P value</th></tr>
<tr><td>Duration of Patient Treatment (months)</td><td>39.4 ± 15.2</td><td>36 ± 11.2</td><td>Not reported</td></tr>
<tr><td>Degree of Disability (Hoehn and Yahr)</td><td>2.5 ± 0.9</td><td>2.4 ± 0.8</td><td>p<0.05</td></tr>
<tr><td>Signs of Parkinson’s Disease (Webster)</td><td>14.7 ± 4.9</td><td>16.3 ± 4.3</td><td>p<0.05</td></tr>
<tr><td>Signs of Parkinson’s Disease (Curs)</td><td>21.3 ±7</td><td>23.2 ± 6.8</td><td>p<0.05</td></tr>
<tr><td>Activities of Daily Living (NUDS),</td><td>39.4 ± 7.2</td><td>35.6 ± 12</td><td>p<0.05</td></tr>
<tr><td>Parkinsonian Disability (UPDRS motor score),</td><td>24.0 ± 8.4</td><td>24.1 ± 7.7</td><td>p<0.05</td></tr>
</table>
</td></tr>
</table>

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Complications in Motor Disability Related to Treatment (Nocturnal /Early Morning Akinesia), N patients	14 3 years 20 final visit	15 3 years 22 final visit	OR 1.38 (95%CI 0.51 to 3.7) Not significant
Complications in Motor Disability Related to Treatment (Wearing Off), N patients	15 3 years 20 final visit	11 3 years 15 final visit	OR 0.65 (95%CI 0.24 to 1.76) Not significant
Complications in Motor Disability Related to Treatment ('On-Off'), N patients	4 3 years 5 final visit	3 3 years 4 final visit	OR 1.36 (95%CI 0.27 to 7.46) Statistically significant
Complications in Motor Disability Related to Treatment (Wearing off and 'On-Off'), N patients	2 3 years 4 final visit	3 3 years 6 final visit	OR 1.69 (95%CI 0.37 to 7.96) Not significant
Complications in Motor Disability Related to Treatment (Interdose Dyskinesias), N patients	13 3 years 22 final visit	10 3 years 16 final visit	OR 0.60 (95%CI 0.22 to 1.60) Not significant
Complications in Motor Disability Related to Treatment (Biphasic Dyskinesias), N patients	2 3 years 3 final visit	1 3 years 1 final visit	OR 0.30 (95%CI 0.01 to 4.43) Not significant
Complications in Motor Disability Related to Treatment ('Off' period), N patients	5 3 years 10 final visit	3 3 years 8 final visit	OR 0.80 (95%CI 0.24 to 2.62) Not significant
Time of Onset of Motor Fluctuations from Start of Treatment, months	10.2 ± 12.9	15.3 ± 16.6	P <0.05 Statistically significant
Time of Onset of Dyskinesias from Start of Treatment, months	16.7 ± 15.7	18 ± 8.4	Not Reported
Adverse Events, nausea/vomiting	7	4	P<0.05
Adverse Events, fatigue/weakness	3	1	P<0.05
Adverse Events, hallucinations/confusion	3	1	P<0.05

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	Notes: ➢ Exclusions: Of 87 patients who entered the study, four were excluded due, one died from an unrelated cause, one had a history of psychosis, and three lived too far from the research centre for regular attendance at follow-up assessments. ➢ Dropout: None of the patients stopped treatment due to loss of effectiveness.
Source of funding	Not reported
Additional comments	➢ An open-label study, with dosage adjustments performed by a non-blinded investigator on the recommendation of a blinded investigator. ➢ Method of randomisation used in the study was not reported. ➢ Anticholinergics use was suspended 4 weeks prior to study entry. ➢ Duration of disease was significantly longer at baseline for the Levadopa-carbidopa group. ➢ All patients who were randomly allocated to the study groups were included in the statistical analysis, however the baseline assessment and subsequent analyses omitted nine patients who were excluded from the study. The study does not state whether these patients were excluded before or after random allocation, so it is unclear whether an ITT analysis was conducted. ➢ AE's were more frequent in the Levadopa-carbidopa plus Bromocriptine group, with significant differences reported for nausea/vomiting, fatigue/weakness, and hallucinations/confusion.
NCC CC ID (Ref Man)	1274

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Evidence Table
Q TXMN2
Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?

Bibliographic reference	H. Allain, A. Destee, H. Petit, M. Patay, S. Schuck, D. Bentue-Ferrer, and P. Le Cavorzin. Five-year follow-up of early lisuride and levodopa combination therapy versus levodopa monotherapy in de novo Parkinson's disease. The French Lisuride Study Group. *European Neurology* 44 (1):22-30, 2000.
Study type	A multi-centre RCT of early Lisuride and Levadopa combined versus Levadopa and placebo, double-blinded for 1 year, followed by a 4-year open study.
Study objective	Comparison of the effect of Levadopa plus placebo with a combined regimen of Levadopa plus lisuride in terms of prevalence of undesirable motor effects.
Evidence level	+
Number of patients	N= 82 Parkinson's disease patients N= 41 levadopa plus lisuride group N= 41 levodopa group Location: France Sites: 8 sites
Patient characteristics	Inclusion Criteria: patients with recently diagnosed idiopathic PD (disease duration less or equal to 3 years; Hoehn and Yahr score less or equal to 3 years). Strict inclusion criteria were applied prior to randomization of patients, but were reported in an earlier paper. Exclusion criteria: Strict exclusion criteria were applied prior to randomization of patients, but were reported in an earlier paper. Patients who were depressive or with impaired cognitive functions were likely to have been excluded.

Characteristics, means (SD)	Levadopa + lisuride	Levadopa
Age, years (SD)	59.0 (8.07)	58.95 (7.44)
Male	20	25
Female	21	16
Mean Hoehn and Yahr Stage (SD)	1.59 (0.4)	1.43 (0.5)
Mean Schwab and England Scale	2.37 (0.62)	2.39 (0.77)
Mean UPDRS Part III (SD)	17.76 (11.07)	21.02 (9.11)
Duration of illness, months	21.24 (11)	20.07 (9.46)

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<table>
<tr><td></td><td>
<table>
<tr><td>Duration of levadopa pre-treatment, months</td><td>5.1 (2.9)</td><td>5.7 (3.3)</td></tr>
<tr><td>Dosage of levadopa (Modopar) at inclusion,mg</td><td>250 (57)</td><td>242.68 (72.9)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Levadopa plus lisuride: 300mg/day levadopa (LD) plus lisuride (Li) with maximum titration of up to 1.2 mg/day for 1 year. During the following 4 years of the open trial, daily dose of lisuride was modifiable in accordance with the optimal efficacy/tolerance ratio acceptable to the study investigators, and 10mg/day selegiline was added.</td></tr>
<tr><td>Comparison</td><td>Levadopa plus placebo: same as levodopa dosage above.</td></tr>
<tr><td>Length of follow-up</td><td>The double-blind stage of the trial lasted for 12 months, followed by a 48-month open stage for both treatment groups.</td></tr>
<tr><td>Outcome measures</td><td>Progression of Levadopa Usage (UPDRS score), Treatment Related Complications (dsykinesia, fluctuations, other complications as per UPDRS IV sub-scores), Preventative Effect of Early Combination Therapy on Levadopa-Induced Motor Impairment (wearing-off effects, fluctuations, involuntary movements as per UPDRS addendum), Adverse Events, Dropout Rate.</td></tr>
<tr><td>Effect size</td><td>
<table>
<tr><th>Outcomes</th><th>LD/Li</th><th>LD</th><th>P value</th></tr>
<tr><td>Disease Progression (UPDRS total score) at 60 months</td><td>Unchanged</td><td>38.37± 15.9 at baseline vs 48.95 ± 28.3 at 60 months</td><td>p<0.01</td></tr>
<tr><td>Disease Progression (Schwab and England score)</td><td>2.37 ± 0.62 at baseline vs 2.17 ±1.05 at 60 months</td><td>2.39 ± 0.77 at baseline vs 3.83 ± 0.97</td><td>p <0.01</td></tr>
<tr><td>Disease Progression (Hoehn and Yahr score)</td><td>Unchanged</td><td>Unchanged</td><td>NS</td></tr>
<tr><td>Treatment Related Complications (UPDRS IV sub-scores)</td><td>0.32 ± 0.69 to 0.73 ± 1.1</td><td>0.49±1.5 to 0.96 ± 1.3</td><td>LOCF; p= NS</td></tr>
<tr><td>Presence of Dyskinesias</td><td>8 (19.5%)</td><td>14 (34.1%)</td><td>Not reported</td></tr>
<tr><td>Study dropouts with Dyskinesias</td><td>3 (17.1%)</td><td>7 (17%)</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

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	Presence of Clinical Fluctuations	9 (22%)	6 (14.6%)	Not reported
	Study dropouts with Clinical Fluctuations	3 (7.3%)	3 (7.3%)	Not reported
	Motor Complications (sum of UPDRS addendum scores)	Not reported	Not reported	LOCF;p<0.05 In favour of combination group
	Presence of Clinical Fluctuations	9 (22%)	6 (14.6%)	Not reported
	Presence of Involuntary Movements	11 (26.8%)	14 (34.2%)	Not reported
	Therapeutic Instability	15 (36.6%)	21 (51.2%)	Not reported
	Persistence of Motor symptoms	1(Fluctuations) 1 (IM) 1 (TI)	2(Fluctuations) 4 (IM) 0 (TI)	Not reported
	Adverse Events (all)	Not reported	Not reported	More reported for combination therapy compared to Levadopa p<0.02
	Withdrawal Rate at 12 Months	6/41 (14.6%)	12/41 (29%)	Not reported
	Withdrawal Rate at 60 Months	17/41 (41.5%)	26/41 (63.4%)	p=0.02
	Cumulative Levadopa at Endpoint (60 months)	387.5 ± 156.2 mg	446.7 ± 139.5 mg	p<0.001
	Notes: ➢ Risk of Motor Complications: no significant between-group difference and remained exceptional and moderate whatever the treatment group. ➢ Adverse Events: Eight patients withdrew from the study due to lisuride intolerance (4 during treatment with selegiline).			
Source of funding	Not reported			
Additional comments	➢ The study reports treatment related complication and motor complication outcome data for the			

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	entire study period, but the study was only blinded for 1 year, with four years of open-label follow-up. ➢ Number of dropouts was significantly greater in Levadopa compared to combination therapy over the five-year study period. ➢ An ITT was carried out at 60 months using the last observation carried forward (LOCF) for dropouts. ➢ Baseline data in the population analyzed at 1 year (N=64) and at 5 years (N=82 with the LOCF) were comparable. ➢ Methods of randomisation and allocation concealment were not reported. ➢ Participant inclusion and exclusion criteria were not comprehensively reported in the current paper.
NCC CC ID (Ref Man)	1914

Evidence Table **Q TXMN2** Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?	
Bibliographic reference	Gimenez-Roldan S, Tolosa E, Burguera JA, Chacon J, Liano H, Forcadell F. Early combination of bromocriptine and levodopa in Parkinson's disease: a prospective randomized study of two parallel groups over a total follow-up period of 44 months including an initial 8-month double-blind stage. *Clinical Neuropharmacology* 1997;**20**:67-76.
Study type	A prospective randomised study of two parallel groups over a total follow-up period of 44 months: levodopa alone or levodopa plus bromocriptine.
Study objective	To endeavour to establish whether the association of bromocriptine allowed a significant reduction in levodopa consumption and whether during follow-up there were any differences between the two groups in frequency of motor response oscillations and chronic dyskinesias.
Evidence level	+
Number of patients	N= 57 Parkinson's disease (PD) patients N= 27 levodopa plus bromocriptine group (Br/LD)

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<table>
<tr><td></td><td>N= 23 levodopa plus placebo group (LD)

Location: Spain Sites: 5 sites</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion Criteria: Aged between 40 and 70 years, a maximum of disease Stage III according to Hoehn and Yahr, and an unequivocal response to levodopa therapy introduced 2-6 months before entering the study. Patients already on amantadine or anticholinergics were allowed to maintain those drugs.
Exclusion criteria: A history of prior exposure to any dopaminergic agonist. Patients who had already developed fluctuations or dyskinesias as manifestations of late levodopa syndrome were excluded, as were patients with a prior history of psychiatric illness.
<table>
<tr><th>Feature</th><th>Br/LD (N=27)</th><th>LD (N=23)</th></tr>
<tr><td>Sex (M/F)</td><td>15/12</td><td>18/5</td></tr>
<tr><td>Age (mean +/- SD; yrs)</td><td>61.0 +/- 7</td><td>59.5 +/- 9</td></tr>
<tr><td>Disease duration (mean +/- SD; mo on presenting)</td><td>9.0 +/- 5.6</td><td>7.4 +/- 5.4</td></tr>
<tr><td>Hoehn and Yahr staging (mean +/-SD)</td><td>1.5 +/- 0.7</td><td>1.6 +/- 0.5</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Levodopa plus bromocriptine. Bromocriptine was introduced by administering a dose of 1.25mg at bedtime for 7 days. The dose was then increased by 1.25mg weekly. After 6 weeks 2.5mg/week increments in three doses daily to a maximum of 15mg by day 63. After maintaining final dose levels for a further month, each investigator attempted to reduce daily LD doses by 20-30% unless the clinical status of the patient was suboptimal. When patient status was unsatisfactory, investigators increased bromocriptine to a maximum of 30mg/day while keeping levodopa doses unchanged. After 8 months the controlled stage of the study ended and the study became “open label”.</td></tr>
<tr><td>Comparison</td><td>Levodopa plus placebo: identical placebo administered as bromocriptine.</td></tr>
<tr><td>Length of follow-up</td><td>The study period lasted for 44 months.</td></tr>
<tr><td>Outcome measures</td><td>Reduction in levodopa consumption, Frequency of motor response oscillations, Frequency of chronic dyskinesias, Daily Life Activities Scale, Schwab and England and the Hoehn and Yahr disease stage,</td></tr>
<tr><td>Effect size</td><td>➢ At the end of the controlled, double-blind stage of the study (8 months) there were no differences in mean daily dosages between groups (507.6+/- 164 vs. 464.8 +/- 296 mg/day) or as compared with the respective baseline dosage for each group.
➢ In patients on combined LD/Br- tendency toward smaller daily requirements of levodopa compared with those on levodopa alone- the difference in dose between the two groups was significantly different (514.4 +/- 240 vs. 725.6 +/- 230 mg/day; p<0.01) after 44 months of continuous treatment in the 40 patients still enrolled in the open-label stage. At this point in time the mean dose of</td></tr>
</table>

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	bromocriptine had been increased by 9.2mg in the combined treatment group, and the mean dose of levodopa was 40.7% lower than in the group receiving levodopa alone. ➢ The number of patients with dyskinesias or describing wearing-off fluctuations severe enough to require changes in treatment was lower than in the group under combined therapy, the difference being significant after 20 and 44 months, respectively (36.8 vs. 9.5 and 47.3 vs. 14.2%). ➢ Mean total UPDRS scores for the LD monotherapy group underwent significant deterioration compared with baseline values (28.8 +/- 15 vs. 35.7 +/- 20) at month 44 after commencement of treatment (p=0.033) but not at earlier evaluations. In contrast, mean total UPDRS scores in the combined therapy group remained significantly below mean baseline values during each follow-up assessment (p<0.001). ➢ On evaluation at 44 months, motor disability in patients under levodopa monotherapy was significantly greater than the baseline values (19.4 +/- 9.6 vs. 22.6 +/- 14.3) in contrast to the combined therapy group, whose UPDRS motor subscale scores were still significantly below their baseline state (17.0 +/- 11 vs. 10.3 +/- 14.1) ➢ No differences in Daily Life Activities Scale scores were found between the two groups except at the follow-up visit at 8 months, when the group under combined therapy scored higher (mean 81.05 vs. 90.4; P=0.0029). No differences in scores were found between the groups in Hoehn and Yahr scale.
Source of funding	Not reported
Additional comments	➢ Seven patients initially recruited (12%) were not included in the analysis due to early dropout (N=1 died and N=7 non-compliant with treatment) meaning an ITT analysis was not performed ➢ No details given of processes with regard to randomisation, concealment and blinding. ➢ No power analysis. ➢ Outcomes assessed after 8 months were not subject to blinding.
NCC CC ID (Ref Man)	2136

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Evidence Table
Q TXMN2
Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?

Bibliographic reference	Gimenez-Roldan S, Tolosa E, Burguera JA, Chacon J, Liano H, Forcadell F. Early combination of bromocriptine and levodopa in Parkinson's disease: a prospective randomized study of two parallel groups over a total follow-up period of 44 months including an initial 8-month double-blind stage. *Clinical Neuropharmacology* 1997;**20**:67-76.
Study type	A prospective randomised study of two parallel groups over a total follow-up period of 44 months: levodopa alone or levodopa plus bromocriptine.
Study objective	To endeavour to establish whether the association of bromocriptine allowed a significant reduction in levodopa consumption and whether during follow-up there were any differences between the two groups in frequency of motor response oscillations and chronic dyskinesias.
Evidence level	+
Number of patients	N= 57 Parkinson's disease (PD) patients N= 27 levodopa plus bromocriptine group (Br/LD) N= 23 levodopa plus placebo group (LD) Location: Spain Sites: 5 sites
Patient characteristics	Inclusion Criteria: Aged between 40 and 70 years, a maximum of disease Stage III according to Hoehn and Yahr, and an unequivocal response to levodopa therapy introduced 2-6 months before entering the study. Patients already on amantadine or anticholinergics were allowed to maintain those drugs. Exclusion criteria: A history of prior exposure to any dopaminergic agonist. Patients who had already developed fluctuations or dyskinesias as manifestations of late levodopa syndrome were excluded, as were patients with a prior history of psychiatric illness.
Intervention	Levodopa plus bromocriptine. Bromocriptine was introduced by administering a dose of 1.25mg at

Feature	Br/LD (N=27)	LD (N=23)
Sex (M/F)	15/12	18/5
Age (mean +/- SD; yrs)	61.0 +/- 7	59.5 +/- 9
Disease duration (mean +/- SD; mo on presenting)	9.0 +/- 5.6	7.4 +/- 5.4
Hoehn and Yahr staging (mean +/-SD)	1.5 +/- 0.7	1.6 +/- 0.5

	bedtime for 7 days. The dose was then increased by 1.25mg weekly. After 6 weeks 2.5mg/week increments in three doses daily to a maximum of 15mg by day 63. After maintaining final dose levels for a further month, each investigator attempted to reduce daily LD doses by 20-30% unless the clinical status of the patient was suboptimal. When patient status was unsatisfactory, investigators increased bromocriptine to a maximum of 30mg/day while keeping levodopa doses unchanged. After 8 months the controlled stage of the study ended and the study became "open label".
Comparison	Levodopa plus placebo: identical placebo administered as bromocriptine.
Length of follow-up	The study period lasted for 44 months.
Outcome measures	Reduction in levodopa consumption, Frequency of motor response oscillations, Frequency of chronic dyskinesias, Daily Life Activities Scale, Schwab and England and the Hoehn and Yahr disease stage,
Effect size	➢ At the end of the controlled, double-blind stage of the study (8 months) there were no differences in mean daily dosages between groups (507.6+/- 164 vs. 464.8 +/- 296 mg/day) or as compared with the respective baseline dosage for each group. ➢ In patients on combined LD/Br- tendency toward smaller daily requirements of levodopa compared with those on levodopa alone- the difference in dose between the two groups was significantly different (514.4 +/- 240 vs. 725.6 +/- 230 mg/day; p<0.01) after 44 months of continuous treatment in the 40 patients still enrolled in the open-label stage. At this point in time the mean dose of bromocriptine had been increased by 9.2mg in the combined treatment group, and the mean dose of levodopa was 40.7% lower than in the group receiving levodopa alone. ➢ The number of patients with dyskinesias or describing wearing-off fluctuations severe enough to require changes in treatment was lower than in the group under combined therapy, the difference being significant after 20 and 44 months, respectively (36.8 vs. 9.5 and 47.3 vs. 14.2%). ➢ Mean total UPDRS scores for the LD monotherapy group underwent significant deterioration compared with baseline values (28.8 +/- 15 vs. 35.7 +/- 20) at month 44 after commencement of treatment (p=0.033) but not at earlier evaluations. In contrast, mean total UPDRS scores in the combined therapy group remained significantly below mean baseline values during each follow-up assessment (p<0.001). ➢ On evaluation at 44 months, motor disability in patients under levodopa monotherapy was significantly greater than the baseline values (19.4 +/- 9.6 vs. 22.6 +/- 14.3) in contrast to the combined therapy group, whose UPDRS motor subscale scores were still significantly below their

	baseline state (17.0 +/- 11 vs. 10.3 +/- 14.1) ➢ No differences in Daily Life Activities Scale scores were found between the two groups except at the follow-up visit at 8 months, when the group under combined therapy scored higher (mean 81.05 vs. 90.4; P=0.0029). No differences in scores were found between the groups in Hoehn and Yahr scale.
Source of funding	Not reported
Additional comments	➢ Seven patients initially recruited (12%) were not included in the analysis due to early dropout (N=1 died and N=7 non-compliant with treatment) meaning an ITT analysis was not performed ➢ No details given of processes with regard to randomisation, concealment and blinding. ➢ No power analysis. ➢ Outcomes assessed after 8 months were not subject to blinding.
NCC CC ID (Ref Man)	2136

Evidence Table **TxNP2** Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?	
Bibliographic reference	Przuntek, H., Welzel, D., Blumner, E., Danielczyk, W., Letzel, H., Kaiser, H. J., Kraus, P. H., Riederer, P., Schwarzmann, D., & Wolf, H. 1992, "Bromocriptine lessens the incidence of mortality in L-dopa-treated parkinsonian patients: prado-study discontinued.[see comment]", *European Journal of Clinical Pharmacology*, vol. 43, no. 4, pp. 357-363.
Study type	Randomised trial, open
Evidence level	1+
Study Objective	To report the mortality results of patients treated with L-dopa compared to L-dopa/Bromocriptine
Number of patients	N=587 early Parkinson's disease patients N=302 L-dopa group N=285 L-dopa and bromocriptine group (L-dopa/Br) Location: Germany and Hungary sites: 101 practicing neurologists treated and recruited
Patient characteristics	Inclusion criteria:

<table>
<tr><td></td><td>De novo PD patients
<table>
<tr><th>Characteristic</th><th>L-dopa (n=302) (%)</th><th>L-dopa/Br (n=285) (%)</th></tr>
<tr><td>Sex male</td><td>51.0</td><td>56.5</td></tr>
<tr><td>Pre-treated with L-dopa/benserazide</td><td>31.5</td><td>30.5</td></tr>
<tr><td>Duration of disease at study onset (months)</td><td>20</td><td>21</td></tr>
<tr><td>Duration of L-dopa pre-treatment months</td><td>2.53</td><td>2.70</td></tr>
<tr><td>Age (y) male</td><td>62.5</td><td>63.0</td></tr>
<tr><td>Age (y) female</td><td>65</td><td>67</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>250 mg L-dopa/benserazide/ 10 mg Bromocriptine- the second 3 months of the study consisted of a gradual substitution of bromocriptine for L-dopa over 3 months in one treatment groups</td></tr>
<tr><td>Comparison</td><td>375 mg L-dopa/benserazide was the median dose on which both groups started for the first 3 months of the study</td></tr>
<tr><td>Length of follow-up</td><td>54 months (4.5 years)</td></tr>
<tr><td>Outcome measures</td><td>Treatment outcomes measures of this study are reported in the systematic review ID 42 only neuroprotective measures are listed here: mortality</td></tr>
<tr><td>Effect size</td><td>➢ Following an interim analysis in 1991- the trial was terminated due to an increased number of deaths in the L-dopa monotherapy group
➢ 18 vs. 8 deaths had been reported in the L-dopa vs. L-dopa/Br groups
➢ Statistical analysis showed a crude p value (double-sided) of 0.07
➢ Adjusted for age and sex (p=0.02)
➢ The risk ratio of L-dopa monotherapy compared to combination therapy was 2.7, a reduction of 63%
➢ For ethical reasons the study was terminated
➢ The median observation on target medication was 38.4 months in the L-dopa only group and 40.1 in the L-dopa/Br group
➢ Causes of death mainly due to cardiovascular complications

Side effects
➢ Mainly: gastro-intestinal complaints, nausea, palpitation, sleep disturbances (which interfered with study medication and patient compliance)
➢ Drop-out/discontinuation occurred in 152/302 L-dopa group and 121/285 L-dopa/Br group</td></tr>
<tr><td>Source of Funding</td><td>Not stated</td></tr>
<tr><td>Additional comments</td><td>➢ Randomisation methods not stated</td></tr>
</table>

	➢ No blinding of investigators- potential bias in interpretation ➢ Death was not considered a main endpoint in the protocol ➢ Power estimates given ➢ Comparability of results between sites not addressed
Citation	
NCC CC ID (Ref Man)	2518

Evidence Table
TxNP2
Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson's disease?

Bibliographic reference	Przuntek H, Welzel D, Gerlach M, Blumner E, Danielczyk W, Kaiser HJ *et al*. Early institution of bromocriptine in Parkinson's disease inhibits the emergence of levodopa-associated motor side effects. Long-term results of the PRADO study. *Journal of Neural Transmission - General Section* 1996;**103**:699-715.
Study type	Randomised trial, open, prospective
Evidence level	+
Study Objective	Paper summarises the completed study (ID2518) and demonstrates the long-term impact of primary combination therapy with particular attention to development of late motor complications.
Number of patients	N=587 early Parkinson's disease patients N=302 L-dopa group N=285 L-dopa and bromocriptine group (L-dopa/Br) Location: Germany and Hungary sites: 101 practicing neurologists treated and recruited
Patient characteristics	Inclusion criteria: de novo PD patients, Hoehn and Yahr stages I to IV. Pre-treatment with levodopa up to 6 months was allowed, but patients pre-treated with anticholinergics, amantadine, or dopamine-agonists were excluded.

Characteristic	L-dopa (n=302) (%)	L-dopa/Br (n=285) (%)
Sex male	51.0	56.5
Pre-treated with L-dopa/benserazide	31.5	30.5
Duration of disease at study onset (months)	20	21

	Duration of L-dopa pre-treatment months	2.53	2.70
	Age (y) male	62.5	63.0
	Age (y) female	65	67
Intervention	250 mg L-dopa/benserazide/ 10 mg Bromocriptine- the second 3 months of the study consisted of a gradual substitution of bromocriptine for L-dopa over 3 months in one treatment groups		
Comparison	375 mg L-dopa/benserazide was the median dose on which both groups started for the first 3 months of the study		
Length of follow-up	54 months (4.5 years)		
Outcome measures	Motor scores, depression scores, side effects and withdrawal rates		
Effect size	➢ The study consisted of 4 phases: the build-up phase (3 mo), substitution phase (3 mo), long-term treatment phase on the target regimen (42 mo) final phase (re-substitution of levodopa) ➢ During the substitution phase 5 mg of Br was assumed to be equivalent to 50mg levodopa Webster scores ➢ There was no change in Hoehn and Yahr scores from start of phase II to end of phase III in 51.0% of patients on monotherapy v 54.7% on combination therapy ➢ A higher stage was reported in 38.1% v 36.5%^ and lower stage in 10.9% v 8.8% Psychological ➢ The mean total score of the Zung Self-rating depression scale was 35.93 ± 9.28 v 34.94 ± 9.09 at the beginning of phase II and 37.44 ± 9.83 v. 36.13 ± 10.22 at the individual last observation Side effects (Mortality reported in ID 2518) ➢ Motor side effects (on-off phenomenon and dyskinesias) were observed in 28.8% of monotherapy patients and 20.0% pf combination (p=0.008) ➢ Probability of experiencing some side effects within 48 mo after enrolment was 0.43 v 0.28 (p=0.0252)- the potential of experiencing some motor side effect due to combination therapy was reduced by one third ➢ Common events: disturbance of falling asleep, disturbance of sleeping, drowsiness, dizziness, dryness of mouth, constipation, palpitation, headache Withdrawals ➢ 674 patients were recruited into study: 9 could not be included in phase for technical reasons ➢ 3 died during phase I, 75 were not eligible for phase II due to inadequate compliance (n=42), protocol violations (n=5), side effects (n=22) or concomitant diseases (n=6) ➢ 587 entered phase II and comprised the intention-to-treat sample		
Source of Funding	Not stated		

Additional comments	➢ Power calculations provided ➢ No methods of randomisation or allocation concealment ➢ Comparability between sites not stated ➢ Open trial design ➢ Intention-to-treat analysis after phase I
Citation	
NCC CC ID (Ref Man)	2520

Evidence Table
Q TxMN2
Are dopamine agonists vs. placebo or levodopa effective in the treatment of functionally disabled of early Parkinson's disease?

Bibliographic reference	J. Kulisevsky, C. Garcia-Sanchez, M. L. Berthier, M. Barbanoj, B. Pascual-Sedano, A. Gironell, and A. Estevez-Gonzalez. Chronic effects of dopaminergic replacement on cognitive function in Parkinson's disease: a two-year follow-up study of previously untreated patients. *Movement Disorders* 15 (4): 613-626, 2000.
Study type	An open label RCT with blind neuropsychologic evaluation
Evidence level	1+
Study objective	Comparison of the effect of Levadopa versus Pergolide in producing sustainable improvement in Parkinson's disease symptoms, including cognitive status and motor function in patients with early-stage Parkinson's disease.
Number of patients	N= 20 Parkinson's disease patients N= 10 levadopa group N= 10 pergolide group Location: Spain Sites: 1 site
Patient characteristics	Inclusion Criteria: Newly diagnosed patients who fulfilled the London Brain Bank Criteria for idiopathic Parkinson's Disease and who had never received antiparkinsonian medication. This included subjects with low mood possibly associated with Parkinson's disease, but without meeting DSM-IV diagnostic criteria for major depression or dysthymia. Exclusion criteria: Patients with a Mini Mental State Examination score of less than 24, history of major psychiatric disorders, psychoactive medication, alcoholism, stroke, neurosurgical operation, or any other condition known to impair mental status other than PD.

Characteristics, mean ± SD	Pergolide N=10	Levadopa N=10

<table>
<tr><td></td><td>
<table>
<tr><td>Age, years</td><td>63.7 ± 10.5</td><td>67.3 ± 7.5</td></tr>
<tr><td>Male</td><td>4</td><td>3</td></tr>
<tr><td>Female</td><td>6</td><td>7</td></tr>
<tr><td>Education, years</td><td>6.7 ± 6.4</td><td>5.2 ± 4.1</td></tr>
<tr><td>Duration of Illness Prior to Treatment, months</td><td>14.1 ± 7.3</td><td>14.4 ± 6.2</td></tr>
<tr><td>Hoehn and Yahr</td><td>1.5 ± 0.6</td><td>1.8 ± 0.5</td></tr>
<tr><td>Predominant Symptom (tremor/akinetic rigid)</td><td>8/2</td><td>8/2</td></tr>
<tr><td>Side of Maximal Involvement (right/left)</td><td>4/6</td><td>5/5</td></tr>
<tr><td>Beck Depression Inventory</td><td>10.1 ± 7.9</td><td>8.5 ± 5.9</td></tr>
</table>
* Fisher’s exact test</td></tr>
<tr><td>Intervention</td><td>Pergolide (PG): Dosage was progressively increased every 3 days up to 1.5 mg/day for all patients, with patients receiving 3 daily doses of the medication. Thereafter doses were titrated on an individual basis by an examiner blinded to the treatment regimen who recommended a dosage modification to a non-blinded examiner.
Pergolide plus levodopa (PG/LD): Patients received pergolide as monotherapy until the day after the 6-month neuropsychological evaluation when levadopa was added.</td></tr>
<tr><td>Comparison</td><td>Levodopa: Dosage was progressively increased every 3 days up to 300mg/day for all patients, with patients receiving 3 daily doses of the medication. Patients received levadopa monotherapy for the entire length of the study.</td></tr>
<tr><td>Length of follow-up</td><td>Patients received a BDI and a comprehensive neuropsychological study at 3, 6, 12, 18, and 24 months after treatment initiation. Safety assessments were performed at all programmed monthly visits.</td></tr>
<tr><td>Outcome measures</td><td>Disease Progression (UPDRS Total Score), UPDRS Motor Score, Motor Speed (Simple Reaction Time and Finger Tap Test), Attention and Short-Term Memory (Span Performance), Verbal Learning (RAVLT), Visuospatial and Visuoconstructive abilities and Long-Term Visual Memory (RCFT), Frontal Tasks (Letter Fluency, Category Fluency, Luria Rhythm, Luria Motor, Arithmetic), Adverse Events.</td></tr>
<tr><td>Effect size</td><td>➢ Disease Progression (UPDRS Total Score): Addition of levadopa in the pergolide group after the 6-month examination did not detract from both groups obtaining a comparable symptomatic benefit.
➢ Motor Speed (Simple Reaction Time and Finger Tapping): No significant differences in time, treatment or treatment-by-time in motor speed tests between baseline and study endpoint. The addition of levadopa to the pergolide group after 6 months produced no significant changes.
➢ Attention and Short-Term Memory (Span Performance): No significant differences in time,</td></tr>
</table>

	treatment or treatment-by-time in patients' span performance for digits (Digit-Span) or visual designs (BVRT) between baseline and study endpoint. The addition of levadopa to the pergolide group after 6 months produced no significant changes. ➢ Verbal Learning (RAVLT): No treatment or treatment-by-time differences were observed. The addition of levadopa to the pergolide group after 6 months produced no significant changes. ➢ Visuospatial and Visuoconstructive abilities and Long-Term Visual Memory (RCFT): All measures of the RCFT decreased at the 18 and 24 month evaluations with improvement on visuospatial and visuoconstructive abilities (copy) becoming non-significant with respect to baseline. When comparing performance on the visuoconstructive ability test at 12 versus 6 months, this had declined in patients in the levadopa only group, whereas the introduction of levadopa in the pergolide group was associated with additional improvement. ➢ Frontal Tasks (Letter and Category fluency): Both letter and category fluency improvement became non-significant with respect to baseline at the study endpoint evaluation, with a t test comparison revealing a significant worsening at the 24 month versus the 18 month evaluation. ➢ Frontal Tasks (Stroop's Paradigm): No significant time, treatment, or treatment-by-time differences were reported from baseline to study endpoint. ➢ Frontal Tasks (Luria Rhythm and Motor tests, Arithmetic): While Luria Motor and Arithmetic tests revealed significant differences in performance for both groups between baseline and study endpoint, performance on the Luria Rhythm test became non-significant with respect to baseline at the 18 and 24 month evaluations, with a statistically significant worsening in performance at 24 months. Patients in the pergolide group showed improvement in arithmetic performance after the addition of levadopa at 6 months compared to the levadopa monotherapy group, which exhibited a decline in performance after 6 months. ➢ Dropout: All 20 patients included in the study completed the planned assessments for the first 12 months, while one patient was lost to follow-up at 18 months.
Source of Funding	The study was partially supported by a grant from Fundacio la Marato de TV3.
Additional comments	➢ The study was open-label with respect to patients' knowledge of treatment received. ➢ A board-certified neuropsychologist blind to the treatment regimen administered all neuropsychological tests. ➢ Method of randomisation used in the study was not reported. ➢ The authors claim that although small, the sample is 'probably' representative of Parkinson's disease patients

	➢ Lack of power calculations
Citation	2287
NCC CC ID (Ref Man)	

TxMN3 – section 7.2.6

Evidence Table **TxMN3** What is the effectiveness of amantadine vs. placebo or levodopa in the treatment of functionally disabled early Parkinson's disease?	
Bibliographic reference	Crosby N, Deane KHO, Clarke CE. Amantadine in Parkinson's disease (Cochrane Review). *The Cochrane Library* 2003.
Study type	Cochrane review of 6 randomised, double-blind, placebo-controlled studies
Evidence level	1++
Study objective	To compare the efficacy and safety of amantadine therapy (monotherapy or adjuvant therapy) versus placebo in treating people with Parkinson's disease.
Number of patients	N=215 patients N=23 (Fahn) N=30 (Fehling) N=42 (Savery) N=50 (Silver) N=42 (Walker a) N=28 (Walker b) Location: USA (all except one trial) and Sweden (Fehling) sites: all one centre trials
Patient characteristics	The mean ages of the patients in the 6 studies ranged from 61 to 66 years of age Overall age of participants ranged from 29 to 82 years Mean time since diagnosis (given in 4 trials) varied from 7.2 to 9.25 years (range 1- 35 years)

	Mean Hoehn and Yahr scores (given in 4 trials) ranged from 2.5 to 3.2 156/215 patients gender was reported in a ratio of 68%: 32% male: female
Intervention	Dose and frequency of amantadine varied ➢ 4 studies used 100mg 2x daily ➢ One study used 50mg/d and increased this to 100mg/d in first 2 weeks ➢ One study used 100mg/d for 3 weeks then increased to 200mg/d for second 3 weeks-then final 3 weeks patients chose which dosage they preferred
Comparison	Two studies stated the mean daily levodopa dose of their subjects ➢ One study was 3.43 g (ranging from 2.0 to 6.0g) ➢ The other study was 3.58g ➢ Only one study used levodopa in combination with a decarboxylase inhibitor (carbidopa)
Length of follow-up	Not stated
Outcome measures	Parkinsonian severity scale, activity impairment scale, Simulated Activities of Daily Living, Clinical Quantitative Neurological Examination, adverse events
Effect size	➢ 2 trials examined amantadine as an adjuvant to optimal levodopa therapy alone (Savery and Walker (b)) ➢ One trial examined amantadine as an adjuvant to optimal levodopa therapy and anticholinergics (if patient had been on them prior to trial) (Fehling) ➢ 2 trials maintained their patients on previous medication during trial (these were stated to be anticholinergics but were not described) (Silver and Fahn) ➢ 1 study reduced patients anticholinergics medication to nil or the lowest dose the patients could tolerate (Walker (a)) ➢ 3 trials were cross-over trials and did not present data from the end of the first arms (Fehling, Walker (b) and Fahn) ➢ Since there was a risk for carry-over effect the data from these trials was not analysed ➢ Fahn only presented data from the amantadine arms so no comparison could be made to the results of the placebo arm ➢ Silver compromised the randomisation by breaking the codes and did not analyse their data on an intention-to-treat basis and so their data was not analysed because of strong bias possibility ➢ Savery measured parkinsonian symptoms and impairments on an ad hoc assessment scale ➢ After 9 weeks of treatment the group treated with amantadine were on average 15.0 points better

	than the placebo group (average baseline score 21.4) in the parkinsonian severity scale ➢ And 28.1 points better (average baseline 38.3) on the activity impairment scale ➢ The statistical significance of this cannot be determined from the data provided by the authors ➢ Size of improvements does suggest they may have been clinically significant ➢ Wallker(a) measured 19 timed Simulated Activities of Daily Living such as putting on a shirt or using a fork ➢ Mean scores at the end of the first treatment arm are available but no standard deviations or baseline scores are provided ➢ Importance of these results to the patients and their clinical significance are unclear ➢ Also performed the Clinical Quantitative Neurological Examination (50 items) ➢ Only mean scores at the end of the first treatment are available but no standard deviations or baseline scores are provided ➢ Clinical significance of these results is unclear **<u>Adverse events</u>** ➢ Walker (a) reports 16 different side-effects 10 of which are presented in patients on amantadine ➢ Including: weight-loss (4), constipation (3), unsteadiness, blurred vision, and urinary straining (2 each) ➢ 26 patients on amantadine reported no side-effects compared with 18 on placebo ➢ Walker (b) used the same patients as Walker (a) and reported no new side effects ➢ Savery reports that amantadine caused on trivial side effects- the total difference between in frequency of side effects was not significant between amantadine and placebo ➢ Fahn reported 6 different side effects caused by amantadine including: insomnia (4), anorexia (5), dizziness and nervousness (2 each) ➢ Fehling reported 14 different side-effects caused by amantadine including: dryness of mouth (14), tiredness (7), abdominal discomfort (4), blurred vision, and giddiness (3) ➢ Silver reported that side effects were encountered in 47% of patients receiving amantadine ➢ Most common was livido reticularis which occurred in 9/34 patients-oedema was seen in 4/9 ➢ 12% of patients on placebo developed adverse events
Source of funding	None stated
Additional comments	➢ Inclusion criteria for studies: all randomised controlled trials comparing monotherapy and adjuvant

	oral amantadine therapy with placebo were considered ➢ 6 trials were found that compared amantadine as either monotherapy or adjuvant therapy ➢ None of the 6 trials provided details on the method of randomisation ➢ Five trials failed to describe allocation concealment ➢ Generalisability of results to female PD population limited by ratio of male: female participants ➢ Authors' conclusions: ''All six of the randomised controlled trials analysed in this review reported a positive effect of amantadine in Parkinson's disease. However poor reporting of results and the small numbers in all of the trials prevents any firm conclusions regarding the efficacy and safety of amantadine in the treatment of Parkinson's disease''. ➢ Trials included: Walker 1972 (a) (b), Savery 1977, Fahn 1975, Fehling 1973, and Silver 1971
NCC CC ID (Ref Man)	51

TxMN4 – section 7.3.5

Evidence Table **TxMN4** What is the effectiveness of MAO-B vs. dopamine agonists in the treatment of early Parkinson's disease?	
Bibliographic reference	Lees, A. J., Katzenschlager, R., Head, J., & Ben Shlomo, Y. 2001, "Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial.[see comment]", *Neurology*, vol. 57, no. 9, pp. 1687-1694.
Study type	Randomised open trial
Evidence level	1+
Study Objective	To report the results of a ten-year follow-up of bromocriptine, L-dopa and L-dopa/selegiline treated PD patients
Number of patients	N=782 de novo PD patients N=249 levodopa alone group N=271 levodopa/selegiline N=262 bromocriptine

<table>
<tr><td></td><td>Location: United Kingdom Sites: 93</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
All patients fulfilled the criteria for a clinical diagnosis of PD
Untreated patients required dopaminergic treatment were included
Patients with co morbid conditions could be included
Patients on anticholinergics and amantadine were included
Exclusion criteria:
Patients who were known to have failed to respond to dopaminergic drugs
Patients with incapacitating cognitive impairment
Characteristics:
Baseline characteristics of three treatment groups were similar in age, sex, duration of PD, disability scores</td></tr>
<tr><td>Intervention</td><td>Bromocriptine alone (arm 3)</td></tr>
<tr><td>Comparison</td><td>Levodopa and decarboxylase inhibitor (arm 1); Levodopa/decarboxylase inhibitor & selegiline (arm 2)</td></tr>
<tr><td>Length of follow-up</td><td>10 years</td></tr>
<tr><td>Outcome measures</td><td>Mortality and disability</td></tr>
<tr><td>Effect size</td><td>➢ 49 patients (16 arm1, 16 arm2, 17 arm3) had diagnosis revised during course of trial
Mortality
➢ Average follow-up 9.2 years
➢ Standardized mortality ratio (SMR) for patients in the study compared to the general population of United Kingdom was 1.78 (95%CI, 1.62 to 1.96)
➢ Statistical significance of difference among 3 arms in first 5 years of study; p=0.27
➢ Hazard ratio of bromocriptine versus levodopa alone was 1.15 (95%CI, 0.90 to 1.47)
➢ After adjustment for age, sex, duration of disease before randomisation, hazard ratio 1.12
➢ Hazard ratio for arms 2 vs. 3: 1.06 (95%CI, 0.84 to 1.34)
➢ Hazard ratio for arms 2 vs. 1: 1.22 (95%CI, 0.95 to 1.55)
➢ Hazard ratio (mortality attributed to PD arm 3 vs. arm 1) was 1.63 (95%CI, 1.0 to 2.7)

Disability
Table: difference (95%CI) in mean Webster disability scores
<table>
<tr><td>Time in trials</td><td>Arm 3 vs. 1</td><td>Arm 3 vs. 2</td><td>Arm 1 vs. 2</td></tr>
<tr><td>Year 1, n=670</td><td>0.9 (0.3 to 1.5)</td><td>1.3 (0.6 to 1.9)</td><td>0.3 (-0.3 to 1.0)</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Year 3, n=688</td><td>1.3 (0.4 to 2.2)</td><td>1.4 (0.6 to 2.3)</td><td>0.2 (-0.7 to 1.1)</td></tr>
<tr><td>Year 5, n=573</td><td>1.0 (0.2 to 2.1)</td><td>1.4 (0.3 to 2.5)</td><td>0.4 (-0.7 to 1.6)</td></tr>
<tr><td>Year 9, n=270</td><td>0.2 (1.5 to 1.5)</td><td>1.0 (0.6 to 2.5)</td><td>0.8 (-0.8 to 2.4)</td></tr>
</table>

Adjusted for baseline disability score. A positive difference indicates worse average disability in arm 1.
After 5 years follow-up the difference in Webster score between arm 1 and 3 was 1.0 (95%CI 0.2 to 2.1) showing that patients in arm 3 were slightly worse on average
Difference in disability between arm 1 and 3 diminishes after 5th year of follow-up
On average patients in bromocriptine arm returned to baseline disability after 3 years, 1 year before levodopa group (arm 1)
Arm 2 vs. 3 analysis was not performed for dyskinesias, dystonia, or on/off fluctuations

<u>Adverse reactions</u>:

Early adverse reactions were more common in bromocriptine arm than patients randomised to levodopa alone
All those re-randomised to another treatment came from arm 3
The median duration before introduction of levodopa in arm 3 was 2.1 years (95%CI 1.3 to 2.5)

</td></tr>
<tr><td>Source of Funding</td><td>Non-profit organization and pharmaceutical company</td></tr>
<tr><td>Additional comments</td><td>

Randomisation was carried out by independent coordinator methods listed
Intention-to-treat analysis
No blinding of investigators –possible bias in result interpretation
If patents did not improve they could be re-randomised to another group
Additional antiparkinsonian drugs were allowed during the trial
Comparability of results from different sites not stated
Trial took place between 1985 to 1990- where selegiline arm was terminated

</td></tr>
<tr><td>Citation</td><td></td></tr>
<tr><td>NCC CC ID (Ref Man)</td><td>2309</td></tr>
</table>

Evidence Table

TxMN4

What is the effectiveness of MAO-B vs. dopamine agonists in the treatment of early Parkinson's disease?

Bibliographic reference	Caraceni T,.Musicco M. Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomized multicenter study. *Parkinsonism & Related Disorders.* 2001;**7**:107-14.
Study type	Randomised open trial
Evidence level	1+
Study objective	To compare the occurrence of motor fluctuations and dyskinesias in previously untreated patients assigned to receive levodopa, a dopamine agonist or deprenyl
Number of patients	N=473 Parkinson's disease patients N= 156 levodopa N=162 dopamine agonist N=155 deprenyl Location: Italy sites: 35 neurological departments
Patient characteristics	<table><tr><th></th><th>Levodopa</th><th>Dopamine agonist</th><th>Deprenyl</th></tr><tr><td>Mean age (years)</td><td>63.4</td><td>63.0</td><td>63.4</td></tr><tr><td>Sex (men: women) (%)</td><td>52.6: 47.4</td><td>48.2: 51.8</td><td>55.5: 44.5</td></tr><tr><td>Mean months from first diagnosis</td><td>4.6</td><td>3.6</td><td>5.0</td></tr><tr><td>Mean months from disease onset</td><td>16.21</td><td>17.7</td><td>16.0</td></tr></table>➢ Diagnosis of PD was made on clinical criteria, when hypokinesia was associated with tremor, rigidity, or both for at least 6 months ➢ Exclusion criteria: interval from diagnosis greater than 2 years, dementia, secondary parkinsonism, and parkinsonian syndromes, taking drugs that could give rise to extrapyramidal signs, and previous treatment for more than 4 months with any of the studied drugs
Intervention	➢ Maximum dose was 10 mg for deprenyl
Comparison	➢ Maximum doses were 750 mg for levodopa plus dopa decarboxylase, 60 mg for bromocriptine, and 6 mg for lisuride

Length of follow-up	5 years
Outcome measures	Occurrence of motor fluctuations (wearing off and early morning akinesia) and dyskinesias
Effect size	➢ The drug doses were increased slowly over 2-4 weeks until clinical efficacy was reached or adverse effects occurred ➢ If deprenyl or dopamine agonists were or subsequently became ineffective levodopa was added ➢ In cases of non-tolerance the assigned drug was substituted for another by neurologist ➢ Patients were seen every 2 months (for first 6 months), then every 6 months ➢ Since no significant difference in the occurrence of principle outcomes was observed between patients assigned to bromocriptine and lisuride a single group of patient assigned to dopamine agonists was considered in the analysis ➢ No differences in the occurrences of the end-points among centres and in particular no significant interaction between treatment and centre was observed <u>Motor fluctuations</u>: ➢ More frequent among patients assigned to levodopa (29.7%) than patients assigned to dopamine agonists (16.7%) or deprenyl (18.7%) ➢ Mean time to motor fluctuations: levodopa: 26 months (SE 2.3), dopamine agonists: 23 (3.2) and deprenyl: 29 (3.2) ➢ Risk of developing motor fluctuations was significantly reduced in patients taking deprenyl or dopamine agonists compared to levodopa ➢ In patients assigned to a dopamine agonist or deprenyl, motor fluctuations occurred more frequently when levodopa was added to or substituted for the initial monotherapy <u>Dyskinesia</u>: ➢ Occurred less frequently in the dopamine agonist (14.8%) and deprenyl (20.7%) groups that in the levodopa group (27.1%) ➢ Dyskinesia occurred in patients assigned to levodopa after a mean period of 26 months (2.3), in dopamine agonist patients in 18 months (2.9) and deprenyl 21 months (2.6) ➢ In patients assigned to dopamine (not deprenyl) the risk of dyskinesia was significanrlt lower than patients assigned to levodopa ➢ Patients originally assigned to dopamine agonist or deprenyl- risk of dyskinesia was increased when levodopa was added to or substituted for original treatment ➢ No significant difference in % of patients whose motor signs deteriorated between 3 groups

	Adverse events ➢ 6% of patients stopped taking levodopa during the follow-up period, 32.7% stopped taking dopamine agonists and 19.4% stopped taking deprenyl ➢ Most patients withdrew from dopamine agonists because of: nausea/vomiting or postural hypotension (or both) (43/53 patients) ➢ Probability of ceasing treatment in patients assigned to deprenyl was 3x higher than patients assigned to levodopa ➢ Most of the withdrawals occurred in the first 6 months of treatment and were due to patient's or physician's determination of inefficacy ➢ Combination therapy was started in 12.9% of levodopa patients, 40.7% of dopamine agonist patients and 63.9% of deprenyl patients ➢ The initiation of levodopa therapy was delayed for a median of 30 months in dopamine agonist group and 15 months in deprenyl group ➢ No significant in mortality was found between the three groups followed-up from 1997
Source of funding	Pharmaceutical and government funding
Additional comments	➢ Rationale of open-trial: financial resources for trial were insufficient to overcome organisational complexities connected with double-blind study ➢ Methods of randomisation and allocation concealment listed ➢ Intention-to-treat analysis ➢ Power of 80% a sample of 500 patients necessary
NCC CC ID (Ref Man)	324

TxMN – section 7.2.2

Evidence Table

TxMN5

What is the effectiveness of immediate-release levodopa vs. placebo in the treatment of functionally disabled early Parkinson's disease?

Bibliographic reference	(ELLDOPA study) Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A *et al*. Levodopa and the progression of Parkinson's disease. *N Engl J Med* 2004;**351**:2498-508.
Study type	Randomised, double-blind, placebo-controlled study (ELLDOPA)
Evidence level	1++
Study objective	To assess the effect of levodopa on the rate of progression of Parkinson's disease (PD).
Number of patients	**Full cohort** — **[^{123}]β-CIT sub-study** N=361 early PD patients — N=142 of full cohort N=92 — 150 mg per day levodopa — N=38 N=88 — 300 mg per day levodopa — N=37 N=91 — 600 mg per day levodopa — N=38 N=90 — placebo — N=29 Location: USA and Canada — sites: 33 and 5 sites respectively
Patient characteristics	The subjects were 30 years of age or older, had received a diagnosis of PD within the past 2 years, had a rating on modified Hoehn and Yahr scale of less than stage 3 and were not likely to require therapy for symptoms of the disease within nine months after enrolment in the study. Patients were excluded if they were receiving antiparkinsonian medication, had been exposed to levodopa or to any dopamine agonist for more than 14 days, had an identifiable cause of parkinsonism, or had a tremor in any limb that was given a score of 3 or more on UPDRS, freezing of gait, loss of postural reflexes, major depression or dementia. The demographic and clinical characteristics of the subjects in the treatment groups were similar at baseline, both in the entire sample and in the neuroimaging study. (Average age 64 years and average disease duration 6 years)
Intervention	Carbidopa-levodopa at a daily dose of 37.5 and 150 mg, 75 and 300mg, or 150 and 600mg
Comparison	Matching placebo
Length of follow-up	Trial duration of 40 weeks, withdrawal of treatment for 2 weeks
Outcome measures	UPDRS scores, neuroimaging data, adverse events and drop-out data

<table>
<tr>
<td>Effect size</td>
<td>
Clinical outcomes (UPDRS)
➢ Levodopa in a dose-response pattern reduced the worsening of symptoms of PD
➢ Change in UPDRS total score at baseline and at week 42 compared to placebo (p<0.001)
o Change in mental component (non-significant), change in ADL component (p<0.001), change in motor component (p<0.01)
➢ The scores on the UPDRS in the 3 levodopa groups worsened during the 2-week washout period
➢ These groups did not deteriorate to the level observed in the placebo group
➢ The group receiving the highest dose of levodopa had the best result

β-CIT outcomes (neuroimaging):
➢ The percent decrease in striatal uptake over 40 weeks of the study treatment was greater among subjects in levodopa than placebo groups (non-significant)
➢ 21/142 subjects (14.7%) had a putaminal uptake of more than 3.25 at baseline (i.e. more than 75% of the age-expected putaminal uptake)
➢ an analysis of the results of SPECT after the exclusion of the 19 patients without a dopaminergic deficit who returned for neuroimaging studyat week 40 showed a significantly greater decrease in uptake among those receiving levodopa than those receiving placebo (p=0.036)

Adverse events
➢ Adverse events were significantly more common in 600mg group than placebo for dyskinesias (p<0.001), nausea (p=0.001), infection (p=0.01), hypertonia (p=0.03) and headache (p=0.03)
➢ Non-significant between other levodopa doses and placebo

Drop-outs
➢ Of the total 361 subjects enrolled- 317 (88%) took the study medication for 40 weeks and 311 (86%) completed the 2 weeks of washout
<table>
<tr><td></td><td>Placebo</td><td>150mg/d</td><td>300 mg/d</td><td>600 mg/d</td></tr>
<tr><td>Total sample size</td><td>90</td><td>92</td><td>88</td><td>91</td></tr>
<tr><td>Did not complete %(n=)</td><td>22% (20)</td><td>15% (14)</td><td>6% (6)</td><td>11% (10)</td></tr>
<tr><td>Worsening symptoms</td><td>13</td><td>5</td><td>1</td><td>2</td></tr>
<tr><td>Adverse events</td><td>3</td><td>2</td><td>2</td><td>1</td></tr>
<tr><td>Withdrew</td><td>2</td><td>2</td><td>2</td><td>3</td></tr>
<tr><td>Lost to follow-up</td><td>1</td><td>3</td><td>-</td><td>2</td></tr>
</table>
</td>
</tr>
</table>

	Other | 1 | 2 | 1 | 2 ➢
Source of funding	Non-profit and government
Additional comments	➢ methods of randomisation and allocation concealment not stated ➢ Sample size calculations included ➢ Intention-to-treat analysis ➢ Statistical analysis for differences among investigators performing the evaluations and in baseline values
Citation	
NCC CC ID (Ref Man)	19725

TxMN6 – section 7.3.1

Evidence Table **Q TXMN6** What is the effectiveness of modified-release levodopa vs. immediate release levodopa in the treatment of early Parkinson's disease?	
Bibliographic reference	Block, G., Liss, C., Reines, S., Irv, J., Nibbelink, D., Aarli, J., Aguilar, M., Ahrens, S., Bakheit, A., Baumel, B., Bertoni, J., Capildeo, R., Castro-Caldas, A., Deza, L., Donaldson, I., Franck, G., Fusillo, J., Gauthier, S., Gershanik, O., Granerus, A. K., Hauser, R. A., Hennessey, K., Hutton, J. T., Joffe, R., Killer, W., Last, B., LeWitt, P., Mamoli, B., Manyam, B., Mark, M., Nakano, K., Nausieda, P., Otero, E., Paulson, G., Pinter, M., Reich, S., Rodnitzky, R., Sage, J., Sampaio, C.., Smith, B., Teravainen, H., Tetrud, J., Tolsa, E., Ulm, G., & Valesco, F. 1997, "Comparison of immediate-release and controlled release Carbidopa/Levodopa in Parkinson's disease. A multicenter 5-year study", *European Neurology*, vol. 37, no. 1, pp. 23-27.
Study type	5 year triple blind, randomised, parallel study
Evidence level	1+
Number of patients	N=618

	Early PD patient (Hoehn-Yahr stage I, II or III) Location: International Sites: 35
Patient characteristics	Hoehn-Yahr stages I, II or III and exhibiting two of five major clinical signs of PD. Levodopa naïve patients Mean age 62 ± 10 years 378 males and 240 females 90% were white
Intervention	Sinemet immediate release (IR) 25/100 twice a day initially with doses adjusted throughout study to optimise clinical response
Comparison	Sinemet controlled release (CR) 50/200 twice a day initially with doses adjusted throughout study to optimise clinical response
Length of follow-up	5 years. Patients initially seen at weeks 1,2,4,8 and 12 after starting treatment and then at 3-month intervals.
Outcome measures	Primary endpoint defined as progression of disease to the onset of motor fluctuations • When more that 20% of waking day was spent in the 'off' state (patient diary) • When more than 10% of the waking day was spent in the 'on with dyskinesia' state (patient diary) • When responses to 50% or more of the questions for the 'motor fluctuation' questionnaire were positive Other outcome measures • New York University Parkinson Disease Scale (NYUPDS) • Northwestern University Disability Scale (NUDS) • Global assessment by the patient • Unified Parkinson Disease Rating scale (UPDRS) • Nottingham Health Profile (NHP)
Effect size	***Primary endpoint*** ➢ No significant difference between treatment groups for motor fluctuations (primary endpoint) either

	by diary data or by questionnaire. After 5 years, 20.6% of the IR group and 21.8% of the CR group patients had motor fluctuations by diary criterion. 16% of each group had motor fluctuations by questionnaire definition. ***Other outcome measures*** ➢ No significant differences between groups in NYUPDS, NUDS, and total UPDRS. ➢ No significant differences between treatment groups in global assessment including Hoehn-Yahr scale and Schwab-England scores from baseline to 5 years. ➢ No significant difference between treatment groups in serious adverse events. ➢ Incidence of withdrawal due to nausea was significantly higher (p=0.007) for the IR group than the CR group. ➢ Activities of daily living scores (ADL) of the UPDRS (mean change from baseline) were significantly better for the CR group compared with the IR group for each of the 5 years - Mean change year 1: Sinemet IR = –3.2 points vs. Sinemet CR = -3.8 points (p = 0.006) - Mean change year 2: Sinemet IR = -2.5 points vs. Sinemet CR = -3.4 points (p = 0.03) - Mean change year 3: Sinemet IR = -1.3 points vs. Sinemet CR = -2.5 points (p = 0.005) - Mean change year 4: Sinemet IR = -0.6 points vs. Sinemet CR = -1.7 points (p=0.004) - Mean change year 5: Sinemet IR = +0.2 points vs Sinemet CR = -0.8 points (p=0.031) ➢ In the Nottingham Health Profile, there was a statistically significant difference in favour of Sinemet CR for emotional reaction and social isolation (p<0.05) ***Dosing*** ➢ Mean daily levodopa doses at baseline; IR 172mg and CR 345mg (241mg bioavailable dose) ➢ Mean daily levodopa doses after 5 years; IR 426mg and CR 728mg (510mg bioavailable dose) ➢ Average number of administrations and tablets at end of study; IR 3.6 administration and 4.3 tablets per day, CR 3.2 administrations (p<0.005) and 3.6 tablets per day (p<0.001)
Source of Funding	Not stated. One primary author from Merck and Co and one from DuPont Pharma.
Additional comments	➢ **Aim**: To evaluate the clinical benefits and complications of immediate and sustained-release carbidopa/levodopa in levodopa naïve Parkinson's disease patients. ➢ No differences in baseline characteristics between groups ➢ 36% had received other antiparkinsonian medications. ➢ Dosages of other antiparkinsonian medications held constant. ➢ 61% of IR (187) and 62% (193) of CR completed the study. Reasons for withdrawal stated.

	➢ Common adverse effects similar in both treatment groups: nausea, dizziness, insomnia, abdominal pain, dyskinesia, headache and depression. ➢ Dosage adjusted for optimum clinical response ➢ Authors noted that rate of motor fluctuations was lower than previous studies, perhaps due to differences in definition of motor fluctuations and/or regimen allowing for altering dose to optimise clinical response. ➢ Higher dose of controlled release Sinemet at end of study (CR 510mg vs IR 426mg) may account for drug's more positive effect on activities of daily living and emotional reaction and social isolation.
Citation	
NCC CC ID (Ref Man)	257

Evidence Table **Q TXMN6** What is the effectiveness of modified-release levodopa vs. immediate release levodopa in the treatment of early Parkinson's disease?	
Bibliographic reference	Dupont, E., Andersen, A., Boas, J., Boisen, E., Borgmann, R., Helgetveit, A. C., Kjaer, M. O., Kristensen, T. N., Mikkelsen, B., Pakkenberg, H., Presthus, J., Stien, R., Worm-Petersen, J., & Buch, D. 1996, "Sustained-release Madopar HBS compared with standard Madopar in the long-term treatment of de novo parkinsonian patients", *Acta Neurologica Scandinavica*, vol. 93, no. 1, pp. 14-20. Ref ID: 778
Study type	5 year double blind, randomised, parallel study
Evidence level	1+
Number of patients	N=134 Early PD patient (Hoehn-Yahr stage I, II or III) Levodopa naive Location: Denmark and Norway Sites: 13
Patient characteristics	Hoehn-Yahr stage I, II or III and exhibiting at least two major clinical signs of PD.

	Madopar standard n = 65 Age 66 ± 9.7 Males 55% Mean duration of PD 2.7 ± 1.9 <u>Madopar HBS (controlled release) n = 69</u> Age 65 ± 10.45 Males 57% Mean duration of PD 2.5 ± 1.7
Intervention	Madopar standard (25mg benserazide + 100mg levodopa) 1 capsule daily in the morning. Dose adjusted throughout study to optimise clinical response
Comparison	Madopar HBS slow release ((25mg benserazide + 100mg levodopa) 1 capsule daily in the morning. Dose adjusted throughout study to optimise clinical response.
Length of follow-up	5 years. Patients evaluated at baseline, at the end of 1.5, 3, 6, 9 and 12 months and subsequently every 6 months.
Outcome measures	Webster rating scale; Northwestern University Disability Scale (NUDS); Hoehn and Yahr stages; Unified Parkinson Disease Rating scale (UPDRS); Adverse events; and BP, pulse and screening laboratory tests
Effect size	➢ <u>Efficacy</u> ➢ No significant difference between groups in Webster rating scale, NUDS, UPDRS or Hoehn and Yahr stages. ➢ <u>Dosing</u> ➢ Mean daily dose of levodopa was not significantly different between groups ➢ Mean number of daily doses did not differ significantly between groups ➢ <u>Adverse effects</u> ➢ No significant difference between groups with respect to incidence of side effects.
Source of Funding	Not stated. One author from Roche A/S
Additional comments	➢ **Aim**: To compare the therapeutic response of Madopar HBS (controlled release) and standard Madopar in a 5 year treatment of de novo parkinsonian patients. ➢ After 6 months of treatment, an additional open-label standard Madopar 62.5mg dose could be added to the first morning dose in case of too long latency of effect.

	➢ Bromocriptine and anticholinergics permitted. ➢ 65/134 patients dropped out of the trial ➢ Reasons for withdrawal comparable for both treatments
Citation	
NCC CC ID (Ref Man)	778

Evidence Table
Q TXMN6
What is the effectiveness of modified-release levodopa vs. immediate release levodopa in the treatment of early Parkinson's disease?

Bibliographic reference	Kinnunen, E., Asikaimen, I., Jolma, T., Murros, K., Pammo, O., Salmi, K., Soikkeli, R., Taalas, J., & Valpas, J. 1997, "Three-year open comparison of standard and sustained-release levodopa/benserazide preparations in newly diagnosed Parkinsonian patients", *Focus on Parkinson's Disease*, vol. 9, no. 2, pp. 32-36.
Study type	3 year randomised open multi-centre study
Evidence level	1+
Number of patients	N=161 newly diagnosed idiopathic Parkinson's disease (PD) patients Location: Finland Sites: 9 Neurological centres
Patient characteristics	Recruitment took place from May 1990 to August 1992 Each patient was assessed neurologically at entry into the study None of the patients had received anti-parkinsonian medication previously Exclusion criteria: no severe cardiovascular, liver, kidney, or mental disorders including dementia, or patients on neuroleptic medication, or patients > 80 years of age.

Characteristic	Madopar standard	Madopar HBS
Number (female/male)	84 (42/42)	77 (37/40)
Age (years; mean ± SD)	66.7 ± 8.6	65.8 ± 8.8
Hoehn and Yahr stage (mean)	1.9	1.9
Schwab & England Scale (mean)	82	82
UPDRS Total (mean ± SD)	24.9 ± 11.9	24.2 ± 9.3

Intervention	77 patients were randomly allotted to receive treatment with Madopar HBS (sustained release preparation) dosage was fixed at the start of the study with 100mg 3x per day (dosage was increased or reduced according to the patient's response throughout the study)
Comparison	84 patients were randomly allocated to receive treatment with Madopar standard dosage was fixed at the start of the study with 100mg 3x per day (dosage was increased or reduced according to the patient's response throughout the study)
Length of follow-up	Follow-up visits occurred at 3,6,12,18,24,30, and 36 months
Outcome measures	UPDRS total scores, Hoehn and Yahr Scale scores, and Schwab & England scores
Effect size	➢ 62% or 161/ 100 of patients enrolled completed the study ➢ 54/ 100 treated with Madopar standard and 46/100 treated with Madopar HBS ➢ After 6 months the daily dose of Levodopa in the group receiving Madopar HBS was 15% higher (p=0.04) ➢ At the end of the study this rose to 17% (p=0.04) compared to the Madopar standard group ➢ The number of daily doses increased in both groups but this was not significant between groups (p=0.22) ➢ During the last 12 months of the study UPDRS total scores of the group receiving HBS treatment increased, and at 36 months the difference was nearly significant (p=0.053) ➢ At the end of the study no significant differences were found between groups in relation to mental, motor, and activity scores of the UPDRS Scale ➢ The Hoehn and Yahr Scale scores (1.8 vs. 1.9), and Schwab and England scores (84 vs. 80%) did not differ significantly between groups ➢ Wearing-off type clinical fluctuations developed more frequently in patients on standard levodopa medication after 30 month's treatment (p=0.01) compared to standard release formula ➢ Occurrence of dyskinesias did not differ significantly between groups ➢ No significant differences were observed in total UPDRS scores ➢ Clinical fluctuations were seen in both groups at 36 months and there was no significant difference ➢ No adverse events occurred more significantly In one group over the other
Source of Funding	None stated
Additional comments	➢ Reasons for discontinuance stated ➢ All investigators were neurologists with experience in treating patients with PD ➢ Patients were assessed with UPDRS at each visit ➢ Hoehn and Yahr scale and Schwab and England test were only used at the beginning and end of the study

	➢ Open study- investigators and patients not blind to allocation
Citation	
NCC CC ID (Ref Man)	304

Evidence Table **Q TXMN6** What is the effectiveness of modified-release levodopa vs. immediate release levodopa in the treatment of early Parkinson's disease?	
Bibliographic reference	Hutton, J. T., Lynne, D. R., & Bianchine, J. R. 1984, "Controlled-release carbidopa/levodopa in the treatment of Parkinsonism", *Clinical Neuropharmacology*, vol. 7, no. 2, pp. 135-139. Ref ID: 783
Study type	Randomised, double-blind, crossover study
Evidence level	1-
Number of patients	N=20 Parkinson's disease (PD) patients Location: USA (no further details) Sites: not stated
Patient characteristics	Subjects with early-stage PD (stage II or III – Hoehn and Yahr classification) Number of subjects at Hoehn and Yahr (H&Y) stages I-III: 20 15 males and 5 females (age 51-81 years; mean 67 years) No patients with co-morbid conditions. No patients taking any other medication apart from anticholinergic medications and amantadine hydrochloride. Recruitment: No description of recruitment
Intervention	Controlled-release carbidopa/levodopa (CSR-1) containing 25mg carbidopa and 100mg levodopa 3 times a day
Comparison	Standard carbidopa/levodopa (Sinemet 25/100) 3 times a day

Length of follow-up	4 weeks Week 1 – Patients stabilised on individually appropriate dosages of carbidopa/levodopa Week 2 and week 3 – Double-blind, randomised crossover study Week 4 – Dose of second drug (either CSR-1 or Sinemet) increased. Repeating clinical assessment and collecting blood and urine specimens.
Outcome measures	Sign and symptom scale (total score) Sign and symptom scale (rigidity) Northwestern disability scale Physiological tremor
Effect size	➢ Patients monitored using Sign and Symptoms Scale and Northwestern Disability scale performed 6-8 hours following morning dosage. Urine and blood samples were taken for bioavailability analyses and a physiological measure of tremor assessed. ➢ No significant difference in Signs and Symptoms (total score) between groups ➢ No significant difference in Northwestern disability scale between groups ➢ Significantly less rigidity in Sinemet 25/100 group compared with CSR-1 (12 of 16 patients $p<0.05$) ➢ Significantly less tremor in Sinemet 25/100 group compared with CSR-1 (11 of 13 patients at 7 hours following dosage $p<0.05$; 11 of 14 patients at 11 hours following dosage $p<0.05$)
Source of Funding	Supported by grant from Merck Sharpe and Dohme Laboratories
Additional comments	➢ **Aim**: To evaluate the efficacy and adverse effects resulting from use of controlled-release preparation CSR-1 compared with standard carbidopa/levodopa ➢ Clinical diagnostic criteria not stated ➢ **Doses of drugs not stated** ➢ Number of sites not stated. Number of investigators not stated. ➢ Detailed methods of outcome measurement not stated. ➢ Methods of randomisation not stated. ➢ No long-term clinical follow-up stated ➢ Technical problems at laboratory prevented analysis of the blood and urine specimens. ➢ Side effects reported frequently for both medications: dry mouth, involuntary movements, fatigue, urinary retention, increased tremor, muscle twitching and sleeping difficulties.
Citation	
NCC CC ID (Ref Man)	783

TxMN9 – section 7.2.7

Evidence Table **TxMN9** What is the effectiveness of anticholinergics vs. placebo or levodopa effective in the treatment of functionally disabled early Parkinson's disease?	
Bibliographic reference	Katzenschlager R, Sampaio C, Costa J, Lees A. Anticholinergics for symptomatic management of Parkinson's disease. (Cochrane Review). *The Cochrane Library* 2003.
Study type	Cochrane Review of 9 RCTs all double-blind cross-over design
Evidence level	1++ (based on Cochrane methodology not individual trials)
Study objective	To determine the efficacy and tolerability of anticholinergics in the symptomatic treatment of Parkinson's disease compared to placebo or no treatment.
Number of patients	N=221 Locations: US x 3, Italy x 2, Finland, UK x3 sites: all single centre studies
Patient characteristics	De novo or advanced PD Considerable differences in baseline characteristics if the patients included in the studies Brumlik: 2 female, 30 male, mean age 62 years, disease duration 2.25 years Cantello: 17 female, 13 male, mean age 65 years, disease duration not stated Livainen: 9 female, 11 male, mean age 61 years, mean disease duration 6 years Kaplan: 11 female, 24 female, age 32-63 years, disease duration not stated Norris: 7 male, 7 female, mean age 67 years, disease duration not stated Piccirilli: 5 female, 12 male, mean age 61 years, mean disease duration 6.8 years Tourtelotte: 29 male patients, mean age 62.5 years, disease duration not stated Vicary: 16 female, 10 male, age 41-77 years, disease duration not stated Whyte: 9 female, 6 male, mean age 59 years, mean disease duration 10 years
Intervention	Anticholinergic drugs either as monotherapy (Kaplan and Brumlik) or an add-on to other treatments Benzhexol (mean doses: 8 to 20 mg/d)(not stated in Kaplan trial) Orphenadrine (mean dose not reported- Whyte) Benztropine (mean dose not reported- Tourtelotte)

	Bornaprine (8 to 8.25 mg/d) Benapryzine (200 mg/d) Methixine (45 mg/d)
Comparison	Placebo or no treatment
Length of follow-up	5-20 weeks trial duration, treatment periods ranged from 2 to 10 weeks
Outcome measures	Almost all of the scales applied were the author's own (Brumlik, Whyte, Livainen, Tourtelotte) or no longer in current use. Only two studies used the Webster Rating Scale (Piccirilli and Cantello).
Effect size	Motor function and disability ➢ Kaplan used electromyography (EMG) to measure tremor amplitude- deterioration occurred in placebo but not on benzhexol (or other 2 anticholinergics investigated) ➢ The neurological examination was improved 6% on placebo and 40% on benzhexol ➢ Brumlik ''a tendency towards a significant improvement'' is reported in tremor duration (but not tremor amplitude) speech intensity and speaking rate compared to placebo measurements ➢ Whyte used author's own 4-item rating scale to assess 12 physical signs and 8 disabilities ➢ A significant improvement from baseline was found on the active drug including rigidity, posture, walking, and total physical signs but not tremor ➢ Livainen applied author's own 5-grade rating scale- statistically significant reduction of resting and postural tremor was found- while no significant improvement on rigidity, hypokinesia, power, gait, pro/retropulsion, sweating, everyday activities (not specified) and mental function ➢ Cantello applied Webster score: tremor showed the most marked improvement from 2.48 at baseline to 1.18 on bornapine versus 2.00 on placebo ➢ Other features such as bradykinesia, rigidity, posture and facial expression also showed a significant improvement on drug with a less marked but still significant improvement on placebo ➢ 8/9 studies reported a statistically significant improvement from baseline in at least one motor function or activity of daily living in patients on active drug ➢ Improvement in active arm was reported to be significantly better than placebo arm in Vicary (total disability score), Livainen (tremor on a 5-item scale) Piccirilli (Webster scale, handwriting, drawing, accelometry), Cantello (''all-round assessment of efficacy'' by investigators and patients) and Tourtelotte (investigators and patients overall impression and a number of poorly defined motor function tests including speed, coordination, gait, and others) ➢ Kaplan found a significant difference between the two arms in that tremor amplitude remained the same on benzhexol and deteriorated on placebo ➢ Norris found no significant difference in tremor from baseline on Methixine measured by

	accelerometry ➢ No study found placebo to be superior to active drug Adverse effects: ➢ Two studies (Norris and Piccirilli) found no neuropsychiatric or cognitive adverse effects ➢ Kaplan did not report this outcome ➢ All other studies reported occurrence of neuropsychiatric effects: confusion (26), disorientation (1), 'altered perception' (1), 'psychic disturbance' (1), insomnia (2), restlessness (1), tiredness (2), memory problems (1), poor concentration (1), irritability (1), hallucinations (21) ➢ The number of patients who experiences any neuropsychiatric adverse events while on active drug was 31 as opposed to 13 on placebo (this excludes the study by Tourtelotte which did not report whether patients experienced any adverse events on placebo) Withdrawals: ➢ No drop outs in 3 studies and 4 drop outs in 2 studies ➢ Whyte: four patients dropped out of placebo allocation. In 3 cases this was due to deterioration of parkinsonism following withdrawal of active drug after patients cross-over to placebo arm- one patient stopped placebo because of subjective lack of benefit ➢ Vicary: two patients dropped out of active drug group because of acute confusional state while on drug- one patient was withdrawn after fracturing an ankle and allocation was not reported ➢ Norris: one patient dropped out due to unspecified adverse events while on placebo and one due to randomisation error ➢ Cantello: 3 patients were withdrawn because of failure to attend and allocation was not reported ➢ Two studies failed to report drop-outs altogether (Kaplan and Brumlik) Comparison of different anticholinergic drugs: ➢ Only one study (Vicary) involved two different anticholinergic drugs (benzhexol and benapryzine) in patients who were on stable levodopa therapy. No significantly better improvement compared to placebo was found on either drug. ➢ A subgroup analysis show showed significantly more improvement on both drugs compared to placebo in those patients who had previously been on any anticholinergics (which had been withdrawn before entry into the study)
Source of funding	Not stated
Additional comments	➢ Robust search strategy

	➢ Only one trial involved 2 anticholinergic drugs ➢ Incomplete recording of methodology and results was frequent ➢ Heterogeneous study designs and poor reporting did not allow pooled statistical analysis ➢ Only one study describes method of randomisation ➢ Only one trial (Kaplan did not specify blinding conditions-possibly single blind study) ➢ In 4 studies no washout period was reported (Whyte, Vicary, Livainen, Cantello) and these studies did not look for carry-over effects ➢ Exact number of drop-outs cannot be determined as not all studies reported numbers ➢ Sample size calculations were not available for any of the included studies ➢ None of the studies performed data analysis on an intention-to-treat basis ➢ Unvalidated and subjective scales were used to assess outcome measures ➢ Authors included: Brumlik 1964, Cantello 1986, Livainen 1974, Kaplan 1954, Norris 1967, Piccirilli 1985, Tourtelotte 1982, Vicary 1973, Whyte 1971
NCC CC ID (Ref Man)	92

Evidence Table **TxMN9** What is the effectiveness of anticholinergics vs. placebo or levodopa in the treatment of functionally disabled early Parkinson's disease?	
Bibliographic reference	Cooper JA, Sagar HJ, Doherty SM, Jordan N, Tidswell P, Sullivan EV. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. *Brain* 1992;**115**:1701-25.
Study type	Randomised, single-blinded, parallel design
Evidence level	1+
Study objective	To compare the effects of levodopa with other anti-parkinsonian drugs and include a range of neuropsychological tests to evaluate the specificity of any effects observed
Number of patients	N= 82 early Parkinson's disease patients N= 25 levodopa-treated N= 20 bromocriptine-treated N=22 anticholinergic-treated

<table>
<tr><td></td><td>N=15 untreated
N=22 healthy controls

Location: UK sites: single</td></tr>
<tr><td>Patient characteristics</td><td>None of the patients had received levodopa or other dopaminergic therapy. All were assessed in the untreated state.
All patients included continued to fulfil the diagnostic criteria of the Parkinson's disease society: akinesia plus rest tremor, rigidity or postural instability and absence of any other condition that may produce signs of parkinsonism.
Groups did not differ at baseline (phase 1).
At phase 1 the untreated group tended to have lower level of motor disability as measured by the King's College Rating Scale score than the other Parkinson's disease groups (p=0.069).

<table>
<tr><th>Characteristic</th><th>Control</th><th>Levodopa</th><th>Bromocriptine</th><th>Anticholinergic</th><th>Untreated</th></tr>
<tr><td>Mean age, yrs</td><td>60.6</td><td>58.2</td><td>57.8</td><td>60.8</td><td>59.2</td></tr>
<tr><td>Sex M/F</td><td>10/12</td><td>13/12</td><td>10/10</td><td>9/13</td><td>10/5</td></tr>
<tr><td>Mean disease duration, months</td><td>N/A</td><td>21.7</td><td>18.6</td><td>22.1</td><td>18.4</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Anticholinergics (ACh): 22/23 benzhexol (mean dose 5.9 mg/d) and 1 /23 orphenadrine (150mg/d)
Or Bromocriptine (Br): mean dose 13.5 mg/d (range 2-40 mg/d)</td></tr>
<tr><td>Comparison</td><td>Levodopa (LD): mean dose 415 mg/d (range 125-1000mg/d)</td></tr>
<tr><td>Length of follow-up</td><td>4 months</td></tr>
<tr><td>Outcome measures</td><td>King's College rating scale and fine finger movements test, large number of neuropsychological tests</td></tr>
<tr><td>Effect size</td><td>Motor control
➢ King's College Rating Scale scores:
➢ From baseline to 4 months follow-up motor control significantly improved in ACh (p<0.05) and LD (p< 0.01) groups not in Br group (p=0.4) or untreated group (p=0.3)
➢ Different anti-PD medications were shown to not have a qualitatively different effect on parkinsonian symptoms
➢ Authors suggest this may be due to low level of disease severity

Neuropsychological tests relevant to anticholinergic treatment:</td></tr>
</table>

	➢ Wechler Memory scale- significant improvement in LD group and untreated group, ACh group deteriorated (not statistically significant) ➢ Deficit of ACH group on some other tests underlying immediate registration of information: Brown Peterson test- specific deficit of Ach group ➢ Similar deficit of ACh group on Associate Learning Subset and early distraction-filled intervals of Brown-Peterson test- not correlated to age of patients ➢ Other cognitive measures showed no change on treatment
Source of funding	Government, Hospital, and Pharmaceutical
Additional comments	➢ Dropouts: 7 PD and 15 controls ➢ Not intention-to-treat ➢ No methods of randomisation or allocation concealment ➢ At phase 1: 15 of the parkinsonian patients elected not to take medication and were retested in an untreated state- rest of PD patients were randomised to either bromocriptine, levodopa or anticholinergic drugs
NCC CC ID (Ref Man)	19567

Evidence Table **TxMN9** What is the effectiveness of anticholinergics vs. placebo or levodopa in the treatment of functionally disabled early Parkinson's disease?	
Bibliographic reference	Parkes JD, Baxter RC, Marsden CD, Rees JE. Comparative trial of benzhexol, amantadine, and levodopa in the treatment of Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry* 1974;**37**:422-6.
Study type	Randomised, double-blind, cross-over trial of 3 treatments (Benzhexol, amantadine, and benzhexol/amantadine) and open un-randomised comparison of 3 treatments to levodopa
Evidence level	1-
Study objective	To study the effects of benzhexol, amantadine, and levodopa separately to previously untreated patients with Parkinson's disease (PD) or post-encephalitic parkinsonism
Number of patients	N=17
Patient characteristics	10 men and 7 women, aged 47-79 years (mean age 63)

	15 had PD and 2 men had post-encephalitic parkinsonism No patient with PD had previously been given treatment for Parkinson's disease Duration of illness was 6 months to 14 years (mean duration 3.1 years) (excluding two patients with post-encephalitic parkinsonism who had a disease duration of over 35 years) Disability of all patients before treatment was very slight
Intervention	Benzhexol (2 mg 4x/day) (amantadine 100 mg 2x daily- see TxMN3)
Comparison	Levodopa treatment in individual determined doses (final daily dosage ranged from 750 mg to 3g)
Length of follow-up	Trial duration 4 weeks for Benzhexol and amantadine, 6 months for levodopa
Outcome measures	Total disability, akinesia, tremor, posture, rigidity
Effect size	➢ Benzhexol, amantadine, and combined benzhexol/amantadine treatments were given in a cross-over design for 4 weeks ➢ Levodopa was not given in double-blind fashion but individually titrated and follow-up for 6 months ➢ 14 patients completed the first 12 week period ➢ 10 reported improvement with amantadine ➢ 9 with benzhexol ➢ 10 with combined benzhexol and amantadine treatment Subjective responses ➢ The combination therapy was rated the best of the three treatments by 8/14 patients ➢ Improvement with benzhexol/amantadine was established within 3 days of treatment ➢ 9 patients completed the levodopa phase ➢ Levodopa was preferred by 6/9 patients over previous 3 treatments ➢ The effect of levodopa increased throughout the treatment period of 6 months Individual drug effects ➢ Benzhexol and amantadine treatment separately each produced a reduction in mean total disability score of 15% from pre-treatment scores ($p<0.05$ each) ➢ The two drugs combined produced a 40% reduction in total disability score at the end of a 4 week treatment period ($p<0.01$) ➢ The difference between the reduction of score produced by combined benzhexol and amantadine and levodopa treatment was not significant ➢ In 9 patients who were given levodopa- the mean improvement had been benzhexol 15%, amantadine 17% and benzhexol/amantadine 42% ➢ Benzhexol gave a slight improvement in rigidity and flexion deformity ➢ The effect on rigidity was a little greater than amantadine but much less than levodopa

	➢ 80% of the reduction in the combined scores for tremor, akinesia, rigidity, and posture with benzhexol was due to improved rigidity and posture ➢ Combined treatment improved all of the symptoms more than the sum of the improvement of each drug separately ➢ Both posture and rigidity was particularly improved p<0.01 ➢ The combined treatment effect was comparable to levodopa ➢ Tremor, akinesia, posture and rigidity improved during levodopa treatment ➢ Disability due to tremor, flexion of posture, and rigidity was approximately halved in each case ➢ The effect on akinesia was less but still 9x greater than benzhexol and 3x greater than amantadine ➢ 10/14 patients showed a reduction in total disability score (improvement)-same for amantadine ➢ The correlation between the response to levodopa and the response to benzhexol as indicated by reduction in total disability was not statistically significant Toxic effects ➢ 8/14 complained of dry mouth before any treatment ➢ This became more severe during benzhexol treatment ➢ Benzhexol and amantadine each produced mental confusion in patients not reported previously
Source of funding	Pharmaceutical
Additional comments	➢ Criteria for diagnosis not stated ➢ Levodopa phase open and not cross-over (not randomised) ➢ 3 week benzhexol treatment phase compared to 6 mo levodopa treatment phase ➢ Not intention-to-treat ➢ 5/17 (30%) drop-outs only 12 entered levodopa phase of trial ➢ no description of methods of randomisation or allocation concealment ➢ no validated rating scales were used to assess disability
NCC CC ID (Ref Man)	19569

TxMN10 – section 7.2.5

Evidence Table

TxMN10

What is the effectiveness of beta-blockers vs. placebo or levodopa in the treatment of functionally disabled early Parkinson's disease?

Bibliographic reference	Crosby, N. J., Deane, H. O., & Clarke, C. E. 2004, "Beta-blocker therapy for tremor in Parkinson's disease.(Cochrane Review)", *The Cochrane Library* no. Issue 2.
Study type	Cochrane Systematic Review (of randomised, placebo-controlled, double-blinded trials)
Evidence level	1++
Study objective	To compare the efficacy and safety of adjuvant beta-blocker (BB) therapy against placebo for the treatment of tremor in patients with Parkinson's disease
Number of patients	N=72 Parkinson's disease (PD) patients Location: UK (Claveria and Marsden) and Australia (Corbett, Henderson) Sites: One (all studies)
Patient characteristics	The baseline characteristics were not given in two trials (Claveria, Marsden) Two trials gave baseline characteristics but did not compare the distribution of the characteristics been actively treated and placebo treated groups (Corbett, Henderson)
Intervention	Adjuvant oral BB therapy: Claveria: oxprenolol 160 mg/ day over 6 weeks Corbett: Oxprenolol 160-320 mg/day over 4 weeks Marsden: propanolol 40 mg/day 1st week, 80 mg/day 2nd week, 120 mg/day last 2 weeks Henderson: propanolol 20mg/day, 40 mg/day and 80 mg/day (each dose was administered once over a period of 2 days and each dose was followed by an assessment of its effect- therefore single doses and not long-term effects were assessed in this trial).
Comparison	Placebo
Length of follow-up	2 days to 6 weeks
Outcome measures	Quality of life, PD activities of daily living rating scales, PD motor impairment rating scales, individual motor performance tests, accelerometer outcomes, electromyographic activity outcomes, patient self-evaluation rating scales, adverse event frequency, number of withdrawals
Effect size	Clinical outcomes: ➢ Corbett, Marsden, and Henderson (cross-over trials) did not present data from the end of first arms

	➢ Since there is a carry-over risk the systematic review did not analyse the data from these trials ➢ Claveria was also a cross-over trial but did present data from first arm of trial ➢ Only mean total score for tremor in each group in the first arm was reported ➢ They did not state baseline scores, numbers of patients in each group, or standard deviations ➢ Magnitude and significance of effect of any changes due to BB therapy could not calculated ➢ They did report there was no significant difference between oxprenolol and placebo ➢ Details of the data analysis are not given so it is not possible to tell whether the non-significance is based on comparison between the first and second arms (which could have been affected by a possible cross-over effect) or between the therapy and placebo groups at the end of each arms Adverse events ➢ Marsden reported mean pulse rate fell from 84 on placebo to 74 with maximum dose of propanolol ➢ 14/22 patients showed a 'substantial' fall in rate but author's did not define what this constituted ➢ One patient was withdrawn from the study when his pulse rate dropped to 56 per minute ➢ Claveria reported no adverse events ➢ Henderson did not state whether any adverse events occurred ➢ Corbett reported adverse events but it is unclear which occurred in the trial with parkinsonism patients and which occurred in a separate trial with patients with essential tremor
Source of funding	No sources of support supplied
Additional comments	➢ None of the preparations used controlled-release forms of BB ➢ Pervious anti-Parkinson medication was unaltered in 3 studies- but Henderson stopped propanolol treatment 1 week before study and levodopa stopped 12 h before each test dose ➢ All 4 trials failed to provide details of the methods of randomisation and concealment allocation ➢ No trials defined the criteria used to differentiate IPD from other forms of parkinsonism ➢ Small sample size (n=72)- could affect generalisability of results ➢ All four trials were double-blinded ➢ All trials too short in duration for long-term effects to be determined ➢ Trials were too small for the frequency of adverse events to be calculated ➢ Systematic review conclusions: in view of this lack of evidence, it is impossible to determine whether BB therapy is a safe and effective treatment for the tremor of PD ➢ Included studies: Claveria (1975), Corbett (1976), Henderson (1994), Marsden (1974)
NCC CC ID (Ref Man)	80

TxCM1 – section 7.5.4

<table>
<tr><td colspan="2">Evidence Table
TxCM1
What is the effectiveness of adding MAO-B vs. placebo in the treatment of later Parkinson’s disease patients with motor complications?</td></tr>
<tr><td>Bibliographic reference</td><td>Presthus J,.Hajba A. Deprenyl (selegiline) combined with levodopa and a decarboxylase inhibitor in the treatment of Parkinson's disease. Acta Neurologica Scandinavica Supplementum. 1983;95:127-33.</td></tr>
<tr><td>Study type</td><td>Randomised, double-blind, placebo-controlled, parallel-group study</td></tr>
<tr><td>Evidence level</td><td></td></tr>
<tr><td>Study objective</td><td>To estimate how much the levodopa dosage can be reduced, when deprenyl is used, without worsening the disease and to see if deprenyl can reduce the ‘off’ periods.</td></tr>
<tr><td>Number of patients</td><td>N=40 Parkinson’s disease (PD) patients
N=20 deprenyl
N=20 placebo

Location: sites:</td></tr>
<tr><td>Patient characteristics</td><td>40 PD patients with at least 3 years history of PD who were undergoing continuous and stabilized treatment with levodopa were included in the study.
<table>
<tr><th></th><th>Deprenyl</th><th>Placebo</th></tr>
<tr><td>Total sample size (n=)</td><td>20</td><td>18</td></tr>
<tr><td>Male: female</td><td>9: 11</td><td>11:7</td></tr>
<tr><td>Mean age yrs</td><td>65.2</td><td>66.5</td></tr>
<tr><td>Disease duration yrs</td><td>10.8</td><td>9.8</td></tr>
<tr><td>Webster score (severity)</td><td>10.4</td><td>10.7</td></tr>
<tr><td>On-off patients</td><td>19</td><td>17</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Deprenyl 5mg daily in first 4 weeks (levodopa dosage was reduced until there was demonstratable impairment) weeks 5-8 10 mg of deprenyl administered daily</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow-up</td><td>2 years</td></tr>
</table>

Outcome measures	Webster rating scale, recording of on-off phenomenon, nocturnal and morning akinesia, adverse events and withdrawals
Effect size	➢ The trial was divided into two periods of 4-weeks ➢ After the second week levodopa dosage was reduced as much as possible Levodopa (LD) dosage ➢ The mean decrease of daily LD dosage per medication period was significant from baseline within all deprenyl treatment periods and within placebo treatment periods at first and total ➢ LD dosage in deprenyl group was reduced by 33 percent ➢ During the first treatment period the decrease in LD was significantly greater in the deprenyl group than the placebo group ($p<0.01$) ➢ The total scores (weeks 0-8) was also significant ($p<0.01$) Webster rating scores ➢ Reduced by 32% in the deprenyl group ➢ No significant reduction within the placebo group ➢ The difference between the two groups was in favour of deprenyl ($p<0.001$) weeks 0-8 ➢ Non-significant for weeks 0-4 and weeks 4-8 ➢ During the second treatment period there was no difference Akinesia ➢ End-of-dose akinesia improved in 9/18 patients in deprenyl group and 3/11 in placebo group ➢ 6/11 with akinesia paradoxia improved in deprenyl group and 2/9 in placebo group ➢ Early morning akinesia improved in 10/18 patients in deprenyl group and 5/13 in placebo group ➢ Nocturnal akinesia was improved in 9/18 in deprenyl and 4/16 in placebo Off periods ➢ Overall estimate of improvement in 'off' periods was 50% in deprenyl and 25% in placebo Dyskinesia ➢ Peak dose dyskinesia improved in 7/15 patients in the deprenyl group and in 3/8 in placebo group ➢ End-of-dose dyskinesia was not observed in any patient and early morning dyskinesia was observed in only one patient Dystonia ➢ Improvement in dystonia was observed in 5/11 deprenyl patients and no change was observed in 6 patients in placebo group Adverse events ➢ No significant difference between the two groups ➢ No rise in blood pressure was noted

	Patient preference ➢ No significant difference between groups Physician preference ➢ Significantly greater improvement in deprenyl group vs. placebo (p<0.01) ➢ Deprenyl vs. placebo: 12 vs. 2 patients improved, 7 vs. 13 patients no change, 1 vs. 3 impaired ➢ 9 patients in deprenyl improved by 4 or more on Webster scores Withdrawals ➢ 2 patients dropped-out of the placebo group ➢ 1 patient failed to continue the study and one patient died Long-term follow-up ➢ All patients in deprenyl group continued deprenyl in long-term treatment ➢ 8 (27%) patients discontinued using it after 3 to 24 months and 2 patients discontinued temporarily ➢ reason for discontinuation was In 4 cases insufficient therapeutic response, 3 cases insufficient response and dyskinesia, in one case dyskinesia and palpitation, one case visial hallucination, and in one case no evident motivation ➢ 12 patients (40%) are still taking 5 mg 2x daily and 4 patients from placebo group are also receiving deprenyl for about 2 years ➢ 7 patients have increased concomitant LD dosage by 125-300 mg daily ➢ 2 have decreased by the same amount and 7 are unchanged ➢ 7 patients have improved Webster scores by 3-7, in 6 no change, and in 3 a decline of 4-6 ➢ no positive correlation between change in dosage and clinical course
Source of funding	Pharmaceutical company supply of study drugs
Additional comments	➢ No methods of randomisation or allocation concealment ➢ Not intention-to-treat analysis ➢ No sample size calculations ➢ 2 drop-outs (5%) reported both in placebo group
Citation	
NCC CC ID (Ref Man)	477

Evidence Table

TxCM 1

What is the effectiveness of adding MAO-B vs. placebo in the treatment of later Parkinson's disease patients with motor complications?

Bibliographic reference	Brodersen P, Philbert A, Gulliksen G, Stigard A. The effect of L-Deprenyl on on-off phenomena in Parkinson's disease. *Acta Neurologica Scandinavica.* 1985;**71**:494-7.
Study type	Randomised, double-blind, placebo-controlled, crossover trial
Evidence level	
Study objective	To study the effect of L-deprenyl on the on-off type problems in a group of Parkinsonian patients.
Number of patients	N=19 Parkinsonian patients
Patient characteristics	Inclusion criteria: Parkinson's disease for some years and treated with levodopa, Sinemet, Madopar or other drugs, one or more on-off type problems (most often freezing episodes, end-of-dose deterioration, or morning akinesia), a Webster score between 6 and 20. Levodopa dosage was allowed to be reduced during study period. Demographics of patients completing the study: average age 67 years (range 54-80 years) with average disease duration of 11 years (range 4-22 years).
Intervention	5 mg deprenyl one a day for 8 weeks; then 2-week washout period before switching to placebo
Comparison	Identical placebo was given once daily for 8 weeks; then same as above
Length of follow-up	None stated (trial duration 2x 8-week treatment periods and 2-week washout, 18 weeks total)
Outcome measures	Webster scores, on-off episodes, patient/physician preference, levodopa dose reduction, adverse events and withdrawal rates.
Effect size	Webster scores ➢ Unchanged for the 14 patients completing the study On-off episodes ➢ Significant reduction per week ($p<0.05$) Patient preference ➢ 3 patients preferred deprenyl, 3 preferred placebo and 8 were indifferent ➢ This impression was shared by the examining physician except in one case Levodopa dose reduction ➢ Often reduced to reduce side effects of deprenyl ➢ Average reduction was 20% (range 0-40%)

	Adverse events ➢ Included mild to moderate hyperkinesias (5 patients), nausea (2 patients), constipation (2 patients), diaphoresis (3 patients), and dizziness (2 patients) ➢ Insomnia and vivid dreaming was noticed in 2 cases Withdrawals ➢ 14/19 patients completed the trial ➢ 4 dropped-out due to intolerable side effects such as nightmares, depression and postural hypotension, confusion, and dizziness with headaches respectively ➢ These side effects occurred during deprenyl treatment ➢ The fifth patient developed a rash following 2 weeks of placebo- medication was discontinued
Source of funding	Pharmaceutical company supplied study medication
Additional comments	➢ Randomisation method was drawing lots ➢ No methods of allocation concealment ➢ Not intention-to-treat analysis ➢ Small sample size ➢ No sample size power calculations
NCC CC ID (Ref Man)	2762

Evidence Table **TxCM1** What is the effectiveness of adding MAO-B vs. placebo in the treatment of later Parkinson's disease patients with motor complications?	
Bibliographic reference	Golbe LI,.Duvoisin RC. Double-blind trial of R-(-)-deprenyl for the "on-off" effect complicating Parkinson's disease. *Journal of Neural Transmission.Supplementum.* 1987;**25**:123-9.
Study type	Double-blind, randomised, placebo-controlled, parallel-group study
Evidence level	
Study objective	To study the effect of addition of deprenyl or placebo to previously optimised levodopa/carbidopa regimen in Parkinson's disease patients with 'on-off' fluctuations.
Number of patients	N=34 Parkinson's disease (PD) patients N=17 deprenyl N=17 placebo

	Location: USA Sites single:
Patient characteristics	Subjects were outpatients aged 35 to 75 who had been receiving carbidopa/levodopa for more than 5 years for idiopathic PD and were experiencing on-off phenomenon unresponsive to adjustments in size and scheduling of levodopa/carbidopa doses. Inclusion criteria also required that the patients be in stages 2,3, or 4 on the 5-point Hoehn and Yahr scale during both the 'on' and 'off' states. Each patient had a total weighted score of at least 60 (maximum possible: 240) for speech, tremor, rigidity, bradykinesia, postural instability, and gait on the disability scale. Mean age of subjects was 62.8 (deprenyl) and 61.5 (placebo), mean Hoehn and Yahr stage when 'on' was 3.0 (deprenyl) and 3.1 (placebo) and mean duration was 10.8 years (deprenyl) and 10.6 years (placebo).
Intervention	Deprenyl 5 mg b.i.d.
Comparison	Placebo
Length of follow-up	Not stated (6-week trial duration)
Outcome measures	Diary elf-evaluations, Disability scale, Investigators Global Improvement, adverse events, withdrawals
Effect size	Diary of self-evaluations ➢ The proportion of patients in the deprenyl-treated group who improved on both 'walking' and 'drug working' was approximately twice that in the placebo group ➢ Degree of improvement among patients receiving deprenyl who improved was about twice that among those receiving placebo that improved. ➢ Out of 22 parameters measured on the Disability scale- only two, facial expression and resting tremor, showed improvement ($p \leq 0.05$) ➢ In no parameter did patients on placebo significantly improve more than deprenyl Investigator's global subjective opinion ➢ Out of 17 deprenyl-treated patients only 2 remained unchanged, 3 slightly improved, 8 improved moderately and 4 improved markedly ➢ Out of the 17 placebo-treated patients 3 were slightly worse, 8 unchanged, 3 slightly improved, one moderately improved and none markedly improved ➢ Patients on deprenyl were more likely than patients on placebo to have experienced improvement than to have worsened or experienced no change ($p \leq 0.01$) Adverse events ➢ 13/15 patients on placebo reported one or more adverse events ➢ 5 reactions among 5 patients were listed as severe (dystonic spasm, tremor, shoulder spasm, chorea, orobuccal dyskinesia)

	➢ 15/17 deprenyl patients had one or more adverse events with 6 events among 6 patients listed as severe (hallucinations, heavy leg, vivid dreams, urinary retention, migraine, and delusions) ➢ One patient receiving deprenyl completed the 6-week study but asked to discontinue immediately after study due to severe mental side effects ➢ Sitting and standing blood pressures and heart rate showed no inter-group difference Withdrawals ➢ Two patients in the placebo group dropped-out of the study because of myocardial infarction and intolerable chorea (respectively) ➢ No patients dropped out of deprenyl group
Source of funding	Pharmaceutical supplied drugs
Additional comments	➢ Methods of randomisation stated ➢ Methods of allocation concealment not stated ➢ 2 patients dropped-out (6%) ➢ not intention-to-treat ➢ no sample size calculations
Citation	
NCC CC ID (Ref Man)	2760

Evidence Table **TxCM1** What is the effectiveness of adding MAO-B vs. placebo in the treatment of later Parkinson's disease patients with motor complications?	
Bibliographic reference	Lieberman AN, Gopinathan G, Neophytides A, Foo SH. Deprenyl versus placebo in Parkinson disease: a double-blind study. *New York.State Journal of Medicine* 1987;**87**:646-9.
Study type	Randomised, double-blind, placebo-controlled, parallel group study
Evidence level	
Study objective	To evaluate deprenyl's efficacy and safety in patients with Parkinson's disease.
Number of patients	N=33 Parkinson's disease (PD) patients N=17 deprenyl N=16 placebo

<table>
<tr><td></td><td>Location: USA Sites:</td></tr>
<tr><td>Patient characteristics</td><td>All patients were no longer responding satisfactorily to levodopa/carbidopa. Inclusion criteria: patient's stage had to be 2,3, or 4 as assessed on their 'on' period using the Hoehn and Yahr scale. They also had to be on a stable dose of Sinemet for at least the previous 3 months. All patients underwent 2 weeks of baseline monitoring before being assigned to one of the treatment groups. Levodopa dose was attempted to be reduced during the 6-week treatment phase of the study.
<table>
<tr><th>Characteristics</th><th>Deprenyl</th><th>Placebo</th></tr>
<tr><td>Mean age (yr)</td><td>60.6</td><td>65.6</td></tr>
<tr><td>Male: Female</td><td>12:5</td><td>10:6</td></tr>
<tr><td>PD duration (yr)</td><td>7.9</td><td>7.1</td></tr>
<tr><td>Levodopa duration (yr)</td><td>7.2</td><td>6.8</td></tr>
<tr><td>Hoehn and Yahr Stage (1-5)</td><td>2.2</td><td>2.4</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Deprenyl 10 mg/day</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow-up</td><td>None stated</td></tr>
<tr><td>Outcome measures</td><td>Parkinsonian signs and symptoms scores, Sinemet dose, hours 'on', overall condition, and adverse events</td></tr>
<tr><td>Effect size</td><td>Deprenyl (baseline versus completion of treatment)
➢ 22% decrease in Parkinsonian symptoms ($p \leq 0.05$)
➢ 17.4% decrease in Parkinsonian signs ($p \leq 0.05$)
➢ 21% decrease in Sinemet dose ($p \leq 0.025$)
➢ No improvement as a group for number of hours 'on'
➢ Adverse events were not increased over baseline levels
➢ Overall condition of 12/17 (71%) were judged to have improved
➢ Patients reported: dose of levodopa lasted longer, transitions between on and off periods were less abrupt, on periods were better, off periods were less severe
Placebo (baseline versus end-of treatment period)
➢ No significant decrease in symptoms, signs, Sinemet dose, hours 'on', or adverse events
➢ Overall condition of 2/16 (12.5%) of patients were judged by observer to be improved

➢ Univariate analysis of covariance between baseline scores and Sinemet doses of patients on deprenyl and patients on placebo- none of the p values for symptoms, signs, hours 'on', Sinemet</td></tr>
</table>

	dose, or adverse events were significant ➢ Univariate analysis of covariance between final scores and Sinemet doses of patients on deprenyl and patients on placebo- only Sinemet dose was significantly less ($p \leq 0.01$) in deprenyl than placebo group ➢ The Parkinsonian sign score was improved but non-significant in deprenyl group Adverse events ➢ There were no differences between deprenyl and placebo groups ➢ On completion of study 3/17 deprenyl-treated patients discontinued the drug- two because they had not achieved any benefit and one because of an adverse event ➢ Out of 16 patients on placebo 15 elected to go deprenyl
Source of funding	Non-profit and pharmaceutical
Additional comments	➢ Methods of randomisation stated ➢ Allocation concealment methods not stated ➢ Small sample size ➢ No sample size power calculations ➢ Intention-to-treat not stated but no drop-outs were reported
NCC CC ID (Ref Man)	88

Evidence Table **TxCM1** What is the effectiveness of adding MAO-B vs. placebo in the treatment of later Parkinson's disease patients with motor complications?	
Bibliographic reference	Golbe LI, Lieberman AN, Muenter MD, Ahlskog JE, Gopinathan G, Neophytides AN *et al*. Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease. *Clinical Neuropharmacology.* 1988;**11**:45-55.
Study type	Randomised, placebo-controlled, parallel-design, multi-centred trial
Evidence level	
Study objective	To investigate deprenyl supplementation of levodopa/carbidopa in patients with PD complicated by symptom fluctuations.
Number of patients	N=96 Parkinson's disease (PD) patients N=50 deprenyl N=46 placebo

	Location: USA sites: three
Patient characteristics	All participants were outpatients, age 35-75 years, with idiopathic PD who had received levodopa/carbidopa (Sinemet) for at least 5 years and were on a stable dose for the 2 weeks prior to entry into the study. All patients were experiencing PD symptom fluctuations that could not be ameliorated by further adjustment in size or timing of levodopa/carbidopa doses. Mean age of patients in deprenyl was 61.4 and placebo was 63.4, mean Hoehn and Yahr stage was 2.5 in deprenyl and 2.6 in placebo, and finally mean disease duration (years) was 9.5 in deprenyl and 8.9 in placebo-treated patients.
Intervention	Deprenyl 5 mg b.i.d
Comparison	Placebo
Length of follow-up	2-week baseline period and 6-week treatment duration
Outcome measures	Modified Columbia University Disease Scale (MCUDS), patient-rated hourly scores
Effect size	Patient rated scores (o= 'bad for me', 2='good for me', or 1=in between) Symptom fluctuations ➢ Patients hourly self-scores for walking: ➢ Deprenyl changed from a score of 1.43 at baseline to 1.52 at 6 weeks and placebo changed from 1.38 to 1.32 ➢ The degree of change in deprenyl and placebo was p=0.002 favouring deprenyl ➢ Patient's hourly self-scores for "drug-working" ➢ Deprenyl changed from 1.29 at baseline to 1.41 at 6 weeks, placebo-treated patients changed from 1.28 at baseline to 1.11 at 6 weeks ➢ The difference between the degree of change wasp<0.001 favouring deprenyl Disability during 'on' state ➢ In 5/22 items in the MCUDS p<0.05 difference between deprenyl and placebo when the mean of the baseline scores of the two treatments was compared to the mean of the 6-week treatment scores ➢ The 5 items were: dressing, dysarthria, hypomimia, sialorrhea, and tremor ➢ None of the changes were large enough to significantly affect parkinsonian disability Subjective global assessment ➢ At the end of the 6-week treatment period- 37 (76%) of the deprenyl group judges themselves to have improved-whereas only 12 (26%) of placebo group though they were improved ➢ The number worsening was small in both groups

	➢ The number of patients subjectively improved relative to the total of those worsening or showing no change was significantly ($p<0.001$) greater in the deprenyl group Adverse events ➢ Most common adverse events: deprenyl: transient nausea- no patient reported vomiting- dizziness (not associated with subjective orthostatic hypotension) ➢ Approximately 60% of patients taking deprenyl and 30% of patients on placebo telephoned to report worsening of peak-dose chorea 2 or 3 days after starting treatment ➢ Concomitant levodopa/carbidopa in most cases was reduced and symptoms resolved by time of next visit
Source of funding	Pharmaceutical
Additional comments	➢ No methods of randomisation or allocation concealment ➢ No sample size calculations ➢ Not intention-to-treat analysis ➢ Inter-centre variability was noted
Citation	
NCC CC ID (Ref Man)	510

Evidence Table **TxCM1** What is the effectiveness of adding MAO-B vs. placebo in the treatment of later Parkinson's disease patients with motor complications?	
Bibliographic reference	Sivertsen B, Dupont E, Mikkelsen B, Mogensen P, Rasmussen C, Boesen F *et al*. Selegiline and levodopa in early or moderately advanced Parkinson's disease: A double-blind controlled short- and long-term study. *Acta Neurologica Scandinavica Supplementum.* 1989;**80**:147-52.
Study type	Randomised, double-blind, placebo-controlled crossover study
Evidence level	
Study objective	The aim of this study was to evaluate the effect of selegiline on the daily dose of levodopa, on parkinsonian disability and on motor fluctuations.
Number of patients	N=42 Parkinson's disease (PD) patients Location: Finland Sites:
Patient characteristics	Inclusion criteria: patients with genuine PD patients in stages I-III, treated with stable doses of

	levodopa. Most patients were in a stable condition with few or flight parkinsonian symptoms, but some showed an end-of-dose deterioration, although they were receiving 4x or more daily doses of levodopa. After 2 weeks treatment of study drug levodopa dose was reduced by approximately 20%. Thirty-eight patients completed the study (16 females and 22 males). Their mean age was 68.9 years at entry and duration of PD was 3.1 years. Two patients were in stage I, 24 in stage II, and 12 in stage III. The mean duration of levodopa treatment was 27.8 months prior to study. Initial mean levodopa dose was 553 mg/day.
Intervention	Selegiline 10 mg/day for 8 weeks, followed by 4 week washout period and then switched to placebo
Comparison	Placebo for 8 weeks, then same as above but switched to selegiline treatment
Length of follow-up	16 months for long-term study follow-up
Outcome measures	Columbia University Disability Score (CUDS)
Effect size	➢ Short-term study: described in intervention section. ➢ Long-term study: after short-term trial patients continued treatment in 2 parallel groups, blindly, with either selegiline or placebo according to period preference from short-term study. Follow-up was performed at 3-month intervals. Trial was planned to continue until deterioration of parkinsonian symptoms indicated a necessity of additional drug treatment or as long as practically possible Results of short-term study Levodopa dose ➢ Addition of selegiline or placebo allowed equal (28 and 27%) reductions of daily levodopa doses ($p<0.01$) without clinical deterioration during the first 8-week period ➢ But this was not marked during the second treatment-period ➢ Thus there was a significant period effect ($p<0.001$) ➢ Analysis of variance showed that the daily levodopa dose was reduced significantly more during selegiline treatment ($p<0.05$) ➢ The number of daily levodopa doses decreased with both treatments ➢ More so with selegiline but difference was not significant Tremor ➢ Addition of selegiline caused improvement of tremor ($p<0.02$) ➢ No significant difference was observed in the score for rigidity, functional performance or total CUDS score

	Adverse events ➢ Selegiline caused no changes in blood pressure ➢ Side effects were few and slight apart from dizziness (8 in selegiline and 3 in placebo) ➢ All side effects disappeared after reduction of levodopa dose ➢ At the start of the study 14 patients were noted to have end-of-dose deterioration- no changes in frequency or severity of these symptoms were observed during the short-term study Withdrawal rates ➢ 42 patients entered the study and 4 dropped-out: one due to suspected unverified hematemesis, a second due to exanthema during placebo treatment, a third patient was excluded as his parkinsonism appeared to be drug-induced, a fourth was withdrawn as she developed a depression during placebo treatment Long-term study (NON-RANDOMISED!) ➢ 18 patients continued on selegiline and 12 on placebo ➢ Two groups were comparable apart from pre-study duration of levodopa and frequency of end-of-dose deterioration ➢ The average levodopa dose was significantly lower ($p<0.001$) lower in the selegiline treated patients ➢ The average dosing frequency was also lower in the selegiline group ($p<0.001$) ➢ No differences occurred in the scores for tremor, rigidity, or functional performance Adverse events ➢ No significant differences between groups in blood pressures ➢ Motor fluctuations occurred more frequently among selegiline-treated patients both initially and during the long-term study ➢ 5 patients developed dyskinesias on selegiline and only one patient on placebo Withdrawal rates ➢ Of the 38 patients completing the short-term study 5 did not enter the long-term study due to: late entrance into trial, lack of preference for one of the two treatment periods or unwillingness to continue ➢ Two patients were withdrawn due to reasons unrelated to the drug test
Source of funding	None stated
Additional comments	➢ Methods of randomisation or allocation concealment not stated ➢ No intention-to-treat statement ➢ No sample size calculations

NCC CC ID (Ref Man)	193

Evidence Table **TxCM1** What is the effectiveness of adding MAO-B vs. placebo in the treatment of later Parkinson's disease patients with motor complications?	
Bibliographic reference	Hubble JP, Koller WC, Waters C. Effects of selegiline dosing on motor fluctuations in Parkinson's disease. *Clinical.Neuropharmacology* 1993;**16**:83-7.
Study type	Randomised, Double-blind, placebo-controlled, 3-period, crossover trial
Evidence level	
Study objective	To examine selegiline dosing effects in Parkinson's disease (PD) patients with motor fluctuations.
Number of patients	N=19 Location: USA sites: two
Patient characteristics	Inclusion criteria included the presence of at least 3 of the 4 cardinal features of PD (bradykinesia, rigidity, resting tremor, and postural instability), symptomatic response to levodopa, and motor fluctuations. Each subject was maintained on a fixed dose of carbidopa/levodopa throughout the study. The mean age was 65 years and the mean disease duration was 9 years. The ratio of men to women was 2.2. The average dosage of levodopa was 538 mg/day.
Intervention	Crossover of 3 treatment periods (0 mg b.i.d., 5 mg q.d., and 5 mg daily b.i.d.) each treatment period was 3 weeks followed by a 14-day washout period during which no study drug was taken.
Comparison	Placebo
Length of follow-up	None stated
Outcome measures	UPDRS, Hoehn and Yahr, Schwab and England Scale, step-second (timed walking instrument), adverse events, patient diaries
Effect size	➢ Patients were evaluated at baseline and at the completion of each treatment period prior to washout (end of weeks 3,8, and 13). ➢ When considered as three treatment groups (ie. all data acquired from a given dose regardless of administration sequence) the following were found to be in favour of treatment but non-significant: o Motor diaries (trend for decreased 'off' time and increased 'on' time with and without dyskinesia o Step-second scores (timed walking) appeared to improve with treatment

	➢ Hoehn and Yahr Staging and Schwab and England scores did not change ➢ Patient responses on UPDRS (subjective component) did not differ on selegiline treatment ➢ Selegiline at 10mg/d was associated with poorer motor assessments on the UPDRS (objective component) compared to placebo and 5 mg/d Analysis of data by dose sequence: ➢ 'On' time was increased during 5mg and 10mg/day dosing within the 0-5-10 mg/day group compared to placebo ($p<0.05$) ➢ 'Off' time was decreased and 'on' time with dyskinesia increased on 5 and 10 mg/day dosing in 0-5-10 mg/day group ($p<0.05$) ➢ No clear superiority or inferiority of a given dosing sequence or dose quantity emerged Adverse events ➢ One subject reported an increase in occurrence of headache while taking selegiline ➢ No other events were reported or observed ➢ 11/16 pf patients chose to remain on selegiline upon completion of study
Source of funding	Pharmaceutical
Additional comments	➢ No methods of randomisation or allocation concealment ➢ No intention-to-treat analysis stated ➢ No of drop-outs not stated ➢ No sample size calculations
Citation	
NCC CC ID (Ref Man)	2752

Evidence Table

TxCM 1

What is the effectiveness of adding MAO-B vs. placebo in the treatment of later Parkinson's disease patients with motor complications?

Bibliographic reference	Waters CH, Sethi KD, Hauser RA, Molho E, Bertoni JM. Zydis selegiline reduces off time in Parkinson's disease patients with motor fluctuations: A 3-month, randomized, placebo-controlled study. *Movement Disorders* 2004;**19**:426-32.
Study type	Randomised, double-blind, placebo-controlled parallel group trial

Evidence level	
Study objective	The efficacy and safety of Zydis selegiline was assessed in Parkinson's disease patients who were experiencing motor fluctuations with levodopa.
Number of patients	N=140 Parkinson's disease patients N=94 selegiline N=46 to placebo Location: USA Sites: 16
Patient characteristics	Patients over 30 years of age with a confirmed diagnosis of PD were eligible if they had a documented response to levodopa with a dope-decarboxylase inhibitor. All patients had end-of-dose deterioration with predictable, mild to moderate motor fluctuations and at least 3 hours of 'off' time per day. Patients were randomly assigned in a 2:1 ratio to receive either selegiline or placebo for 12 weeks. Patients in selegiline group were predominantly male (63%) and had a mean PD duration of 6.3 years, and a mean age of 66 years. The placebo group was also mostly male (65%), had a slightly higher duration of PD 7.5 years, and a mean age of 64 years. No significant differences between groups at baseline.
Intervention	Zydis selegiline (1.25-2.5 mg once daily) for 12 weeks
Comparison	Placebo
Length of follow-up	None stated (14 week trial duration)
Outcome measures	'On' time, 'Off' time, Clinical Global Impression (CGI) scale and Patient's Global Impression (PGI) scale, adverse events, withdrawal rates
Effect size	➢ 14 week trial (2 week baseline screening period, 12 week treatment period) 'Off' time ➢ Patients on selegiline experiences significant reductions in percentage of off time at both weeks 4 to 6 ($p=0.003$) and weeks 10 to 12 ($p<0.001$) in favour of selegiline ➢ These improvements were observed across all visits ➢ All were significant except for week 6 ➢ Total number of 'off' hours was reduced by 2.2 hour/day from baseline whereas the placebo group had a reduction of 0.6 hours 'On' time (dyskinesias free) ➢ Improvements were also seen in selegiline group ➢ By week 6 improvements were 9.5% in selegiline and 3.3% change in placebo ($p=0.038$) ➢ Further improvement was seen at week 12 with 12% improvement relative to baseline in selegiline

	and 3% change in placebo (p=0.008) ➢ Number of daily dyskinesias-free 'on' hours for selegiline patients increased 1.8 h at week 12 ➢ The time 'on' with dyskinesias with selegiline increased 0.4 h whereas placebo increased by 0.3 h (not significant) ➢ There were no significant changes in mean number of daily hours asleep or in mean percentages of asleep time throughout the study Secondary efficacy measurements ➢ CGI scores showed significant improvement in selegiline group week 10 (p=0.004) and week 12 (p=0.026) compared with the placebo group ➢ PGI scores showed significant differences at week 4 (p=0.028) and throughout weeks 8 to 12 (p<0.05) in favour of selegiline Adverse events ➢ Most frequently observed adverse event in selegiline group that were judged by investigators to be drug-related were: dizziness (6 cases), dyskinesias (4 cases), hallucinations (4 cases), headache (4 cases), dyspepsia (4 cases) ➢ Most of these events were reported during the first 6 weeks of treatment at the 1.25 mg dose ➢ 32% of the selegiline group experienced at least one drug-related event compared with 21% placebo patients ➢ no apparent differences between treatment groups by dose level, or between active and placebo groups Withdrawal rates ➢ 93% of selegiline patients completed the trial and 92% of placebo ➢ Most frequent reasons for early termination in both groups was adverse events (3 selegiline, placebo 1) and protocol deviations (selegiline 2 patients) ➢ Protocol deviations involved non-compliance with study medication by exceeding the dosing specified
Source of funding	None stated
Additional comments	➢ Methods of randomisation or allocation concealment not stated ➢ Data was analysed on an intention-to-treat basis ➢ Treatment effects, investigator or centre effects, treatment-by-centre group interactions were all analysed ➢ Sample size calculations were provided
NCC CC ID (Ref Man)	428

Evidence Table

TxCM1

What is the effectiveness of adding MAO-B vs. placebo in the treatment of later Parkinson's disease patients with motor complications?

Bibliographic reference	Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Archives of Neurology* 2005;**62**:241-8.
Study type	Randomised placebo-controlled double-blind parallel group study
Evidence level	1++
Study objective	To determine the safety, tolerability and efficacy of rasagiline in levodopa-treated patients with PD and motor fluctuations
Number of patients	N=472 Parkinson's disease (PD) N=164 Rasagiline 0.5 mg/d N=149 Rasagiline 1.0 mg/d N=159 placebo Location: International sites: 57
Patient characteristics	Levodopa-treated patients with motor fluctuations were enrolled at 57 participating Parkinson Study group sites between December 2000 and June 2002. Eligibility criteria: patients with idiopathic PD who were in a modified Hoehn and Yahr stage of less than 5 in the 'off' state, were 30 years or older, and experienced at least 2.5h of 'off' state daily.

Characteristic	Rasagiline 0.5 mg/d (n=164)	Rasagiline 1.0 mg/d (n=149)	Placebo (n=159)
Age, yr	62.6 ± 9.5	62.9 ± 8.9	64.5 ± 9.9
Male sex	102 (62.2%)	99 (66.4%)	104 (65.4%)
Disease duration, yr	9.3 ± 5.6	8.8 ± 5.4	9.7 ± 4.9
Daily LD dose, mg	750 ± 379	815 ± 471	821 ± 485
Hoehn and Yahr stage	2.1 ± 0.7	2.0 ± 0.6	2.1 ± 0.7

<table>
<tr><td></td><td>➢ No significant differences between groups at baseline</td></tr>
<tr><td>Intervention</td><td>Rasagiline 1.0 or 0.5 mg/d</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow-up</td><td>26 weeks of treatment</td></tr>
<tr><td>Outcome measures</td><td>Off time, On time, clinical global impression, UPDRS scores, on time, Schwab and England ADL scores, PDQUALIF scores, adverse events, withdrawal rates</td></tr>
<tr><td>Effect size</td><td>Levodopa dose
➢ Between baseline and week 26- patients receiving placebo decreased their mean ± SD daily levodopa dosages by 12 ± 142 mg
➢ Patients receiving 0.5mg rasagiline decreased their dosages by 32 ± 133 mg
➢ In each group the median change in levodopa dosage was 0 mg

Efficacy of rasagiline treatments (in favour of rasagiline where p<0.05):
<table>
<tr><th>Change from baseline</th><th>0.5 mg rasagiline v placebo</th><th>1.0 mg rasagiline v placebo</th></tr>
<tr><td></td><td colspan="2">Mean (95%CI; p value)</td></tr>
<tr><td>Off time</td><td>-0.49 (-0.91 to –0.08; 0.2)</td><td>-0.94 (-1.36 to –0.51; <0.001)</td></tr>
<tr><td>Secondary end-points</td><td></td><td></td></tr>
<tr><td>Clinical global impression</td><td>-0.39 (-0.64 to –0.13; 0.003)</td><td>-0.68 (-0.94 to –0.42; <0.001)</td></tr>
<tr><td>UPDRS ADL score (off time)</td><td>-1.20 (-2.08 to –0.32; 0.008)</td><td>-1.34 (-2.24 to –0.43; 0.004)</td></tr>
<tr><td>UPDRS motor score (on time)</td><td>-2.91 (-4.59 to 1.23; <0.001)</td><td>-2.87 (-4.58 to –1.16; 0.001)</td></tr>
<tr><td>PDQUALIF summary score</td><td>-2.18 (-4.49 to 0.14; 0.07)</td><td>-1.48 (-3.86 to 0.90; 0.22)</td></tr>
<tr><td>Exploratory end-points</td><td></td><td></td></tr>
<tr><td>Daily on time</td><td></td><td></td></tr>
<tr><td>Without dyskinesia</td><td>0.51 (0.00 to 1.03; 0.050)</td><td>0.78 (0.26 to 1.31; 0.004)</td></tr>
<tr><td>With dyskinesia</td><td>-0.05 (-0.41 to 0.31; 0.79)</td><td>0.37 (0.00 to 0.74; 0.048)</td></tr>
<tr><td>Schwab and England ADL</td><td></td><td></td></tr>
<tr><td>During on time</td><td>0.92 (-1.51 to 3.35; 0.46)</td><td>3.00 (0.49 to 5.51; 0.02)</td></tr>
<tr><td>During off time</td><td>0.96 (-0.69 to 2.61; 0.25)</td><td>0.63 (-1.06 to 2.33)</td></tr>
</table>
➢ The mean adjusted total daily off time decreased from baseline by 1.85 h (29%) in patients on 1.0 mg rasagiline, by 1.41 h (23%) with 0.5 mg rasagiline and 0.91 h (15%) on placebo</td></tr>
</table>

- Post hoc analysis if UPDRS subscores during on times revealed significant improvements ($p<0.05$) in rigidity, bradykinesia, and tremor in patients treated with 1.0 mg rasagiline (as rated on UPDRS scale) and in postural instability and gait and tremor in patients treated with 0.5 mg.

Adverse events

- The number of patients discontinuing for any reason or because of an adverse event was not significantly different between treatment groups (p=0.85)
- Adverse events were reported in 87 of patients receiving placebo, 91% receiving 0.5 mg rasagiline and 95% of patients receiving 1.0 mg rasagiline
- Adverse events more common in rasagiline groups included:

Event	**Placebo (n=159)**	**0.5 mg rasagiline (n=164)**		**1.0 mg rasagiline (n=149)**	
	N (%)	N (%)	P value	N (%)	P value
Weight loss	4 (2.5)	4 (2.4)	0.76	14 (9.4)	0.02
Vomiting	2 (1.3)	6 (3.7)	0.31	10 (6.7)	0.03
Anorexia	1 (0.6)	3 (1.8)	0.64	8 (5.4)	0.04
Balance difficulty	1 (0.6)	9 (5.5)	0.03	5 (3.4)	0.19

- Dyskinesias were reported as an adverse event by 10% receiving placebo and by 18% receiving either dose of rasagiline (p=0.03
- Depression was significantly less common in patients receiving 0.5 mg rasagiline compared with placebo (p=0.04)
- There were 22 serious adverse events in 14 patients receiving placebo, 42 in 21 patients receiving 0.5 mg rasagiline, 27 in 18 patients receiving 1.0 mg rasagiline
- The most common serious adverse events (all 3 groups combined) were related to accident/injury (n=6), arthritis, worsening of PD, melanoma, stroke (n=3), and urinary tract infection (n=3)
- None were significantly more common in patients on rasagiline

Withdrawals

- 414 patients (87.7% of enrolled) completed the 26-week study
- Subset 359 (76.1% of enrolled) completed the study without deviating from the protocol
- Most common deviations were: premature terminations (12%), fewer than 6 acceptable daily diaries (10% mainly in patients who terminated prematurely), change in daily levodopa or other anti-PD medication dosage by more than 20% from baseline during the last 20 weeks of the study

	(4%)
Source of funding	Pharmaceutical
Additional comments	➢ Methods of randomisation stated ➢ Methods of allocation concealment not stated ➢ Power calculations provided ➢ Intention-to-treat analysis ➢ Comparability between sites analysed
NCC CC ID (Ref Man)	19833

Evidence Table

TxCM1

What is the effectiveness of adding MAO-B vs. placebo in the treatment of later Parkinson's disease patients with motor complications?

Bibliographic reference	Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe W, Stocchi F *et al*. Rasagiline as an adjunct to levodopa in Parkinson's disease patients with motor fluctuations; the LARGO study. *Lancet* 2005.
Study type	Randomised, double-blind, placebo-controlled trial
Evidence level	1++
Study objective	To investigate rasagiline efficacy and safety in levodopa-treated patients with motor fluctuations.
Number of patients	N=687 PD patients N=231 rasagiline N=227 entacapone N=229 placebo Location: Israel, Argentina, Europe Sites: 74 centres
Patient characteristics	Eligibility: had a clinical diagnosis of PD, as defined by the presence of at least 2 of the cardinal signs of PD (resting tremor, bradykinesia, rigidity) without any other known cause of parkinsonism, and a modified Hoehn and Yahr stage of < 5 in OFF state. Patients had to be receiving at least 3 daily doses of LD, not including bedtime dose, and not more than 8 daily doses of LD. For exclusion criteria: see paper for details.

	Rasagiline	Entacapone	Placebo
Age, yrs	63.9 (9.0)	63.0 (9.4)	64.8 (8.8)
Gender, male (n; %)	154; 66.7	139; 61.2	132; 57.6
PD duration, yrs	8.7 (4.9)	9.2 (4.7)	8.8 (4.8)
LD treatment duration, yrs	7.5 (4.6)	7.6 (4.5)	7.6 (4.7)

<table>
<tr><td></td><td>
<table>
<tr><td>Levodopa dose (mg)</td><td>722 (334)</td><td>706 (321)</td><td>697 (295)</td></tr>
<tr><td>OFF time (hours)</td><td>5.58 (2.37)</td><td>5.60 (2.59)</td><td>5.55 (2.44)</td></tr>
<tr><td>Total UPDRS</td><td>33.6 (17.6)</td><td>32.2 (16.6)</td><td>33.7 (18.8)</td></tr>
</table>
➢ Analysis of baseline demographics and clinical characteristics revealed no major differences between groups
</td></tr>
<tr><td>Intervention</td><td>Rasagiline (1.0 mg/d) or entacapone (200 mg with each LD dose)</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow-up</td><td>18-week trial duration</td></tr>
<tr><td>Outcome measures</td><td>Change in total daily OFF time, clinical global improvement (CGI) score, responder analysis (≥ 1 h reduction in daily OFF time), Unified Parkinson’s disease Rating Scale (UPDRS)</td></tr>
<tr><td>Effect size</td><td>
➢ 2-4 week levodopa optimisation/placebo run-in phase
➢ At the start of the 18-week double-blind phase, patients were randomised to receive as adjunct medication either rasagiline or entacapone or placebo- using a double-dummy technique
➢ During the first 6 weeks the investigator could lower LD dose if dyskinesia worsened
➢ The LD dosage remained constant for the final 12 weeks
24-hour diaries
<table>
<tr><th></th><th>Difference, rasagiline v placebo (95%CI, p value)</th><th>Difference, entacapone v placebo (95%CI, p value)</th></tr>
<tr><td>Daily OFF time</td><td>-0.78 (-1.18 to –0.39, p=0.0001)</td><td>-0.80 (-1.20 to –0.41, p<0.0001)</td></tr>
<tr><td>Daily ON time without troublesome dyskinesia (hours)</td><td>0.82 (0.36 to 1.27, p=0.0005)</td><td>0.82 (0.36 to 1.27, p=0.0005)</td></tr>
<tr><td>Daily ON time with troublesome dyskinesia (hours)</td><td>0.09 (-0.28 to 0.46, p=0.6209)</td><td>0.04 (-0.32 to 0.41, p=0.8157)</td></tr>
<tr><td>Responder rate (n;%)</td><td>2.5* (1.62 to 3.85, p<0.0001)</td><td>2.0* (1.29 to 3.06, p=0.0019)</td></tr>
</table>
➢ OFF= a period of relatively poor overall function (ie. increasing PD signs)
➢ ON= a period of relatively good overall function and mobility
➢ Responder was defined as a patient showing an improvement of 1 hour or more in the change from baseline in mean total daily OFF time
➢ * odds ratio
</td></tr>
<tr><td>Source of funding</td><td>Pharmaceutical</td></tr>
<tr><td>Additional comments</td><td>➢ Randomisation methods stated</td></tr>
</table>

	➢ Methods of allocation concealment not stated ➢ Intention-to-treat analysis for primary outcome measures
NCC CC ID (Ref Man)	19840

TxCM2 – section 7.5.3

Evidence Table

TxCM 2

What is the effectiveness of adding dopamine-agonists vs. placebo in the treatment of later Parkinson's disease patient with motor complications?

Bibliographic reference	Pogarell O, Gasser T, van Hilten JJ, Spieker S, Pollentier S, Meier D *et al*. Pramipexole in patients with Parkinson's disease and marked drug resistant tremor: a randomised, double blind, placebo controlled multicentre study. *Journal of Neurology, Neurosurgery & Psychiatry* 2002;**72**:713-20.
Study type	Double-blind, randomised, placebo-controlled, multi-centre, parallel group study
Evidence level	1++
Study objective	To compare tremorlytic properties of pramipexole, a non-ergoline dopamine agonist to those of placebo as add on medication in patients with Parkinson's disease.
Number of patients	N=88 early or advanced Parkinson's disease (PD) patients N=44 pramipexole N=40 placebo Location: 2 European countries (Germany and The Netherlands) sites: 4
Patient characteristics	Early or advanced PD patients with marked drug resistant tremor under a stable and optimised antiparkinsonian medication. Patients of both sexes with Parkinson's disease (Hoehn and Yahr stage I-IV as assessed at least 12 hours off medication) according to the UK PD brain bank criteria.

	Pramipexole (n=44)	Placebo (n=39)	Total (n=83)

Sex (%) M:F	68:32	77:23	72:28
Age, mean (SD)	62.0 (10.1)	65.4 (7.1)	63.6 (8.9)
Duration of PD, mean (SD)	6.5 (4.0)	6.0 (3.5)	6.3 (8.3)
Range	0.9-17	2.0-16	0.9-17
Duration of drug treatment, mean (SD)	3.9 (3.1)	3.6 (3.5)	3.8 (3.3)
Levodopa dose (mg), median (range)	300 (50-700)	300 (100-1700)	300 (50-1700)

Intervention	7 week dose titration interval and 4 week maintenance period Individual dose adjustments from 0.375 to 4.5mg/day (maximum 4.5 mg/day). At the end of maintenance period there was a one-week dose reduction to withdraw medication.
Comparison	Placebo- matching regimen of 3x daily
Length of follow-up	Trial duration up to 12 weeks
Outcome measures	Primary end-point: absolute change in tremor score on unified Parkinson's disease rating scale (UPDRS) (sum of tremor-related items 16,20,21) in 'on' periods Secondary end-points: percentage change in tremor score, the absolute and percentage changes in long-term tremor EMG tremor registration, and the change in tremor self-rating scales, adverse events

Effect size

	Pramipexole	Placebo	Difference between groups (95%CI)	Difference in mean relative changes (%)	P value
Tremor scores (UPDRS)					
Tremor score	-5.8 (5)	-1.5 (3.2)	-4.4 (-6.2 to –2.5)	-34.7	<0.0001
Item 16	-0.7 (0.9)	-0.2 (0.7)	-0.6 (-0.9 to –0.2)	-21.5	<0.01
Item 20	-3.6 (3.3)	-1.0 (2.2)	-2.6 (-3.8 to –1.4)	-37.9	<0.0001
Item 21	-1.5 (1.6)	-0.3 (1.1)	-1.2 (-1.8 to –0.6)	-35.6	<0.0001
UPDRS scores:					
UPDRS II/III (sum score)	-18.8 (13.9)	-3.8 (8.3)	-15 (-20 to –10)	-30.9	<0.0001
UPDRS II (average on-off)	-3.6 (3.8)	-0.1 (2.6)	-3.5 (-4.9 to –2.0)	-25.2	<0.0001
UPDRS III ("on")	-15.2 (11.6)	-3.7 (6.8)	-11.5 (-15.7 to –7.4)	-34.1	<0.0001
Patient's diary					
Daily living	-4.7 (8.6)	3.4 (8.0)	-8.1 (-11.7 to –4.5)	-43.4	<0.0001
Severity	-1.6 (2.1)	0.6 (2.2)	-2.2 (-3.1 to –1.3)	-39.5	<0.0001
Long term EMG					
Tremor occurrence (%)	-19.3 (14.8)	-4.1 (13.2)	-15.2 (-21.4 to –9.0)	-45.7	<0.0001

Global assessment (%) (patients with improvement)						
Investigator's assessment	56.8	12.8	44.0 (26.1 to 61.9)	NA	<0.0001	
Patient's assessment	56.8	17.9	38.9 (20.0 to 57.7)	NA	<0.0001	

Values are mean (SD) or n (%) for pramipexole and placebo groups, p values are given for the difference in the mean absolute changes (controlled for differences between study centres), NA (not applicable)

Efficacy (see table above)

- Tremor score in favour of pramipexole
- Tremor score shoed the improvement under pramipexole increased in a dose dependent manner during the ascending dose interval and seemed to remain stable between the beginning and end of maintenance
- All UPDRS tremor items showed a statistically significant result in favour of pramipexole for rest tremor and postural tremor as well as for reported tremor
- Pramipexole was significantly superior to placebo in both patients with and without "off" periods at baseline
- Post-hoc analyses revealed levodopa, amantadine, and selegiline did not influence treatment outcome- nor did levodopa dose when stratified as >300 mg versus ≤ 300mg
- UPDRS sub-scores were all in favour of pramipexole
- Patient's diaries revealed a significant improvement in favour of pramipexole with respect to impairment of daily living and severity of tremor
- Global assessment from both patient and investigators estimation was significantly improved in favour of pramipexole

Safety

- Global clinical impression of tolerance was rated as good in 94% of patients an did not differ between groups
- Mean duration was comparable between groups
- Higher overall incidence of adverse events in pramipexole group
- 85.7% reported at least one adverse event, 93.2% in pramipexole group and 77.5% in placebo (p=0.06)
- Common events (incidence of 10% or higher) in either treatment group were fatigue, dizziness, insomnia, nausea, aggravated parkinsonism, abdominal pain, tremor and headache.
- Except for aggravated parkinsonism and tremor each of the other events were reported more frequently in pramipexole
- Tremor was reported more in placebo group

	Withdrawals ➢ 2 patients both from placebo group ➢ One withdrew after first treatment dose without post-baseline efficacy measurements so intention-to-treat population became 83 patients, 44 in pramipexole and 39 in placebo ➢ One patient on placebo discontinued during the ascending dose due to lack of therapeutic effect
Source of funding	Pharmaceutical
Additional comments	➢ Methods of randomisation and allocation concealment stated ➢ Intention-to-treat analysis ➢ Sample size calculations provided (n=42 in each arm to detect significant difference with 80% probability at the 5% level of significance) ➢ 2 of the investigators were employees of the pharmaceutical sponsor ➢ Relatively small sample size (generalisability) ➢ Male dominated population ➢ Differences between centres statistically controlled
NCC CC ID (Ref Man)	2512

Evidence Table **TxCM 2** What is the effectiveness of adding dopamine-agonists vs. placebo in the treatment of later Parkinson's disease patient with motor complications?	
Bibliographic reference	Mizuno Y, Yanagisawa N, Kuno S, Yamamoto M, Hasegawa K, Origasa H *et al*. Randomized, double-blind study of pramipexole with placebo and bromocriptine in advanced Parkinson's disease. *Movement Disorders* 2003; 18:1149-56.
Study type	Multi-centre, controlled, double-blind, randomised, parallel-group study
Evidence level	1++
Study objective	To compare the efficacy and safety of pramipexole with placebo in the treatment of advanced Parkinson's disease (PD) as an adjunct to levodopa.

<table>
<tr><td>Number of patients</td><td>N=325 PD patients

Location: Japan sites: 38</td></tr>
<tr><td>Patient characteristics</td><td>Patients were recruited from April 1999 to March 2000. Patients of both sexes at least 20 years of age, diagnosed as having PD. Patients who exhibited any therapeutically problematic issues based on levodopa therapy were included. No statistical imbalance among the 3 groups based on sex, age, duration of PD, modified Hoehn and Yahr staging on scale, the total score of UPDRS II and III, and the daily dose of levodopa.

<table>
<tr><td>Variable</td><td>Pramipexole</td><td>Bromocriptine</td><td>Placebo</td></tr>
<tr><td>Patients (n=)</td><td>102</td><td>104</td><td>107</td></tr>
<tr><td>Sex, male (%)</td><td>58.8</td><td>47.1</td><td>52.3</td></tr>
<tr><td>Age (yr) mean</td><td>65.46</td><td>64.53</td><td>63.96</td></tr>
<tr><td>Duration of PD</td><td>4.79</td><td>5.03</td><td>5.73</td></tr>
<tr><td>Daily levodopa dose (mg) mean</td><td>404.90</td><td>377.88</td><td>401.92</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Pramipexole (PPX) up to 4.5 mg/d (average daily dose at the final maintenance was 3.24 mg)</td></tr>
<tr><td>Comparison</td><td>Bromocriptine (BR) up to 22.5 mg/d (average daily dose at the final maintenance was 17.75 mg)
Placebo</td></tr>
<tr><td>Length of follow-up</td><td>Duration of the trial was 12 weeks (ascending dose period up to 8 weeks and maintenance dose period of at least 4 weeks) followed by a 1 to 4 week dose reduction period.</td></tr>
<tr><td>Outcome measures</td><td>Primary: change from baseline on final maintenance of the total score of UPDRS II; activities of daily living (ADL) scale (average on and off scores), and the total score of UPDRS III, motor examination scale (performed during on time with the last dose of levodopa).
Secondary: UPDRS I, IV, and I to III, modified Hoehn and Yahr staging scale, Clinical Global Impression on Efficacy (CGI) and responder analysis on the changes of UPDRS II and III and I to IV.</td></tr>
<tr><td>Effect size</td><td>Primary end-points:
➢ The total scores of both UPDRS II and III were significantly reduced in PPX group ($p<0.001$) compared to placebo
➢ Efficacy of PPX group on both primary end points was not statistically inferior to BR group
➢ BR group was also significantly better than placebo group- but the magnitude of response was less than that of the PPX group
➢ Mean changes in UPDRS II and III scores for the PPX group were greater for each visit throughout</td></tr>
</table>

	the treatment period than for placebo or BR groups Secondary end-points: ➢ No significant differences for the PPX group in UPDRS I compared to placebo or BR ➢ UPDRS IV favoured placebo over PPX (p=0.006) but no difference between PPX & BR (p=0.789) ➢ Modified Hoehn and Yahr staging scale: PPX group showed a significant improvement compared with the placebo group (p<0.001) and a trend toward significant improvement compared with BR group (p=0.053) ➢ CGI: greater improvement in PPX compared to BR (p=0.022) and placebo (p<0.001) ➢ Improvement rates defined as "effective" and/or "very effective" for the CGI were 61.8% in the PPX group and 47.1% in the BR group and 28.0% in placebo ➢ The proportion of responders (defined as showing a 30% or more reduction in UPDRS II and III and I to IV total scores from baseline) were significantly larger in PPX group than placebo group for each variable (p<0.01) ➢ No significant differences was observed between PPX and BR in these response rates ➢ The rates of responders in PPX were 56.9% in UPDRS II, 63.7% in UPDRS III and 68.1% in UPDRS I to IV ➢ The rates of responders in BR were 49.0% in UPDRS II, 60.6% in UPDRS III and 51.9% in UPDRS I to IV ➢ The rates of responders in placebo were 29.9% in UPDRS II, 36.4% in UPDRS III and 36.4% in UPDRS I to IV Adverse events: ➢ The rate of adverse events in the PPX group 85.3% not significant compared to BR group (90.5%) or placebo (76.9%) ➢ The majority of withdrawals in all treatment groups was dropout during the ascending dose period ➢ Main adverse events reported in more than 10% of patients: dyskinesia, dizziness, headache, somnolence, hallucination, dry mouth, anorexia, dyspepsia, nausea, vomiting, constipation
Source of funding	Pharmaceutical
Additional comments	➢ Methods of randomisation and allocation concealment specified ➢ All study personnel and participants were blinded to the study medication ➢ Sample size calculations were performed ➢ Intention-to-treat analysis ➢ No comparability between centres analysis

NCC CC ID (Ref Man)	2405

Evidence Table **TxCM 2** What is the effectiveness of adding dopamine-agonists vs. placebo in the treatment of later Parkinson's disease patient with motor complications?	
Bibliographic reference	Hilten Jv, Ramaker C, Beek WJT vd, Finken MJJ. Bromocriptine for levodopa-induced motor complications in Parkinson's disease (Cochrane Review). *The Cochrane Library* 2003.
Study type	Cochrane review: 7 RCTs; 5 parallel studies; 2 crossover (Bateman and Gron)
Evidence level	1++
Study objective	To assess the efficacy and safety of adjunct bromocriptine (BR) therapy compared to placebo in the treatment of Parkinson's disease (PD) in patients with motor complications.
Number of patients	N=396 Parkinson's disease Patients N=11 (Bateman) N=20 (Gron) N=36 (Hoehn) N= 23 (Jansen) N=40 (Schneider) N=44 (Temlett) N=222 (Toyokura) Location: UK (Bateman), Denmark (Gron), US (Hoehn), Holland (Jansen), Germany (Schneider), South Africa (Temlett), Japan (Toyokura) Sites: 59 (Toyokura) no other trials reported number of sites.
Patient characteristics	Mean age of all participants was 62.9 years (range 30-81 years). Only Toyokura reported age at onset. The mean disease duration ranged from 8.5 (Gron, Jansen) to more than 13 years (Temlett). The mean pre-trial LD treatment duration ranged from at least one year (Toyokura) to seven years (Hoehn).
Intervention	Five trials introduced BR at 2.5 mg/d; two trials started with BR 1.25mg/d (Hoehn and Toyokura).

	Maximum BR dosages ranged from 20mg/d (Hoehn and Temlett) to 100mg/d (Jansen). Only Schneider allowed a LD reduction during the trial.
Comparison	Placebo
Length of follow-up	Study duration was highly variable. 4 weeks (Schneider) to 32 weeks (Hoehn). The mean duration of included trials was 14.2 weeks.
Outcome measures	Motor complications, impairment, disability, LD dose reduction, side effects, withdrawal rate
Effect size	Motor complications **Dyskinesia** ➢ 3 trials reported an increase in occurrence of dyskinesia in BR group (Jansen, Temlett, Toyokura) ➢ Only Toyokura reported this difference to be statistically significant ➢ Schneider reported no difference- and this was the only study to allow LD dose reduction ➢ Hoehn reported no difference but did not mention statistical evaluation of this outcome data **Wearing off** ➢ No difference (marginal) between 2 groups was found in two studies (Hoehn and Toyokura) ➢ Schneider and Toyokura reported improvement of patients in the BR tier with respect to on-off fluctuations ➢ The difference was significant in Schneider and non-significant in Toyokura ➢ Two trials reported no change in on-off time (Jansen, Temlett) **Dystonia** ➢ BR improved with respect to severity and duration vs. placebo (Hoehn) ➢ Temlett reported no differences between groups ➢ Two trials did not report data on motor complications at end of the first phase of their trials- review did not analyse these results (Bateman and Gron) **Impairment** ➢ BR reduced impairment scores vs. placebo in 2 studies (Jansen and Schneider) ➢ Only patients with baseline scores of less than 50 (modified Columbia scale, max score 96) showed a significant improvement (Hoehn) ➢ Toyokura found non-significant improvement in impairment level ➢ Temlett did not provide outcomes at the moment patients using placebo were switched to BR

	➢ Gron and Bateman did not provide data at moment of crossover **Disability** ➢ Jansen and Schneider found significant improvement for disability in BR group ➢ Toyokura found non-significant difference between groups ➢ Temlett, Bateman and Gron did not provide data on disability at the end of the first phase of their trials and therefore results were no evaluated by the review **LD dose reduction** ➢ Schneider reported a statistically non-significant reduction in LD for both groups **Side effects** ➢ Occurrence of side effects was reported by two trials (Hoehn and Toyokura) and partly by two others (Jansen and Schneider) ➢ Compared to placebo Hoehn found only transient nausea, vomiting and episodic sweating slightly more frequently in BR group (statistical significance not available) ➢ Toyokura found no statistically significant differences in incidences between the two groups ➢ Three trials revealed only side effects responsible for withdrawal of patients Withdrawal ➢ No differences were found between BR and placebo groups ➢ All causes: Odds ratio 1.15 (95% CI 0.65 to 1.95, p=0.6)
Source of funding	
Additional comments	➢ Search period between 1974 to 1998 ➢ Not all included trials adequately described patient population ➢ There were substantial differences between the studies concerning the mean pre-trial dosages of LD and the reported ratios of LD/decarboxylase inhibitor ➢ All authors were contacted to obtain additional information- only 4 responded (Bateman, Jansen, Toyokura and Temlett) one author was deceased (Gron) ➢ Additionally obtained information showed 4 trials used an adequate randomisation procedure (Bateman, Jansen, Temlett, Toyokura) and 3 trials were adequately concealed until outcome assessment (Jansen, Temlett, and Toyokura) ➢ All were double-blind ➢ No trials were intention-to-treat

	➢ No washout reported in 2 crossover trials ➢ Trials included: Bateman 1978, Gron 1977, Hoehn 1985, Jansen 1978, Schneider 1982, Temlett 1990, Toyokura 1985
NCC CC ID (Ref Man)	47

Evidence Table

TxCM 2

What is the effectiveness of adding dopamine-agonists vs. placebo in the treatment of later Parkinson's disease patient with motor complications?

Bibliographic reference	Clarke CE,.Deane KH. Cabergoline for levodopa-induced complications in Parkinson's disease (Cochrane Review). *The Cochrane Library* 2003.
Study type	Cochrane review: two Phase II and one phase III randomised controlled double blind parallel trials
Evidence level	1++
Study objective	To compare the efficacy and safety of adjuvant cabergoline therapy versus placebo in patients with Parkinson's disease, already established o levodopa and suffering from motor complications.
Number of patients	N=268 Parkinson's disease (PD) patients N=188 Hutton (Phase III) N=43 Miguel (Phase II- unpublished) N=37 Steiger (Phase II) Location: USA (Hutton), Spain (Miguel), UK (Steiger) Sites: 10 (Hutton), 5 (Miguel), 2 (Steiger)
Patient characteristics	Patients with a clinical diagnosis of Parkinson's disease who had developed long-term motor complications of dyskinesia and/or end-of-dose deterioration were considered.

Study	(N=)		Mean age		H&Y baseline		Drop-outs (%)	
	C	P	C	P	C	P	C	P
Hutton	123	65	63.4	62.8	2.0	2.0	13 (11)	11 (17)
Miguel	23	20	60	62			5 (22)	6 (30)
Steiger	19	18	60.8	63.4	3.5	3.5	1 (5)	2 (11)

Intervention	Cabergoline: (present licensed limit of 6.0 mg/d) Hutton: 5.0 mg/d (mean dose 3.66 mg/d) Steiger: 10.0 mg/d (mean dose 5.4 mg/d) Miguel: 3.0 mg/d (mean dose 2.64 mg/d) Levodopa dose reduction was allowed in Miguel and Hutton but not Steiger
Comparison	Placebo
Length of follow-up	Trial duration: Steiger (Phase II) 12 weeks Miguel (Phase II) 6-10 weeks Hutton (Phase III) 24 weeks
Outcome measures	Off time, dyskinesia, motor impairment and disability (Unified Parkinson's disease Rating Scale (UPDRS) and Schwab and England score), Levodopa Dose reduction, adverse events, withdrawals
Effect size	➢ Reviewers report ''in spite of obtaining further information from the manufacturer, it proved impossible to obtain data on the reduction in off time in hours for all of the studies'' Off time ➢ The reduction in off time of 1.14 hours/day more with cabergoline than placebo (weighted mean difference [WMD] 95%CI –0.06 to 2.33, p=0.06) Dyskinesia ➢ Dyskinesia rating scale (Steiger) no difference was seen between the two arms of the study and no data was reported ➢ Dyskinesia reported as an adverse event was not available from Hutton ➢ There was a trend towards an increase with cabergoline in one of the phase II studies (Miguel) (odds ratio 6.49, 95%CI 0.13 to 330.02, p=0.4) Motor impairment and disability ➢ Hutton: statistically significant advantage of cabergoline over placebo for UPDRS ADL score and UPDRS motor score ➢ Presumed by reviewers this was measured in the on phase ➢ No advantage was seen in Miguel but reviewers attribute this to small dosage of cabergoline and small sample size ➢ No differences in Schwab and England scale were seen in Miguel and Steiger ➢ But the number of patients rated as much or very much improved in Steiger was greater with cabergoline Levodopa (LD) dose

	➢ Hutton: LD dose reduction was significantly greater with cabergoline (WMD 149.6 mg/d, 95%CI 94.1 to 205.1, p<0.00001) ➢ Reviewers comment this difference may have been greater if dose changes had not rpevented Steiger and data had been available for Miguel study Adverse events ➢ There was a trend towards more dopaminergic adverse events with cabergoline but this did not reach statistical significance at the p<0.01 level ➢ Nausea (p=0.06), postural hypotension (p=0.03), hallucinations (p=0.15), confusion (p=0.05), dyskinesia (p=0.40), insomnia (p=1.00), sleep disorder (p=0.50), somnoler (p=0.40) Withdrawals ➢ There was a trend towards fewer withdrawals from cabergoline (odds ratio 0.58, 95% CI 0.28 to 1.18, p=0.13) ➢ Author's comment this may be due to cabergoline's efficacy
Source of funding	Not stated
Additional comments	➢ Miguel was unpublished but details were provided by manufacturer- possible publication bias ➢ Not intention-to-treat (the two phase II trials (Miguel and Steiger) selected patients to continue in the study after titration only if they responded to the trial medication, so only data up to the end of the titration period has been included in the review ➢ Details of randomisation and allocation concealment were described in two trial reports (Hutton and Miguel) information on the third trial (Steiger) was obtained from one of investigators ➢ None of the trials reported sample size calculations ➢ Trials included: Hutton 96, Miguel 93, Steiger 96
NCC CC ID (Ref Man)	52

Evidence Table **TxCM 2** What is the effectiveness of adding dopamine-agonists vs. placebo in the treatment of later Parkinson's disease patient with motor complications?	
Bibliographic reference	Clarke CE,.Speller JM. Lisuride for levodopa-induced complications in Parkinson's disease (Cochrane

	Review). *The Cochrane Library* 2003.
Study type	Cochrane review: no trials found
Evidence level	1++
Study objective	To compare the efficacy and safety of adjuvant lisuride therapy versus placebo in patients with Parkinson's disease, already established on levodopa and suffering from motor complications.
Number of patients	N=0
Patient characteristics	N/A
Intervention	Oral Lisuride therapy
Comparison	Placebo
Length of follow-up	N/A
Outcome measures	N/A
Effect size	No randomised controlled trials comparing lisuride with placebo in advanced Parkinson's disease with motor complications was found by the review.
Source of funding	Not stated
Additional comments	➢ Author's conclusions:" well designed randomised controlled trials demonstrating efficacy and safety are required before the use of lisuride in later Parkinson's disease can be supported.
NCC CC ID (Ref Man)	54

Evidence Table **TxCM 2** What is the effectiveness of adding dopamine-agonists vs. placebo in the treatment of later Parkinson's disease patient with motor complications?	
Bibliographic reference	Clarke CE,.Speller JM. Pergolide for levodopa-induced complications in Parkinson's disease (Cochrane Review). *The Cochrane Library* 2003.
Study type	Cochrane review: Large, multi-centre double, blind parallel group, RCT
Evidence level	1++
Study objective	To compare the efficacy and safety of adjunct pergolide therapy versus placebo in patients with

	Parkinson's disease (PD) suffering from complications of levodopa therapy
Number of patients	N=376 PD patients N= 189 pergolide-treated patients N=187 placebo-treated patients Location: USA Sites: 16
Patient characteristics	Patients with a clinical diagnosis of PD who developed dyskinesias, end-of-dose deterioration or both. Patients were comparable for age, sex, duration of PD, severity of disease, and levodopa dose at randomisation. Mean Hoehn and Yahr at baseline: 3.1 pergolide group, 3.3 placebo group. Inclusion criteria: included a minimum severity of disease ion certain items of the weighted unique rating scale (modified Columbia scale).
Intervention	Pergolide: blind titration to 0.25 mg tds over two weeks, then 0.25mg increment or decrement every third day. Mean dose of pergolide in active arm was 2.94 mg/d. Changes in levodopa dose allowed.
Comparison	Placebo
Length of follow-up	Trial duration=24 weeks
Outcome measures	Parkinson's disease rating scales, levodopa dosage, 'off' time measurements, frequency of dropouts and adverse events.
Effect size	Off time ➢ The mean 'off' time was reduced by 1.8 hours with pergolide compared with 0.2 hours with placebo (p<0.001) Dyskinesia ➢ Dyskinesia developed or deteriorated in 62% of pergolide-treated compared with 25% placebo-treated patients (odds ratio 4.64, 95% CI 3.09 to 6.97, p<0.00001) ➢ Excess in dyskinesia prevalence and severity had disappeared by the end of the study as levodopa was reduced Reduction in levodopa dose ➢ Mean reduction was more in those receiving pergolide than placebo (235mg v 51mg, p<0.001) Clinical rating scales ➢ Significant improvements with pergolide compared with placebo on Hoehn and Yahr and both motor and activities of daily living parts of a modified Columbia rating scale Adverse events ➢ Significantly more patients suffered nausea (24% v 13%, odds ratio 2.13, 95%CI 1.27 to 3.58), and

	hallucinations (14% v. 3%, Odds ratio 3.86, 95% CI 1.87 to 7.96) on pergolide compared to placebo Withdrawals ➢ No difference was found in the numbers retained on treatment at the end of the study (pergolide 84% v placebo 82%) ➢ However withdrawals due to adverse events was greater in those taking pergolide (9.5% v 4.3%) (Odds ratio 0.88, 95%CI 0.51 to 1.51) ➢ Drop-outs: 30 (16%) pergolide, 33 (18%) placebo
Source of funding	Not stated
Additional comments	➢ The majority of RCTs identified by the review formed part of a large multi-centre study which was published in full- therefore the small reports were excluded from the review ➢ Randomisation methods stated but no allocation concealment methods ➢ Analysed on intention-to-treat basis ➢ Not clear whether those analysing data were blinded to treatment assignment ➢ Trials included: North American 94 (Olanow)
NCC CC ID (Ref Man)	56

Evidence Table **TxCM 2** What is the effectiveness of adding dopamine-agonists vs. placebo in the treatment of later Parkinson's disease patient with motor complications?	
Bibliographic reference	Clarke CE, Speller JM, Clarke JA. Pramipexole for levodopa-induced complications in Parkinson's disease (Cochrane Review). *The Cochrane Library* 2003.
Study type	Cochrane review: 4 phase II (2 short-term and 2 medium term) double blind, parallel group RCTs
Evidence level	1++
Study objective	To compare the efficacy and safety of adjuvant pramipexole therapy versus inactive placebo in patients with Parkinson's disease (PD), already established on levodopa.
Number of patients	N=669 patients with later PD N=162 (Guttman)

	N=360 (Leiberman) N=78 (Pinter) N=69 (Wermuth) Location: multinational (Guttman), North America (Lieberman), Austria, Germany, Switzerland (Pinter), Danish centres Sites: 34 (Guttman), 26 (Leiberman), 9 (Pinter), 8 (Wermuth)
Patient characteristics	Patients with a clinical diagnosis of PD who had developed long-term complications of dyskinesias and/or end-of-dose deterioration. The 2 groups in each trial were well matched at baseline for age, sex, duration, and severity of PD [except for Pinter study in which the proportion of women in the pramipexole group was higher (41%) than placebo arm (30%)].
Intervention	Pramipexole: mean dose in the active treatment arm was given in 3/ 4 studies, and was comparable in 2 studies: 3.36 mg/d (Guttman) and 3.59 mg/d (Pinter) but higher 4.59 mg/d in third study (Wermuth). The maximum allowed doses were similar in 4 trials: 4.5 mg/d (Guttman, Lieberman) and 5.0 mg/d (Pinter, Wermuth). Reduction of levodopa dose was allowed in all but Pinter study.
Comparison	Placebo
Length of follow-up	Trial duration: < or =36 weeks (Guttman), < or =31 weeks (Leiberman), 11 weeks (Pinter), 11 weeks (Wermuth)
Outcome measures	Off time, dyskinesia, clinical rating scales, levodopa dose reduction, quality of life, adverse events, withdrawal rates
Effect size	Off time ➢ From data obtained from the manufacturer, a meta-analysis was performed on the reduction in the time patients spent in off state of the 4 included trials ➢ Highly significant benefit of pramipexole (weighted mean difference (WMD) 1.77 hours, 95%CI 1.21 to 2.34, p<0.00001) ➢ Off time was significantly reduced in the larger 2 phase III trials (31% v 7% in Leiberman and 15% v 3% in Guttman) ➢ No statistical comparison was given in the 2 phase II trials but there was a trend towards a greater reduction in off time with pramipexole (10% v 3% in Wermuth and 12% v 2% in Pinter) Dyskinesia

	➢ No significant changes ion dyskinesia rating scale in any of the 4 trials ➢ Dyskinesia as an adverse event was reported more frequently with pramipexole ➢ A significant improvement occurred in UPDRS complication score (part IV) in 2 studies but not in the remaining trials Clinical rating scales ➢ Method of recording and analysing UPDRS ADL score varied between trials ➢ Some reported score in off state, some in on state, and some as an average of on and off ➢ Significant improvements in favour of pramipexole occurred in all 4 trials regardless ➢ Significant improvements in UPDRS motor scores in 'on' state were reported in 3/ 4 studies ➢ Both Hoehn and Yahr and Schwab and England scale significantly improved in 1 of the 2 studies in which these scales were reported ➢ Pinter: clinician's global impression scale showed a large number of patients with a "satisfactory or good improvement" with pramipexole compared to placebo (Odd Ratio (OR) 5.84, 95%CI 2.40 to 14.21, p=0.0001) Levodopa dose reduction ➢ Dose reduction was allowed in 3 studies ➢ Data provided by manufacturers ➢ Significant difference in favour of pramipexole (WMD 114.82 mg, 95% CI 86.64 to 143.01, p<0.00001) Quality of life ➢ Guttman: superiority of pramipexole over placebo for Functional Status Questionnaire (FSQ) Basic ADL, and Mental Health Scales and European Quality if Life (EuroQol) scale Adverse events ➢ Higher incidence of dopaminergic adverse events: Nausea (p=0.17), postural hypotension (p=0.07), hallucinations (p=0.0001), confusion (p=0.17), dyskinesia (p=0.00001) ➢ Only statistically significant in pramipexole for hallucinations (OR 2.63, 95% CI 1.61 to 4.32) Withdrawal rates ➢ Significant difference in 'all cause' withdrawal rate in favour of pramipexole (OR 0.64, 95%CI 0.44 to 0.93, p=0.02) ➢ Drop-outs (%): Guttman [16 (20) pramipexole v 33 (40) placebo], Leiberman [30 (17) v 39 (22)], Pinter [5 (15) v 6 (14)] and Wermuth [6 (17) v 5 (15)]
Source of funding	Not stated
Additional comments	➢ Details of randomisation and allocation concealment were poorly reported in all 4 trials- further details were obtained from the manufacturer

	➢ Sample size calculations were not provided in one of the phase III studies ➢ Trials included: Guttman 97, Leiberman 97, Pinter 99, Wermuth 98
NCC CC ID (Ref Man)	58

Evidence Table

TxCM 2

What is the effectiveness of adding dopamine-agonists vs. placebo in the treatment of later Parkinson's disease patient with motor complications?

Bibliographic reference	Clarke CE,.Deane KHO. Ropinirole for levodopa-induced complications in Parkinson's disease (Cochrane Review). *The Cochrane Library* 2003.
Study type	Cochrane review: randomised double blind placebo-controlled trials
Evidence level	1++
Study objective	To compare the efficacy and safety of adjuvant ropinirole therapy versus placebo in patients with Parkinson's disease already established on levodopa therapy and suffering from motor complications.
Number of patients	N=263 Parkinson's disease patients N=164 randomised to ropinirole N=68 (Korcyn) N=149 (Leiberman) N=46 (Rascol) Location: USA and Israel (Korcyn), USA (Leiberman), UK and France (Rascol) Sites: 8 (Korcyn), 16 (Leiberman), 2 (Rascol)
Patient characteristics	No major differences were apparent in baseline characteristics of patients in included trials.

Study	Mean Hoehn and Yahr		Mean age		Drop-outs (%)	
	Ropinirole	Placebo	Ropinirole	Placebo	Ropinirole	Placebo
Korcyn	2.9	2.8	62.3	63.7	15 (33)	4 (18)
Rascol	2.9	3.0	62	63	2 (9)	9 (39)
Leiberman	2.8	2.8	-	-	21 (22)	19 (35)

Intervention	Ropinirole: Leiberman 24 mg/d Rascol 8mg/d (mean dose actually administered 3.3 mg/d) Korcyn 10mg/d (mean dose actually administered 3.5 mg/d)
Comparison	Placebo
Length of follow-up	Trial duration 26 weeks (Leiberman), 12 weeks (Rascol and Korcyn)
Outcome measures	Composite scores, dyskinesia, levodopa dose, adverse events, withdrawal rates
Effect size	➢ The phase II trials (Rascol and Korcyn) used very low doses of ropinirole and very small sample size, which suggested to the reviewers that these studies were unreliable in comparison to the lager phase III study ➢ Leiberman: authors of the paper report compared the proportion of patients who achieved a 20% or > reduction off time AND a 20% or > reduction in levodopa (LD) dose ➢ This composite score was achieved by 35% of those given ropinirole compared to 13% with placebo (p=0.003) ➢ The manufacturer to express change in 'off time hours' supplied additional data. ➢ The difference in the reduction in off time was greater with ropinirole than placebo but not significant (weighted mean difference (WMD) 0.31 hours, 95%CI –1.02 to 1.64) ➢ This was reported back to the manufacturers by the reviewers ➢ The manufacturers re-examined original off time data and discovered that the number of hours spent in the off phase in the ropinirole and placebo groups was significantly different at the start of the trial ➢ They performed an analysis of covariance (ANCOVA) on intention-to-treat basis using each patient's baseline off time as covariate ➢ This yielded a reduction in off time of 1.2 hours more with ropinirole than placebo which was significant (95%CI 0.04 to 2.32, p=0.04) ➢ The residuals from this analysis were non-normal indicating a violation of the assumptions of the ANCOVA and suggesting that a non-parametric methodology should be used ➢ ANCOVA of the ranked data continued to show a significant difference in favour of ropinirole (p<0.01) Dyskinesia ➢ Was not measured with rating scales in any of the trials ➢ Data on dyskinesia as a new adverse event was reported by Leiberman

	➢ Dyskinesia was significantly increased in those who received ropinirole (odds ratio (OR) 2.90, 95%CI 1.36 to 6.19) Motor impairments ➢ Poor reporting of measurements of motor impairment in these trials ➢ Additional data from manufacturer of Leiberman trial- there were significantly more patients 'much' or 'very much' improved in ropinirole compared with placebo (OR 2.98, 95%CI 1.53 to 5.80, p=0.001) using a standard seven point rating scale Levodopa dose ➢ Could not be reduced in two trials (Rascol and Korcyn) ➢ Leiberman the dose could be reduced significantly more with ropinirole than with placebo (WMD 180 mg/d, 95%CI 106 to 253) Adverse events ➢ No significant differences, apart from dyskinesias, in Leiberman study Withdrawal rates ➢ There was a trend towards fewer withdrawals from ropinirole in Leiberman but this was not significant (OR 0.52, 95% CI 0.24 to 1.09)
Source of funding	Not stated
Additional comments	➢ Only Leiberman trial used doses of ropinirole in line with current UK practice ➢ Reporting outcome measures was complicated in two studies by the use of composites of several measurements- so additional data was secured from manufacturer ➢ Randomisation and allocation concealment methods described ➢ One of the studies analysed on per-protocol basis ➢ Sample size calculations were not presented in the published reports ➢ Korcyn is an unpublished study provided by manufacturer ➢ Trials included: Korcyn 90, Leiberman 98, Rascol 96
NCC CC ID (Ref Man)	60

Evidence Table

TxCM 2

What is the effectiveness of adding dopamine-agonists vs. placebo in the treatment of later Parkinson's disease patient with motor complications?

Bibliographic reference	Wong KS, Lu C-S, Shan D-E, Yang C-C, Tsoi TH, Mok V. Efficacy, safety, and tolerability of pramipexole in untreated and levodopa-treated patients with Parkinson's disease. *Journal of the Neurological Sciences* 2003; 216:81-7.
Study type	Randomised, double-blind, placebo-controlled, parallel study
Evidence level	
Study objective	To evaluate the efficacy ad safety of the non-ergot dopamine agonist pramipexole in untreated and levodopa treated Chinese patients with early or advanced Parkinson's disease (PD).
Number of patients	N=150 early and late PD patients Location: Hong Kong, Taiwan Sites: 5
Patient characteristics	Eligibility criteria: at least 30 years of age, symptomatic idiopathic Parkinson's disease, stage 1-4 on the modified Hoehn and Yahr scale, 3/ 4 of the cardinal signs of PD (rigidity, bradykinesia, resting tremor, and postural instability), good response to levodopa (LD) and stable dosage for at least 1 month prior to study entry (for late PD patients only). Approximately 70% of placebo and pramipexole-treated patients were receiving LD concomitantly

Variable	Placebo	Pramipexole	P value
No. of patients	77	73	
Age (yrs), mean ± SE	60.94 ± 1.11	58.84± 1.28	0.21
No. of years since onset of symptoms, mean ± SE	4.33 ± 0.36	4.49 ± 0.40	0.77
Males, N (%)	56 (72.7)	48 (65.8)	0.35

	All other baseline characteristics: UPDRS part II total score mean, UPDRS part III total score mean, Modified Hoehn and Yahr scale mean were similar for both treatment groups.
Intervention	Pramipexole (PPX): began at 0.125 mg TID (0.375 mg/d) to maximum of 1.5 mg TID (4.5 mg/d)
Comparison	Placebo, 1 dose, every 8 h, 3x daily
Length of follow-up	Trial duration: 15 weeks
Outcome measures	Unified Parkinson's disease Rating scale (UPDRS) parts II and III, modified Hoehn and Yahr score,

	number of 'off' hours, mini-mental state examination (MMSE)
Effect size	➢ The adjusted mean change-from-baseline values for the combined total scores of the UPDRS parts II and III were consistently greater with PPX than with placebo ➢ Statistically significant differences were seen between placebo and PPX groups were seen at the end of treatment weeks 3,7,11, and 15 ➢ Improvement in mean UPDRS scores in PPX group ranged from 3.40 points in week one to 12.14 points at end of maintenance period week 15 ($p<0.001$) compared to placebo group who did not exceed 2.89 points for any study visit ➢ Regardless of LD use, mean UPDRS total scores showed a consistently greater improvement in PPX-treated patients than placebo-treated ➢ Mean scores for PPX-treated patients not receiving concomitant LD showed a greater improvement than those receiving LD ➢ Adjusted mean changed from baseline were consistently greater in the PPX group than the placebo patients with a relatively larger treatment effect in UPDRS part III scores in the UPDRS part II scores ➢ Mean scores were significant at 3,7,11,and 15 for UPDRS III scores (data not shown) ➢ Mean score were significant at 7, 11, 15 for UPDRS part II scores (data not shown) ➢ UPDRS scores analysed according to LD use, patients taking PPX plus LD showed consistently greater improvement than patients taking placebo plus LD ➢ Patients taking PPX without LD showed little difference from those patients taking placebo without LD ➢ Regardless of LD use patients receiving PPX showed consistently greater improvements on UPDRS III scores than patients receiving placebo ➢ For all but one individual item in the UPDRS parts II and III, mean changes from baseline to the end of treatment favoured PPX over placebo ➢ Modified Hoehn and Yahr score: regardless of whether patients were receiving or not receiving LD a greater proportion ion the PPX group than the placebo group had improved at each treatment throughout the study ➢ Mean number of "off" hours/day for patients receiving PPX and on LD improved during the study mean baseline 7.07h, mean end-of-treatment 6.15h) while the placebo group worsened over the course of the study (mean baseline 5.59h, and mean end-of-treatment 6.87h/day) ➢ MMSE virtually no change observed in the mean scores for either treatment group during study Adverse events

	➢ More adverse events were reported overall in patients in pramipexole group (86.3%) versus placebo (71.4%) ➢ Most adverse events were mild or moderate in intensity ➢ Most were observed during dose-escalation phase than maintenance phase for both groups ➢ Fewer than 10% of patients in both groups experienced events which led to discontinuation ➢ Nearly all of the events were in patients on concomitant levodopa ➢ Most commonly adverse events (≥ 10%): dizziness, constipation, nausea, dry mouth, dyskinesia, hallucinations, and somnolence
Source of funding	Pharmaceutical
Additional comments	➢ Conducted from November 1998 and January 2000 ➢ Intention-to-treat analysis ➢ Sample size calculations performed ➢ Data analysed for differences between early and late PD patients (i.e. people on levodopa or not) ➢ Allocation and randomisation methods not discussed
NCC CC ID (Ref Man)	1823

TxCM3 – section 7.5.6

Evidence Table **TxCM 3** What is the effectiveness of adding amantadine vs. placebo in the treatment of later Parkinson's disease patient with motor complications?	
Bibliographic reference	Crosby NJ, Deane HO, Clarke CE. Amantadine for dyskinesia in Parkinson's disease. (Cochrane Review). *The Cochrane Library* 2004.
Study type	Cochrane review: 3 Randomised, placebo-controlled, double-blind, cross-over designed
Evidence level	1++
Study objective	To compare the efficacy and safety of adjuvant amantadine therapy versus placebo in treating dyskinesia in patients with Parkinson's disease, already established on levodopa, and suffering from

	motor complications.
Number of patients	N= 53 patients N=11 (Luginger) N=24 (Snow) N=18 (Verhagen Metman) Location: Austria (Luginger), New Zealand (Snow), USA (Verhagen Metman) Sites: single centre (all trials)
Patient characteristics	Snow and Verhagen Metman: neither provided data about the characteristics of the individual participants nor of the two groups at baseline. Snow: examined 24 patients (10 male, 14 female) with a mean age of 64 years. On average they had PD for 10.6 years, dyskinesias for 3.1 years, and were taking 834 mg/d of LD. Verhagen Metman: treated 18 patients (12 male, 16 female) with a mean age of 60 years. On average they had PD for 13 years, Hoehn and Yahr score 3.5 and were taking 1074 mg/d LD. Luginger: examined 11 participants (4 male, 7 female) with a mean age of 63.5 years. On average they had PD for 16.2 years, dyskinesias for 10.1 years, and were taking 777 mg/day of levodopa (LD).
Intervention	Amantadine (+ LD) Luginger Two weeks of active drug 300mg/d titrated over 3 days with daily 100mg increments- followed by one-week (washout) and then crossover. Snow Three weeks of active drug (100mg/d for first week followed by 200 mg/d for the remaining 2 weeks) (no washout) and then crossover. Verhagen Metman Three weeks of active drug (titrated patients up to 300mg or 400mg/d over the first 4 to 6 days of the 3-week treatment arm) (no washout) and then crossover.
Comparison	Placebo
Length of follow-up	No follow-up reported Trial duration: 5 weeks (Luginger), 6 weeks (Snow), 6 weeks (Verhagen Metman)
Outcome measures	'Marconi dyskinesia rating scale' (Luginger) Unified Parkinson's disease Rating Scale (UPDRS), revised version of the Abnormal Involuntary Movement Scale (AIMS) (Snow and Verhagen Metman)
Effect size	➢ None of the trials have the results of the first arms- they only presented the combined data from both active treatment arms and both placebo arms ➢ Since a washout period was not incorporated in 2 of the studies a strong possibility of carry-over effect and these studies were not analysed on intention-to-treat (Verhagen Metman and Snow)

	➢ Data from these trials were not used in the review ➢ Luginger with one week washout may still suffer carryover effect ➢ Luginger stated there were no differences between patients receiving amantadine in the first of second treatment periods ➢ Dyskinesia severity following levodopa challenge was reduced after oral amantadine treatment by 6.4 points (41%) when compared to placebo arm Adverse events ➢ One patient experienced reversible oedema of both feet during active amantadine treatment (Luginger) and one patient experienced dizziness on placebo ➢ Snow reported no adverse events for all 24 patients ➢ Verhagen Metman reported a range of adverse events: confusion (200mg/d amantadine), worsening of hallucinations (300mg/d amantadine), reappearance of palpitations (100mg/d amantadine) and nausea (100mg/d amantadine). As well one patient complained of an exacerbation of hallucinations (300 mg/d) another of slightly worsened dry mouth and constipation and two reported confusion on 400mg/d which resolved when dose was reduced to 300mg/d Withdrawals ➢ One patients withdrew from the Luginger study due to dizziness on placebo ➢ Two patients withdrew from the Snow trial, one because treatment was working and they did not want to cross-over (this turned out to be amantadine arm) and other was poorly compliant on placebo ➢ 4 patients withdrew from the Verhagen Metman because of mild and transient adverse events
Source of funding	None stated
Additional comments	➢ Only one trial included a wash-out period (Luginger) ➢ Snow did not report method of allocation concealment but did describe method of randomisation ➢ Verhagen Metman did not describe method of randomisation but did report allocation concealment ➢ Only Snow stated the criteria (UK Brain Bank) for diagnosis of PD patients ➢ Small sample size limits generalisability ➢ Possibly underpowered studies ➢ All 3 trials were double-blinded ➢ The Marconi dyskinesia rating scale used by Luginger does not appear to be examined for reliability or validity?

	➢ All trials did not analyse on intention-to-treat basis ➢ Included trials: Luginger (2000), Snow (2000), Verhagen Metman (1998)
NCC CC ID (Ref Man)	50

Evidence Table **TxCM 3** What is the effectiveness of adding amantadine vs. placebo in the treatment of later Parkinson's disease patient with motor complications?	
Bibliographic reference	Thomas A, Iacono D, Luciano AL, Armellino K, Di Iorio A, Onofrj M. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry* 2004;**75**:141-3.
Study type	Randomised, double-blind, placebo-controlled study
Evidence level	1+
Study objective	To assess the duration of the antidyskinetic effect of amantadine on levodopa induced dyskinesia
Number of patients	N=40 Parkinson's disease patients (PD) N=20 amantadine group N=20 placebo group Location: Sites
Patient characteristics	24 men and 16 women, mean age 62.7 (5.2) years. Advanced idiopathic Parkinson's disease patients complicated by motor fluctuations and L-dopa induced dyskinesia affected all patients. Hoehn and Yahr stage 2.6 (0.2), L-dopa daily dose 730 (190) mg, L-dopa doses per day 5.5 (0.5), disease duration 7.9 (2.2), Universal Parkinson's disease Rating Scale (UPDRS) motor subscale score 51.9 (8.5).
Intervention	Amantadine 300mg/day
Comparison	Identical capsules containing agar gel were used as placebo
Length of follow-up	12 month duration, 1 month follow-up (withdrawal)
Outcome measures	Universal Parkinson's disease Rating Scale (UPDRS), Dyskinesia Rating Scale (DRS), Investigator

	Global Assessment (IGA) of dyskinesia. The primary endpoint was occurrence of dyskinesia worse than or equal to that recorded before the initiation of treatment
Effect size	➢ Key variables were equally distributed at baseline in the two groups of patients ➢ Treatment duration was significantly in favour of amantadine group (p=0.01) ➢ The 'beneficial' effect of amantadine lasted on average 4.9 months, compared with just 1.3 months for the ''placebo effect'' p<0.001 ➢ 15 and 30 days after treatment onset amantadine induced reduction of DRS total scores (by 45%) and UPDRS item 32-34 scores were highly significant compared with baseline and placebo effects p<0.001 ➢ IGA scores increased in the amantadine group by 2.1 (0.1) points- resulting in global impression of improvement in all amantadine treated patients ➢ Placebo group showed small decrease of UPDRS items 32-34 (8%), reported by 2 patients, were not paralleled by similar changes of DRS and IGA scores (not significant) ➢ UPDRS scale I-III scores and ''off' time were reduced and ''on'' time was increased in amantadine group ➢ Only UPDRS score reductions were statistically significant versus baseline and placebo (p<0.01) ➢ Following 8 months all amantadine patients reported an increase in UPDRS item 32-34 scores, indicating a dyskinesia time increase of 50%: 5 patients at 3 months, 4 patients at 4 months and 2 at 5 and 6 months, 2 at 7 months, and one a 8 months ➢ DRS and IGA worsening corresponded to subjective reports ➢ Six placebo patients withdrew at one month, 12 at 2 and 3 months because dyskinesia scores were unchanged or increased by 1 point (DRS or UPDRS 0.6 ± .05) in comparison with baseline ➢ In last visit prior to treatment withdrawal no differences with baseline could be evidenced in amantadine group and placebo group- DRS and UPDRS scores were slightly lower in amantadine group compared to placebo (9-6%, not significant) Treatment withdrawal: ➢ Following amantadine withdrawal- 2 patients experienced hypothermia, one was severely confused

	(amantadine was re-introduced), 11 patients experienced an abrupt increase of dyskinesia to 100% of daily time ➢ The DRS score was increased by 5.3 (1.8) points above the scores reported at the last assessments ➢ Worsening subsided in 1-2.5 weeks, with a reduction of daily L-dopa dose by 10-18% and by fractioning L-dopa doses to 1 or 2 administration more than previous daily schedules ➢ Assessments performed 1 month after withdrawal did not show differences between amantadine and placebo group or with baseline for any key variables Withdrawals: ➢ 5 patients withdrew because of side effects: one because of tachycardia at 30 days; two at 2 months because of psychosis and livedo reticularis in the amantadine group; two in the placebo group because if dizziness (15 days) and somnolence (3 months)
Source of funding	Not stated
Additional comments	➢ Method of randomisation stated- allocation concealment not stated ➢ Power calculations reported ➢ Not intention-to-treat ➢ Drop-outs n=3 amantadine group and n=2 placebo group
NCC CC ID (Ref Man)	318

TxCM6 – section 7.6.2

Evidence Table **TxCM6** What is the effectiveness of adding dopamine-agonists vs. COMT inhibitors in the treatment of later Parkinson's disease patients with motor complications?	
Bibliographic reference	Deane KHO, Spieker S, Clarke CE. Catechol-O-methyltransferase inhibitors versus active comparators for levodopa-induced complications in Parkinson's disease. *The Cochrane Library* 2004.
Study type	Cochrane review: 2 RCTs, open-label, parallel group
Evidence level	1++
Study objective	To compare the efficacy and safety of adjuvant COMT inhibitor therapy versus active comparators in

	patients with Parkinson's disease (PD), already established on levodopa and suffering from motor complications.
Number of patients	N=349 PD patients with motor fluctuations N=203 (Koller- pergolide) N=146 (TSG- bromocriptine) Locations: USA, UK and Australia (Koller), France (TSG) Sites: 3 (Koller), 19 (TSG)
Patient characteristics	Patients with a clinical diagnosis of idiopathic PD who had developed long-term motor complications of dyskinesia and/or end-of-dose deterioration. Patients were well balanced across the arms of the studies in terms of age and Hoehn and Yahr score). Koller: mean age 65 years, mean disease duration 7.5 years, mean levodopa dose 574 mg/d TSG: mean age 63 years, mean disease duration 9.6 years, mean levodopa dose 765 mg/d
Intervention	Tolcapone: (Koller) 100 mg t.i.d with possible increase to 300 mg t.i.d, (TSG) 200 mg t.i.d
Comparison	Pergolide (Koller) titrated to max dose of 5mg/d by week 9, final mean dose of 2.2 mg/d Bromocriptine (BR) (TSG) titrated to max dose of 30 mg/d by day 24, final mean dose of 22.5 mg/d
Length of follow-up	Trial duration (Koller) 12 weeks and (TSG) 8 weeks
Outcome measures	Levodopa dose reduction, "off" time, UPDRS, quality of life, adverse events, withdrawal rates
Effect size	Levodopa dose (LD) reduction ➢ Koller: LD dose decreased by a mean of 108 mg in Tolcapone group v 92 mg in pergolide (non-significant= NS) ➢ TSG: at week 8 total daily LD dose decreased by a mean of 124 mg in the Tolcapone group compared to 30 mg in BR group ($p<0.01$) Total "on"/"off" time ➢ Koller: not presented ➢ TSG: Tolcapone produced a non-significant decrease of 36 min in "off" time compared with BR and non-significant increase of 42 min in "on" time with Tolcapone v BR UPDRS ➢ Koller: UPDRS ADL score improved by 1.9 points with Tolcapone v 1.6 points with pergolide (NS) ➢ TSG: UPDRS ADL improved 0.9 points with Tolcapone v 0.1 BR (NS) ➢ Koller: UPDRS motor scores improved 3.3 tolcapone v 2.7 pergolide (NS) ➢ TSG: UPDRS motor scores improved 3.1 tolcapone v 3.3 BR (NS) Quality of Life ➢ Koller: Sickness Impact Profile (SIP) improved by 4.1 point in tolcapone v 3.5 point in pergolide

	(NS) and PD Questionnaire 39 (PDQ-39) improved 7.1 points in tolcapone and 4.5 points in pergolide (p=0.005) Adverse events ➢ Review took results with P=0.01 or less to be statistically significant ➢ Combined results of both trials showed more nausea (Odds ratio (OR)=0.42, p=0.0003), constipation (OR=0.26, p=0.00007) and orthostatic complaints (OR=0.24, p=0.0002) in pergolide and bromocriptine groups than tolcapone groups. Withdrawals ➢ Koller: withdrawals due to adverse events- a trend towards pergolide for more withdrawals (Peto OR=0.34, p=0.02) ➢ Neither study showed any significant differences for all cause withdrawal
Source of funding	No internal sources of support. External sources Pharmaceutical and non-profit
Additional comments	➢ The trials were open label because both active comparators required titration phases ➢ Koller used a blinded rater ➢ No trials were found which compared entacapone to active comparator ➢ Both intention-to-treat analysis
Citation	
NCC CC ID (Ref Man)	19625

TxCM7 – section 7.5.5

Evidence Table **TxCM 7** What is the effectiveness of adding COMT inhibitors vs. placebo in the treatment of later Parkinson's disease patients with motor complications?	
Bibliographic reference	Deane KHO, Spieker S, Clarke CE. Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease. *The Cochrane Library* 2004.

Study type	Cochrane review: 14 RCTs (1phase II and 13 phase III studies)
Evidence level	1++ (in regards to the Cochrane review's methodology and not the trials therein)
Study objective	To compare the efficacy and safety of adjuvant COMT inhibitor therapy versus placebo in patients with Parkinson's disease (PD), already established on levodopa and suffering motor complications
Number of patients	N=2566 N=1560 entacapone (Brooks, Fenelon, Im, Myllyla, Poewe, PSG, Rinne, Ruottinen) N=1006 tolcapone (Alder, Baas, Dupont, Kurth, Myllyla, Rajput) Location: US, Europe, multi-national, South Korea, sites:
Patient characteristics	Patients with a clinical diagnosis of idiopathic PD who had developed long-term motor complications of dyskinesia and/or end-of-dose deterioration. Patients were well balanced in both groups in terms of age and Hoehn and Yahr stage. Levodopa dose reduction not allowed in 1/8 entacapone studies but was allowed in all 6 tolcapone studies.
Intervention	Tolcapone (range from 100 mg and 200 mg, 50 mg, 200 and 400 mg (most common was 200) or entacapone 200mg (up to 10 doses per day)
Comparison	Placebo
Length of follow-up	Trial duration between 6 weeks and 12 months
Outcome measures	LD dose reduction, "off" time, "on" time, UPDRS (activities of daily living& motor function)adverse events, withdrawal rates
Effect size	ENTACAPONE (ET) ➢ 7 were parallel studies and one was a small crossover study (n=26) LD dose reduction ➢ Ruottinen did not allow LD dose reduction ➢ LD dose reduction: weighted mean difference (WMD) 55mg/d (95%CI 37 to 74 mg/d, p<0.00001) ➢ Myllyla insufficient data to calculate change but claimed significant reductions, p<0.01 ➢ Fenelon also claimed significant reductions p=0.02 but provide no data "Off" time ➢ Mean difference was 41 minutes (95%CI 13 min to 1 hour 8 min, p=0.004) ➢ Im did not provide data that could be used to calculate change in hours ➢ Fenelon stated more patients receiving ET improved in at least one category of the UPDRS item 39 (proportion of days spent off) v placebo but data was not amenable to further analysis ➢ Myllyla and Ruottinen did not measure this outcome "On" time

	➢ Mean difference was 1 hour 1 minute (95%CI 37 min to 1 hour 23 min, p<0.00001) ➢ Im did not provide data that could be used to calculate change in hours ➢ Ruottinen provided mean difference in "on" time (34 min (95%CI 16 min to 54 min) but this data was reported from the end of the crossover trial (data from first arm was not available) ➢ Fenelon and Myllyla did not provide data for this outcome UPDRS ➢ Changes in activities of daily living (ADL) were significant in 4 trials Myllyla (p<0.001), Poewe (p<0.01), PSG (p=0.03), Rinne (p<0.01), ➢ Changes in motor score were significant in 4 trials: Myllyla (p<0.01), Poewe (p<0.01), PSG (p=0.02), Rinne (p<0.05) ➢ Unable to calculate accurately the mean difference in either ADL or motor sections of the UPDRS Adverse events ➢ Tables summarising most common adverse events were not available from Fenelon and Im ➢ Only consider events where the p value is smaller than 0.01 ➢ ET increased: dyskinesia (Peto Odds Ratio (OR)=2.23, p<0.00001), nausea (OR=1.93, p=0.0006), vomiting (OR=4.16, p=0.01), diarrhoea (OR=2.69, p=0.0001) and constipation (OR=2.27, p=0.007) ➢ Dizziness was of borderline significance (OR=1.95, p=0.01) and hallucinations was not increased Withdrawal rates ➢ Two published abstracts did not note the withdrawal rate due to adverse events or all causes ➢ ET increased likelihood participants would withdraw due to adverse events (OR=1.52, p=0.02) or to all causes (OR=1.40, p=0.04) TOLCAPONE (TP) ➢ 6 parallel group RCTs LD dose reduction ➢ the weighted mean difference in LD dose reduction showed a dose response trend (this could not be tested further) and a fall off with the highest dose ➢ 50mg tolcapone produced a levodopa dose reduction of 72mg/d (95%CI 27mg to 117mg, p=0.001) ➢ 100mg gave a 156 mg/d reduction (95% CI 120mg to 191mg, p=0.00001) ➢ 200 mg gave a 148 mg/d reduction (95%CI 123mg to 174mg, p=0.00001) ➢ 400 mg gave a 55mg/d reduction (95%CI 18mg to 93mg, p=0.003) ➢ The analysis of the results for the 200mg tolcapone showed significant heterogeneity (p<0.00001) which could not be resolved by the removal of any one study from the analysis) Off time reduction

	➢ Data available from 4/6 trials (Adler, Baas, Kurth and Myllyla)(Rajput did not provide standard error of means so was not analysed) ➢ 3 trials used patient completed diaries for 16 hour days ➢ Kurth did not present data with standard deviations- therefore the review used the investigator's evaluation of 'off' time over a 10 hour day ➢ Weighted mean difference in 'off' time reduction showed that 50mg was the least effective 1 hour 25 minutes, 95%CI 46 min to 2 hours 3 minutes, p=0.00002) ➢ The remaining doses were equivalent: ➢ 100mg: 1 hour and 32 min off time reduction (95%CI 54 min to 2 hours 10 min, p=0.00001) ➢ 200 mg: 1 hour and 38 min (95%CI 1 hour 11 min to 2 hours 5 min, p=0.00001) ➢ 400 mg: 1 hour 35 min (95%CI 55 min to 2 hours 16 min, p=0.00001) ➢ None of the analyses showed any significant heterogeneity between studies On time increase ➢ Available from the same four studies (Adler, Baas, Kurth and Myllyla) ➢ 3 trials used patient 16h day diaries, while Kurth used investigators evaluation of 'on' time 10h day ➢ Overall on time increases were similar to off time reductions ➢ 50mg: 1 hour 38 min increase in on time (95%CI 56 min to 2 hours 20 min, p=0.00001) ➢ 100mg: 1 hour 48 min (95%CI 1 hour 7 min to 2 hours 29 min, p=0.00001) ➢ 200mg: 1 hour 55 min (95%CI 1 hour 26 min to 2 hour 23 min, p= 0.00001) ➢ 400mg: 1 hour 32 min (95%CI 48 min to 2 hours 16 min, p=0.00004) ➢ None of the studies showed significant heterogeneity between them Activities of daily living ➢ Assessed using UPDRS in four studies (Adler, Dupont, Myllyla, Rajput) ➢ Only Dupont found a statistically significant difference in UPDRS ADL scale ($p<0.05$) at 200 mg, placebo change increase of 0.4 versus tolcapone 200 mg reduction of 1.1 points Motor function ➢ Assessed by UPDRS motor section in 5 studies (Adler, Baas, Dupont, Myllyla, and Rajput) ➢ Only one study (Baas) found a significant difference ($p<0.01$) at 200 mg, placebo reduction of 2.1 versus tolcapone 200mg reduction of 6.5 points Adverse events ➢ Only reported for studies where there was the p value was less than 0.01 ➢ Significant increase in risk of dyskinesia at 50mg, 100mg, and 200mg doses (Peto odds ratio (p values) of 3.48 (0.0002), 3.96 (0.00001) and 4.51 (0.00001) ➢ Significant increase in risk of nausea at the 100mg, 200mg and 400 mg doses (Peto odds ratio (p

	values) of 2.03 (0.003), 2.64 (0.00001) and 2.80 (0.009) ➢ Borderline increase in risk of vomiting at 50, 100 and 200mg doses (Peto odds ratio (p value) 5.60 (0.01), 4.28 (0.01) and 3.67 (0.003) ➢ Significant increase in the risk of diarrhoea at 200 mg dose (Peto odds ratio (p value) 2.52 (0.003) ➢ Increased risk of hallucinations at 200 mg dose (Peto odds ratio, p value) 2.65 (0.002) Withdrawals ➢ Withdrawals due to adverse events were reported in all 6 trials ➢ No significant increase in withdrawals due to adverse events in patients on tolcapone Combined meta-analysis ➢ Levodopa dose reduction (mg/day): 19 studies, n=2209, weighted mean difference 91.66 (95%CI 79.12 to 104.20, p<0.00001) in favour of COMT inhibitors ➢ "Off time" reduction (hours): 14 studies, n=1584, WMD 1.30 (95%CI 1.06 to 1.55, p<0.00001) in favour of COMT inhibitors ➢ "On" time increase (hours): 14 studies, n=1663, WMD 1.47 (95%CI 1.23 to 1.71, p<0.00001) in favour of COMT inhibitors ➢ UPDRS ADL (part II): no numeric data ➢ UPDRS motor section (part III): no numeric data ➢ Adverse events: dyskinesia, nausea, vomiting, diarrhoea, constipation, hallucinations, dizziness all statistically significant all in favour of placebo ➢ Withdrawal rate due to adverse events: 16 studies, n=2292, Peto Odds ratio 1.51 (95%CI 1.16 to 1.96, p=0.002) in favour of placebo ➢ Withdrawal rate all cause: 9 studies, n=1551, Peto odds ratio 1.33 (95%CI 1.00 to 1.78, p=0.05) in favour of placebo
Source of funding	None stated
Additional comments	➢ Brooks study examined 300 patients but only 172 had fluctuating symptoms so the results of this trial relate only to these 172 participants ➢ Im did not state entacapone dosage ➢ Levodopa dose reduction was not allowed in Ruottinen ➢ For entacapone studies manufacturers had to be contacted for further results and methodology ➢ Methods of randomisation and allocation concealment only described 3/7 papers ➢ 2 entacapone papers Fenelon 2002 and Im 2002 were published only as abstracts ➢ 4/7 entacapone papers were intention-to-treat analysis, 1 per protocol, 2 not stated ➢ Authors included: (entacapone) Brooks 2003 (UK-Irish), Fenelon 2002, Im 2002, Myllyla 2001

	(FILOMEN), Poewe 2002 (CELOMEN), PSG 1997 (SEESAW), Rinne 1998 (NOMECOMT), Ruottinen 1996a ➢ Ruottinen was the only crossover study (rest were parallel) and was a phase II study (the rest were phase III) ➢ Author's included: (tolcapone) Adler 1998 (TFSGIII), Baas 1997, Dupont 1997 (TIPSII), Kurth 1997 (TFSGI), Myllyla 1997 (TIPS1), Rajput 1997 ➢ All were parallel designed phase III studies
Citation	
NCC CC ID (Ref Man)	19624

Evidence Table
TxCM 7
What is the effectiveness of adding COMT inhibitors vs. placebo in the treatment of later Parkinson's disease patients with motor complications?

Bibliographic reference	Reichmann H, Boas J, Macmahon D, Myllyla V, Hakala A, Reinikainen K *et al*. Efficacy of combining levodopa with entacapone on quality of life and activities of daily living in patients experiencing wearing-off type fluctuations. *Acta Neurologica Scandinavica* 2005;**111**:21-8.
Study type	Randomised, double-blind, placebo controlled, phase IV study
Evidence level	1+
Study objective	To compare the efficacy of levodopa/dopa decarboxylase inhibitor (DDCI) plus entacapone with levodopa/DDCI plus placebo on measures of parkinsonian disability and health related quality of life in subjects with Parkinson's disease (PD) experiencing motor fluctuations
Number of patients	N=270 idiopathic PD patients N=174 entacapone N=96 placebo Location: multinational sites: multi-centred
Patient characteristics	PD patients experiencing 'wearing-off' type motor fluctuations were randomised to receive study treatment. Patients were required to be at least 35 years of age with a mean of at least 3h/day of 'off time' as recorded in-home diary after screening visit. For other inclusion and exclusion criteria see paper. The majority of patients included had mild to moderate PD.

Patient characteristics	Entacapone (n=174)	Placebo (n=96)

	Age, yrs (range)	67 ± 8 (42-83)	66 ± 9 (41-82)
	Males (%)	94 (54)	57 (59)
	Age at PD onset, yrs (range)	60 ± 10 (32-80)	60 ± 10 (36-78)
	Duration of PD, yrs (range)	7.5 ± 4.7 (0-24)	7.1 ± 4.0 (1-20)
	Duration of levodopa treatment, yrs (range)	6.9 ± 4.6 (0-24)	6.7 ± 4.0 (0-20)
	Duration of fluctuations, yrs (range)	2.7 ± 3.1 (0-19)	2.4 ± 2.2 (0-10)
	Total levodopa daily dose, mg	566 ± 243	533 ± 231
Intervention	Entacapone (200 mg/d) plus levodopa/DDCI (patients continued to take their own previous levodopa/DDCI preparations with the study drug)		
Comparison	Placebo plus levodopa/DDCI		
Length of follow-up	Trial duration of 13 weeks		
Outcome measures	UPDRS, Global assessments, quality of life, daily dose of LD, adverse events, withdrawal rates		
Effect size	Efficacy ➢ Improvement in UPDRS II (ADL) scores in entacapone group versus placebo at both weeks 5 and 13 (treatment difference: –1.6 [95%CI -2.4 to –0.8], p=0.0001)) ➢ No significant differences between groups for PDQ-39 summary index scores ➢ UPDRS I (mentation, behaviour and mood) scores slightly decreased from baseline in entacapone group but not significant (no changes in placebo group) ➢ UPDRS III (motor) decreased in entacapone group compared to placebo (treatment difference –1.9 (95%CI –3.7 to –0.2, p=0.03) ➢ Mean UPDRS total score decreased in entacapone group versus placebo (treatment difference –3.6 (95%CI –6.0 to –1.2, p=0.004) ➢ Global assessment by study investigator greater in entacapone group versus placebo (p<0.001) and proportion of subjects improved was greater ➢ Global assessment of change evaluated by both investigator and patient, the proportion of subjects improved was greater in those patients receiving entacapone versus placebo ➢ For the total population there were no differences between treatments in the PDQ-39 subscores ➢ There were no significant differences between treatments for any of the SF-36 variables or the EQ-5D self-rating questionnaire utility score ➢ Patient home diaries showed mean ‘off’ time decreased and the mean ‘on’ time increased in both treatment groups- no significant differences ➢ Dyskinesia sum score (UPDRS IVA) no significant differences between treatment groups ➢ Fluctuation sum score (UPDRS IVB) decreased significantly in entacapone group compared to		

<table>
<tr><td></td><td>placebo (treatment difference: -0.3, 95%CI-0.5 to –0.1, p=0.02)
➢ Severity of PD (UPDRS part V; Hoehn and Yahr staging) was improved in entacapone compared to placebo but not statistically significant
➢ UPDRS IV (Schwab and England) scores showed that the proportion of patients with improvement was greater and the proportion of patients with worsening was smaller in entacapone versus placebo
➢ Difference in part IV scores between groups was significant at week 5 (p=0.045) but not at week 13
➢ Mean daily dose of LD decreased slightly in those patients who received entacapone but not statistically significant compared with placebo
Adverse events

➢ 113 (65%) entacapone and 47 (49%) of placebo patients reported adverse events
➢ a total of 311 adverse events occurred in entacapone (2.8 events per subject) and 104 in placebo group (2.2 events per subject)
➢ Most frequently reported adverse events:
<table>
<tr><th></th><th>Entacapone</th><th>Placebo</th><th>P value</th></tr>
<tr><td>Nausea</td><td>28 (16)</td><td>5 (5)</td><td>0.009</td></tr>
<tr><td>Discolouration of urine</td><td>20 (12)</td><td>0 (0)</td><td>0.0001</td></tr>
<tr><td>Dyskinesia</td><td>16 (9)</td><td>5 (5)</td><td>Non-significant</td></tr>
<tr><td>Diarrhoea</td><td>13 (8)</td><td>1 (1)</td><td>0.02</td></tr>
<tr><td>Parkinsonism aggravated</td><td>10 (6)</td><td>17 (18)</td><td>0.002</td></tr>
<tr><td>Constipation</td><td>9 (5)</td><td>0 (0)</td><td>0.03</td></tr>
</table>
Withdrawal rates
➢ 45 (17%) of subjects discontinued prematurely (27/174 entacapone and 18/96 placebo)
➢ Reported reasons for discontinuation: adverse events for 26 (10%) of patients, an unsatisfactory response to treatment for 14 (5%) of patients, a wish to discontinue for three subjects (1%) and other reasons for 2 subjects (1%)</td></tr>
<tr><td>Source of funding</td><td>Pharmaceutical</td></tr>
<tr><td>Additional comments</td><td>➢ Methods of randomisation and allocation concealment not stated
➢ Power calculations provided
➢ Intention-to-treat analysis
➢ Centre comparability was analysed</td></tr>
</table>

Citation	
NCC CC ID (Ref Man)	19864

Evidence Table

TxCM1

What is the effectiveness of adding MAO-B vs. placebo in the treatment of later Parkinson's disease patients with motor complications?

Bibliographic reference	Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe W, Stocchi F *et al*. Rasagiline as an adjunct to levodopa in Parkinson's disease patients with motor fluctuations; the LARGO study. *Lancet* 2005.
Study type	Randomised, double-blind, placebo-controlled trial
Evidence level	1++
Study objective	To investigate rasagiline efficacy and safety in levodopa-treated patients with motor fluctuations.
Number of patients	N=687 PD patients N=231 rasagiline N=227 entacapone N=229 placebo Location: Israel, Argentina, Europe Sites: 74 centres
Patient characteristics	Eligibility: had a clinical diagnosis of PD, as defined by the presence of at least 2 of the cardinal signs of PD (resting tremor, bradykinesia, rigidity) without any other known cause of parkinsonism, and a modified Hoehn and Yahr stage of < 5 in OFF state. Patients had to be receiving at least 3 daily doses of LD, not including bedtime dose, and not more than 8 daily doses of LD. For exclusion criteria: see paper for details.

	Rasagiline	Entacapone	Placebo
Age, yrs	63.9 (9.0)	63.0 (9.4)	64.8 (8.8)
Gender, male (n; %)	154; 66.7	139; 61.2	132; 57.6
PD duration, yrs	8.7 (4.9)	9.2 (4.7)	8.8 (4.8)
LD treatment duration, yrs	7.5 (4.6)	7.6 (4.5)	7.6 (4.7)
Levodopa dose (mg)	722 (334)	706 (321)	697 (295)
OFF time (hours)	5.58 (2.37)	5.60 (2.59)	5.55 (2.44)
Total UPDRS	33.6 (17.6)	32.2 (16.6)	33.7 (18.8)

- Analysis of baseline demographics and clinical characteristics revealed no major differences between groups

<table>
<tr><td>Intervention</td><td>Rasagiline (1.0 mg/d) or entacapone (200 mg with each LD dose)</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow-up</td><td>18-week trial duration</td></tr>
<tr><td>Outcome measures</td><td>Change in total daily OFF time, clinical global improvement (CGI) score, responder analysis (≥ 1 h reduction in daily OFF time), Unified Parkinson’s disease Rating Scale (UPDRS)</td></tr>
<tr><td>Effect size</td><td>

2-4 week levodopa optimisation/placebo run-in phase
At the start of the 18-week double-blind phase, patients were randomised to receive as adjunct medication either rasagiline or entacapone or placebo- using a double-dummy technique
During the first 6 weeks the investigator could lower LD dose if dyskinesia worsened
The LD dosage remained constant for the final 12 weeks

24-hour diaries
<table>
<tr><th></th><th>Difference, rasagiline v placebo (95%CI, p value)</th><th>Difference, entacapone v placebo (95%CI, p value)</th></tr>
<tr><td>Daily OFF time</td><td>-0.78 (-1.18 to –0.39, p=0.0001)</td><td>-0.80 (-1.20 to –0.41, p<0.0001)</td></tr>
<tr><td>Daily ON time without troublesome dyskinesia (hours)</td><td>0.82 (0.36 to 1.27, p=0.0005)</td><td>0.82 (0.36 to 1.27, p=0.0005)</td></tr>
<tr><td>Daily ON time with troublesome dyskinesia (hours)</td><td>0.09 (-0.28 to 0.46, p=0.6209)</td><td>0.04 (-0.32 to 0.41, p=0.8157)</td></tr>
<tr><td>Responder rate (n;%)</td><td>2.5* (1.62 to 3.85, p<0.0001)</td><td>2.0* (1.29 to 3.06, p=0.0019)</td></tr>
</table>

OFF= a period of relatively poor overall function (ie. increasing PD signs)
ON= a period of relatively good overall function and mobility
Responder was defined as a patient showing an improvement of 1 hour or more in the change from baseline in mean total daily OFF time
* odds ratio

</td></tr>
<tr><td>Source of funding</td><td>Pharmaceutical</td></tr>
<tr><td>Additional comments</td><td>

Randomisation methods stated
Methods of allocation concealment not stated
Intention-to-treat analysis for primary outcome measures

</td></tr>
<tr><td>NCC CC ID (Ref Man)</td><td>19840</td></tr>
</table>

Evidence Table
TxCM 7
What is the effectiveness of adding COMT inhibitors vs. placebo in the treatment of later Parkinson's disease patients with motor complications?

<table>
<tr><td>Bibliographic reference</td><td>Olanow CW, Kieburtz K, Stern M, Watts R, Langston JW, Guarnieri M et al. Double-blind, placebo-controlled study of entacapone in levodopa-treated patients with stable Parkinson disease. Archives of Neurology 2004;61:1563-8.</td></tr>
<tr><td>Study type</td><td>Randomised, double-blind, placebo-controlled study</td></tr>
<tr><td>Evidence level</td><td></td></tr>
<tr><td>Study objective</td><td>To determine if the addition of entacapone administration provides benefit to levodopa-treated PD patients who have a stable response to levodopa and do no experience motor fluctuations.</td></tr>
<tr><td>Number of patients</td><td>N=750 PD patients
N=373 entacapone
N=377 placebo

Location: USA Sites: 5?</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria was based on: a good response to levodopa and at least 2 of the following: rigidity, resting tremor, and bradykinesia. Levodopa doses had to be stable for at least one month, with a maximum of four daily doses of the regular 3 daily does of controlled-release formulation. Participants could not experience end-of-dose wearing off with 4 hours of levodopa use.
<table>
<tr><th></th><th>Entacapone</th><th>Placebo</th></tr>
<tr><td>Mean age (y)</td><td>69.8 ± 9.3</td><td>70.2 ± 9.4</td></tr>
<tr><td>Sex, % male</td><td>72.9</td><td>68.7</td></tr>
<tr><td>Duration of PD, mean ± SD, y</td><td>4.4 ± 3.5</td><td>4.5 ± 3.5</td></tr>
<tr><td>Duration of LD prescription, y</td><td>3.6 ± 3.1</td><td>3.6 ± 3.3</td></tr>
<tr><td>LD dose, mean ± SD, mg</td><td>401.3 ± 191.9</td><td>406.2 ± 179.1</td></tr>
</table>
No significant differences between groups.</td></tr>
<tr><td>Intervention</td><td>200 mg of entacapone</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow-up</td><td>26 week trial duration</td></tr>
</table>

Outcome measures	UPDRS, LD dose, PDQ-39, SF-36, Parkinson's symptom inventory (PSI), Global assessment
Effect size	➢ No significant difference between groups for UPDRS scores ➢ Levodopa dose was reduced from baseline in entacapone compared to placebo (p=0.004) ➢ PDQ-39 ((out of 9 parameters) 3 were significant in favour of entacapone: total score (p<0.001), mobility (p=0.001) and ADL (p<0.001) ➢ SF-36 (out of 10 parameters) 3 were significant in favour of entacapone: physical functioning (p=0.047), vitality domain (p=0.04), physical component (p=0.009) ➢ PSI: (2 parameters) both significant: frequency (p=0.007) and distress (p=0.02) ➢ Global assessment was also significant in favour of entacapone: investigator improved (p=0.08) and subject improved (p=0.02) Adverse events ➢ Nausea and dyskinesia were most common and more frequent in entacapone group
Source of funding	Pharmaceutical
Additional comments	➢ Methods of randomisation stated ➢ Power calculations provided ➢ Allocation concealment methods not stated ➢ LD dose could not be increased during study- only decreased ➢ Intention-to-treat analysis ➢ Number of sites not clearly stated ➢ Multi-centre analysis not provided
Citation	
NCC CC ID (Ref Man)	104

TxCM8 – section 7.5.2

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	Juncos JL, Fabbrini G, Mouradian MM, Chase TN. Controlled release levodopa-carbidopa (CR-5) in the management of parkinsonian motor fluctuations. *Archives of Neurology* 1987;**44**:1010-2.
Study type	Randomised, double blind, crossover study
Evidence level	1+
Study objective	A comparative evaluation of controlled-release versus standard Sinemet in patients with wearing off and on-off phenomenon.
Number of patients	N=23 patients with idiopathic Parkinson's disease (PD) Location: USA sites: single clinical centre
Patient characteristics	17 men, 6 women. Aged 30 to 71 years (mean 58 ± 2 years). Parkinsonian symptoms had been present for 3 to 24 (mean 13 ± 1) years and disease severity in the unmedicated state ranged from mild to severe (Hoehn and Yahr stages II to V). Patients had received levodopa (LD) for two to 17 (mean 10 ± 1) years. Ten patients exhibited wearing-off responses while 13 exhibited the on-off phenomenon.
Intervention	Controlled-release 5 (CR-5) (LD 200 mg; carbidopa 50 mg) for one month then crossed-over to other treatment.
Comparison	Sinemet (LD 200 mg; carbidopa 25 mg) for one month then crossed-over to other treatment.
Length of follow-up	4 months
Outcome measures	LD dosage, parkinsonian scores, on-off scores, withdrawals, follow-up
Effect size	➢ An initial open phase was conducted during which the optimal antiparkinsonian dose and inter-dose interval for each treatment was determined. ➢ A period of 7 to ten days during which patients received their regular dose of Sinemet separated each treatment Levodopa dose ➢ The optimal dose requirement for levodopa when administered as CR-5 was 30% ± 10% higher then when given as sinemet (1.1 ± 0.1 vs. 0.9 ± 0.1 mg/kg/ h respectively; p<0.01) ➢ To prevent nocturnal dyskinesias and vivid dreams the last evening dose of CR-5 had to be

reduced to about 60% of the mean daytime dose (160 ± 19 vs. 280 ± 29 mg; p<0.05)

- The optimal interdose interval with CR-5 was 53% ± 7% (p<0.001) longer with sinemet increasing from 2.7 ± 0.3 to 3.9 ± 0.2 hours in patients with wearing-off and from 2.0 ± 0.1 to 3.1 ± 0.1 hours in those with on-off phenomenon

Parkinsonian scores

- Mean parkinsonian scores were better with CR-5 for the 15 patients completing the study

Table: Parkinsonian severity (by patient group) (mean ± SEM)

Patient group (n=)	Sinemet	CR-5	Improvement
All (15)	1.5 ± 0.2	1.0 ± 0.2	31 ± 8 (P<0.01)
Wearing-off (9)	1.3 ± 0.2	0.7 ± 0.1	42 ± 11 (P<0.01)
On-off (6)	1.7 ± 0.3	1.5 ± 0.3	15 ± 11

Table: Parkinsonian variance (by patient group) (mean ± SEM)

Patient group	Sinemet	CR-5	Improvement
All (15)	1.2 ± 0.2	1.0 ± 0.3	21 ± 13
Wearing-off (9)	0.9 ± 0.1	0.5 ± 0.1	34 ± 15 (p<0.05)
On-off (6)	1.6 ± 0.4	1.7 ± 0.5	4 ± 25

- There was a close correlation between improvement in parkinsonian scores and symptom variance (p<0.02)
- Differences in dyskinesia scores or variance between 2 treatments did not attain statistical significance (by patient group) (mean ± SEM)

Time on-off

- The time ‘on’ with CR-5 was longer than sinemet (p<0.05)
- While the number of patients ‘off’ episodes was substantially reduced (p<0.001) in all patients especially those with wearing-off (p<0.001)

Withdrawals

- 8 patients withdrew from the study while in the CR-5 open phase because of persistent day-to-day inconsistencies in antiparkinsonian response (5 patients), delayed onset of drug-action or lack of subjective surge in response usually associated with Sinemet (6 patients)
- With a single exception all of these CR-5 treatment failures had severe on-off fluctuations

	Follow-up ➢ All patients completing the study elected to continue CR-5 therapy ➢ They reported the convenience of less frequent dosing, improved sleep and night time mobility, and decreased early more akinesia and dystonia ➢ After four months of close follow-up all but one had sustained benefit
Source of Funding	None stated
Additional comments	➢ Not intention-to-treat analysis ➢ No details of randomisation or allocation concealment methods ➢ Small sample size
Citation	
NCC CC ID (Ref Man)	109

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	Lieberman A, Gopinathan G, Miller E, Neophytides A, Baumann G, Chin L. Randomized double-blind cross-over study of Sinemet-controlled release (CR4 50/200) versus Sinemet 25/100 in Parkinson's disease. *European Neurology* 1990;**30**:75-8.
Study type	Randomised, double-blind, crossover trial
Evidence level	1+
Study objective	To investigate sinemet controlled-release (CR) versus sinemet 25/100 (IR) in patients with response fluctuations.
Number of patients	N=24 Parkinson's disease (PD) patients Locations: USA sites: single
Patient characteristics	There were 15 males and 9 females with response fluctuations. There mean age was 66.2 years (range 51-77 years), mean duration of PD was 9.3 years (range 2-37 years), and mean duration of response fluctuations was 3.5 years (range 1-10 years). Mean stage (Hoehn and Yahr scale) in 'on'

	period was 2.5 (range 2-4), mean stage in 'off' period was 3.7 (range 3-5). Mean dose of levodopa was927 mg (range 350-2000 mg). All patients required 4 or more doses of levodopa per day.
Intervention	Sinemet controlled-release 25/250 (CR)
Comparison	Sinemet immediate-release 25/100 (IR)
Length of follow-up	None stated
Outcome measures	Does, UPDRS, Hoehn and Yahr stage, 'On-off' time, patient and physician rated global improvement
Effect size	➢ After a 4-week titration phase patients entered a 16-week crossover study (8-week arms). Patients were examined at 2,4,6 and 8 weeks. Doses ➢ Patients on CR (mean 5.0, range 3-8 doses/day) took fewer doses per day than IR (mean 6.2, range 4-11) ($p \leq 0.05$) Clinical rating scales ➢ There were no significant differences between the mean scores in any of the five subsets of the UPDRS, Hoehn and Yahr, or number of hours patients were 'on' or 'off' ➢ When the number of patients who experienced their best response (lowest score) on CR was compared to IR on each of the 5 UPDRS subsets (then on subsets consisting of dyskinesias and response fluctuations) the differences were significant (i.e. more patients on CR had fewer dyskinesias and response fluctuations) ($p<0.05$) ➢ Significantly more patients had more 'on' hours on CR than IR ($p<0.05$) ➢ More patients experiences an improvement in Hoehn and Yahr stage on CR ($p<0.05$) ➢ More patients rated themselves as globally improved on CR vs. IR ($p<0.05$) ➢ More physicians rated the patients as globally improved on CR vs. IR ($p<0.05$) Withdrawal rates ➢ 35 patients enrolled into study- during open-phase 4 patients dropped-out because of increased dyskinesias and 5 patients dropped because of increased parkinsonism, 2 more dropped out because patients could not get a rapid response (CR)
Source of Funding	Non-profit and pharmaceutical
Additional comments	➢ No randomisation or allocation concealment methods stated ➢ No drop-outs in double-blind period of study stated ➢ No sample size calculations- small sample size ➢ No clinical criteria for PD diagnosis stated
Citation	
NCC CC ID (Ref Man)	157

Evidence Table **Q TXCM8** What is the effectiveness of modified-release levodopa vs. immediate release levodopa in the treatment of early Parkinson's disease?	
Bibliographic reference	Cedarbaum, J. M., Hoey, M., & McDowell, F. H. 1989, "A double-blind crossover comparison of Sinemet CR4 and standard Sinemet 25/100 in patients with Parkinson's disease and fluctuating motor performance", *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 52, no. 2, pp. 207-212.
Study type	Randomised, cross-over, double-blind
Evidence level	1+
Study objective	To compare sinemet CR4 and standard sinemet 25/100 in patients with response fluctuations.
Number of patients	N=19 Idiopathic Parkinson's disease Location: USA Sites: One
Patient characteristics	Mean age was 58.3 (SEM 1.9) years, mean duration of disease 11.07 (SEM 0.99) years, mean duration of response fluctuations was 3.78 (SEM 0.66) years, Hoehn and Yahr disability scores when 'off' at least 2 (mean=2.86, SEM 0.23). All had end-of-dose wearing off pattern of response fluctuations; all but 2 patients suffered peak-dose dyskinesia.
Intervention	Sinemet controlled–release (CR) (levodopa/carbidopa 200/50 mg)
Comparison	Standard sinemet 25/100 immediate-release (IR) (dose was adjusted to optimise performance before actual entry into study).
Length of follow-up	Trial duration: 24 weeks (8 week open label dose titration phase and 16-week double-blind phase)
Outcome measures	Modified Cornell-UCLA scoring system, UPDRS, Schwab and England activates of daily living (ADL) scale,
Effect size	➢ The dose titration phase was divided into 2 segments ➢ The first period was used to adjust the optimum dose for IR, with max 'on' time ➢ Second period was used to adjust the optimum dose for CR4 ➢ Following the 8-week dose titration phase 16 patients entered the 16-week double-blind phase ➢ Patients were randomised into 2 groups

	➢ Half received pace IR tablets and active CR4 tablets and vice versa for the other group ➢ If dose adjustments had to be made during this phase of the trial then both tablets were adjusted concurrently ➢ At the end of each 8-week double-blind phase, 8 hour observation studies were performed ➢ Parkinsonian disability and dyskinesias were rated at half hourly or hourly intervals ➢ 11 patients expressed a preference for CR, one for SRD and 2 had no preference ➢ Number of doses per day was 42% less for the CR4 than for IR (4.14 vs. 7.14) (p<0.0001) ➢ Mean interdose interval was increased 86% from 2.39 on IR to 4.57 on CR4 (p<0.0001) ➢ Mean daily intake of levodopa was increased 21.8% from 1128.6 mg/d IR to 1371.4mg/d CR (p<0.0003) ➢ A substantial part of this increase may have been due to patients bed-time dose of CR4 to extend benefits into the night (only 2 patients reported improved sleep patterns and getting out of bed) ➢ 28.6% reduction in the number of daily 'off' periods from 2.97 on IR to 2.12 on CR4 (p<0.02) ➢ 11.6% increase waking day spent 'on' from 70.12 IR to 78.28 CR (p<0.02) ➢ Percentage of ''on'' time spent with dyskinesia was unchanged
Source of Funding	Non-profit organisations, pharmaceutical organisations, and government funding
Additional comments	➢ 14/19 patients completed the study; reasons for patient drop-outs listed ➢ No sample size calculations-Small sample size ➢ No randomisation or allocation concealment methods ➢ No patients dropped-out during the blinded portion of the trial ➢ Not intention-to-treat analysis
Citation	
NCC CC ID (Ref Man)	261

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	Feldman RG, Mosbach PA, Kelly MR, Thomas CA, Saint Hilaire MH. Double-blind comparison of

	standard Sinemet and Sinemet CR in patients with mild-to-moderate Parkinson's disease. *Neurology* 1989;**39**:96-101.
Study type	Randomised, double-blind, double-observer, crossover trial
Evidence level	1+
Study objective	To describe the results of an investigation assessing the efficacy and safety of sinemet CR in mild to moderately impaired Parkinson's disease patients.
Number of patients	N=41 Location: USA sites: 2 centres
Patient characteristics	There were 23 (56%) male and 18 (44%) female patients included. Patients had a mean disease duration of 7.1 years (±6.2) and an average age of 63.1 (± 8.8). 20 patients were at Hoehn and Yahr stage II (mild disability) and 21 at stage III (mild to moderate) with a mean Hoehn and Yahr rating of 2.5 (± 0.5). 40% exhibited wearing off phenomena.
Intervention	Sinemet controlled-release 50/200 (CR)
Comparison	Standard sinemet 25/100 immediate-release (IR)
Length of follow-up	2x 6 week treatment periods
Outcome measures	Levodopa dose, New York University Parkinson's disease rating scale (NYUPDS), Northwestern University disability scale (NUDS), adverse events
Effect size	➢ Efficacy was assessed at weeks 2,4,6 of double-blind period Levodopa (LD) dose ➢ Week 6, IR group had a mean LD dose of 493 (± 221) mg ➢ Week 6, CR group had a mean LD dose of 590 (± 265) mg ➢ Patients on CR took 19.7% more LD at the ed of the 6 week double-blind phase than IR patients NYUPDS ➢ Week 6- trend towards less impairment with CR group ➢ The CR group has a mean NYUPDS score 5.2 (±2.4), while IR group had a mean score of 5.7 (± 2.4) (p=0.11) ➢ A significant difference on gait disturbance subscale was found, with CR patients being rated as less impaired (p=0.05) ➢ On all subscales CR patients were less impaired than or equal to IR patients NUDS ➢ Trend towards less impairment in CR groups

	➢ Total score was 8.5 (±3.5) for CR and 9.1 (±3.5) for IR (p=0.14) ➢ CR patients were less impaired or equal to IR on 6 subscales ➢ Eating subscale was less impaired on CR (p<0.01) Other scales ➢ No differences were found between the CR and IR groups on patients' global rating, physicians' global rating, patient's medication preference, Hoehn and Yahr stage, and patients rating of 'wearing-off' phenomena ➢ Overall no significant differences between CR and IR on any major efficacy measures ➢ NUDS and NYUPDS there was a non-significant trend for CR patients to be less impaired Adverse events ➢ No differences in overall number of side effects, nor incidence of any individual side effect ➢ No serous adverse drug-related events were reported
Source of Funding	
Additional comments	➢ 38/41 completed the trial ➢ Not intention to treat analysis ➢ No randomisation or allocation concealment methods stated ➢ No sample size calculations- small sample size ➢ No comparability between sites
Citation	
NCC CC ID (Ref Man)	277

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	Hutton JT, Morris JL, Bush DF, Smith ME, Liss CL, Reines S. Multicenter controlled study of Sinemet CR vs. Sinemet (25/100) in advanced Parkinson's disease. *Neurology* 1989;**39**:67-72.
Study type	Randomised, double-blind, crossover study

Evidence level	1+
Study objective	To evaluate clinical response, including fluctuations in motor response, and to evaluate safety and tolerability during optimal treatment with both sinemet CR and sinemet 25/100
Number of patients	N=202 patients with idiopathic Parkinson's disease (PD) Location: USA Sites: 8 centres
Patient characteristics	132 men, 70 women. Mean patient age was 65 years; mean duration of PD was 10 years. 89 (44%) were categorized as Hoehn and Yahr stage III, 54 (27%) were stage II, and 49 (24%) were stage IV. All patients had complaints of motor fluctuations averaging 3.5 years. All patients required Sinemet at least 4x daily.
Intervention	Using optimal dosage regimens determined during the titration phase patients received Sinemet CR
Comparison	Or Sinemet 25/100
Length of follow-up	
Outcome measures	Average doses, patient's diaries, physician global improvement scale, UPDRS, Schwab and England Activities of Daily living score (SEALD), Hoehn and Yahr, Patient perspective, adverse events, withdrawals
Effect size	➢ 24 week crossover trial was divided up into two 4-week open label dosage titration periods, followed by two 8-week double-blind treatment periods ➢ Outcome measures collected at weeks 2,4,6 and 8 Average daily doses ➢ During week 8 of the double blind periods there was a median 33% decrease in the average frequency of daily dosing between standard sinemet (mean 6.8 doses per day) and sinemet CR (mean 4.5 doses per day) ➢ 79% of patients received fewer daily doses during the last week of sinemet CR treatment compared to sinemet 25/100 ➢ the average daily levodopa intake increased by a median 25% with sinemet CR (mean 1238 mg per day) compared to sinemet 25/100 (mean 975 mg per day) Efficacy ➢ Data from weeks 4, 6 and 8 of the two treatments during the double-blind periods were compared ➢ Data from week 2 was not considered since dosage titration continued through this period Patient's diaries

	➢ Patients diaries indicated a lower average percentage time 'off' when patients were receiving treatment with sinemet CR ➢ Differences were significant at weeks 4 and 6 ($p<0.01$) and near significant at week 8 ($p=0.07$) ➢ Difference in terms of percent of waking day spent 'off' ranged between 3 and 4% and equivalent to 30 to 40 minutes per day ➢ Mean waking time 'off' decreased approximately 10% and mean waking time 'on' increased by 4% UPDRS ➢ Generally better with CR therapy but no consistent significant differences ➢ Analysis of percentage of waking day in the 'off' state (item 38 in the clinical fluctuations subsection) yielded a significant difference in favour of sinemet CR at all time periods ($p<0.01$) Physicians global improvement ratings ➢ Sinemet CR was significantly better than standard sinemet at each time period ($p<0.05$) ➢ At week 8 physicians rated 38% of the patients as more improved on sinemet CR ➢ 39% were rated similarly on the 2 preparations SAELD scale ➢ Patients were rated higher on the SEALD score, both 'on' and 'off' at each time period when they were receiving sinemet CR ➢ The differences were significant ($p<0.05$) with the exception of the 'off' rating at week 6 ($p<0.06$) Hoehn and Yahr ➢ There were no significant differences in patients' Hoehn and Yahr scores Patient perspective ➢ At the end of the each double-blind period patients judged sinemet CR to be significantly better ($p<0.01$) than standard sinemet with respect to both helpfulness of medication and improvement in clinical fluctuations ➢ At the end of the study patients were requested to state their preference, if any, for the two treatments ➢ 54% preferred sinemet CR and 27% preferred sinemet 25/100 ($p<0.01$) ➢ No preference for either treatment period was indicated by 19% of patients ➢ The order of treatment was not significant Adverse events ➢ No significant difference in reported incidence of adverse events between 2 treatments ➢ 47/202 (23%) had clinical adverse experiences during standard sinemet dosage titration ➢ Of the 186 patients entering the CR dose titration period 69 (37%) had adverse events

	➢ Of these patients 22/69 the adverse events were continuous from the standard sinemet dosage titration period ➢ Most common side effects for standard sinemet and sinemet CR titration periods were, respectively: dyskinesia (7 and 8%), hallucinations (4 and 4%) and nausea (4 and 4%) ➢ During the double-blind period 24 (15%) had adverse events on standard sinemet and 31 (20%) had adverse events on CR ➢ 33 (21%) had adverse experiences on both treatments ➢ Most common clinical adverse events during standard sinemet and sinemet CR double-blind periods were, respectively: dyskinesia (6 and 9%), hallucinations (4 and 5%), nausea (3 and 2%), vomiting (3 and 1%) and confusion (1 and 3%) ➢ Nine non-fatal adverse events occurred during the study, 4 with standard sinemet and 5 qith sinemet CR ➢ Only hallucinations during sinemet CR dose titration was considered definitely study-drug related Withdrawals ➢ 202 patient entered the study and 35 patients withdrew during the dosage titration phase periods ➢ 16 patients withdrew from the Sinemet 25/100 phase (11 due to insufficient therapeutic response) ➢ 19 patients withdrew from the Sinemet CR phase (8 due to insufficient therapeutic effect, 4 due to adverse clinical experiences, 2 for lack of cooperation) ➢ 167 entered the double-blind phase and of these 9 patients withdrew ➢ 5 from sinemet and 4 from sinemet CR
Source of Funding	None stated
Additional comments	➢ 156 patients completed the 24 week trial (77%) ➢ Double dummy technique ➢ No details of randomisation or allocation concealment technique ➢ Intention-to-treat? Not clear ➢ No sample size calculations ➢ Not multi-centre comparability analysis
Citation	
NCC CC ID (Ref Man)	293

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	Hutton JT, Morris JL, Roman GC, Imke SC, Elias JW. Treatment of chronic Parkinson's disease with controlled-release carbidopa/levodopa. *Archives of Neurology* 1988;**45** :861-4.
Study type	Double-blind cross over study
Evidence level	1+
Study objective	To evaluate clinical response, including motor response fluctuations, and to evaluate safety and tolerability during optimal treatment with both sinemet CR and sinemet 25/100
Number of patients	N=25 idiopathic Parkinson's disease (PD) patients
Patient characteristics	The patient's completing the study (n=21) included 15 men and 6 women. All patients had motor response fluctuations. All had motor response fluctuations. Their mean age (± SD) was 67.2 ± 8.3 years (range 52 to 78 years). The mean duration of PD was 10.2 ± 3.8 years (range 4 to 20 years). The Hoehn and Yahr stage mean was 2.7 ± 0.86 (range 2 to 4). All patients required sinemet at least 4x daily.
Intervention	Sinemet CR individually titrated optimal doses
Comparison	Sinemet 25/100 individually titrated optimal doses
Length of follow-up	None stated
Outcome measures	Levodopa dose, UPDRS, adverse events
Effect size	➢ Divided into two 4-week open-label titration periods, followed by two 8-week double-blind treatment periods ➢ Efficacy was measured at the ends of weeks 2,4,6,8 of the double-blind phase Levodopa dose ➢ During weeks 7 and 8 the mean (SD ±) number of sinemet CR (3.7 ± 0.58 doses/day) was significantly reduced compared with the mean number of doses of sinemet 25/100 ($p<0.001$) ➢ The mean (SD±) daily amount of levodopa taken 1098.6 ± 427.2 mg of sinemet CR compared to 902.4 ±382.3 mg of sinemet was significant ($p<0.005$) UPDRS ➢ Disability scores and motor-response fluctuation data from patient diaries during week 8 of the double-blind periods were analyzed to compare efficacy

	➢ Lower scores on all sections of the UPDRS scale indicate better functioning for CR ➢ No significant differences between the 2 agents were detected in UPDRS disability scores or daily motor-response fluctuations Open-label results ➢ Data was analysed from week 4 of the open-label dose titration period ➢ UPDRS activities of daily living scores during 'on' periods were rated as significantly superior for sinemet CR than sinemet 25/100 9p<0.001) as were activities of daily living when patients were 'off' (p<0.01) ➢ Motor examination scores were superior for sinemet CR compared with sinemet 25/100 (p<0.001) ➢ No significant differences between treatments for mood and mentation or complications of therapy ➢ During open-label conditions patients reported significantly more 'on' time without dyskinesias, expressed as a percentage of waking hours while taking sinemet CR (p<0.01) ➢ On the last day of the study 11 patients reported they preferred the blind period during which they were receiving sinemet CR; 7 patients preferred sinemet 25/100; and 3 stated no preference Double-blind phase ➢ Under double-blind conditions, no significant differences were detected between the two preparations on any of the efficacy measures used ➢ Correlation coefficients between 'on' time at week 8 of the double-blind phase and patient demographic variables were analysed ➢ When patients were receiving sinemet CR time 'on' correlated positively with age (p<0.05) ➢ The correlation of these two variables with sinemet 25/100 was not significant ➢ The correlation between gender and time 'on' while patients were taking sinemet CR approached significance (p=0.056) with men responding better than women ➢ The correlation of gender with on time while patients were taking sinemet CR was not significant ➢ For sinemet CR, the multiple regression of age/gender and time 'on' yielded a multiple correlation coefficient of 0.781 (p<0.001) ➢ Age and gender differences were both significant (p<0.05) ➢ The multiple correlation of age/gender and on time was not significant Adverse events ➢ Safety and tolerability appeared to equivalent ➢ No new side effects detected

	➢ 21/25 patients completed the 24-week trial
Source of Funding	Pharmaceutical company
Additional comments	➢ No randomisation or allocation concealment methods ➢ Small sample size ➢ No sample size calculations ➢ Intention-to-treat analysis not specified
Citation	
NCC CC ID (Ref Man)	295

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	LeWitt PA, Nelson MV, Berchou RC, Galloway MP, Kesaree N, Kareti D *et al*. Controlled-release carbidopa/levodopa (Sinemet 50/200 CR4): Clinical and pharmacokinetic studies. *Neurology* 1989;**39**:45-53.
Study type	Randomised, double-blind, crossover trial
Evidence level	1+
Study objective	To compare the safety and efficacy of sinemet 50/200 (CR) to sinemet 25/100 (IR)
Number of patients	N=25 Parkinson's disease (PD) patients Location: USA sites: single
Patient characteristics	Patients required 4 or more daily doses of levodopa (LD) to control motor fluctuations, notably wearing-off of antiparkinsonian effect. The age of the subjects ranged from 48 to 75 years (mean 63). The mean duration of parkinsonism was 10.4 ± 5.8 years. Almost all had received levodopa for most of the PD patient history. Hoehn and Yahr stage ranged from I to IV.
Intervention	Sinemet controlled-release 50/200 (CR)
Comparison	Sinemet immediate-release 25/100 (IR)
Length of follow-up	None stated- 16 week trial duration

Outcome measures	LD dosage, UPDRS (motor), NYUPDS, patient diaries adverse events, withdrawal rates
Effect size	➢ 8 weeks into the trial patients were switched from one treatment to the other. The same clinical conducted ratings during the double-blind phase at weeks 2,4,6 and 8 using several assessment scales LD doses ➢ At the end of the double-blind study the mean daily number of IR doses needed was 10.2 (range 5 to 19) while sinemet CR was 5.4 (range 3 to 7) ➢ Intervals between doses for IR averaged 2.1 hours (range 1.0 to 3.75) and for CR was 3.8 hours (range 2.7 to 6.0) ➢ The total intake for carbidopa/levodopa was 335 (±201.1)/1340 (±804.5) IR and 445.5 (±311.3)/1781.5 (±1245.0) CR ➢ Differences between each comparison were significant ($p<0.05$) Rating scales: ➢ UPDRS: Small but significant improvement in motor ratings for CR ($p<0.05$) ➢ Patient hourly diary scores: 'on' time (without dyskinesia) 54.5% IR vs. 42.1% CR ($p<0.05$) ➢ Patient hourly diary score 'on' time (with dyskinesia) 8.3% SRD vs. 37.1% CR ($p<0.05$) ➢ Patient hourly diary score 'off' time 37.1% IR vs. 20.7% CR ($p<0.05$) ➢ Patient-rated total mean 'on' time increased with CR versus IR but at expense of increased occurrence of dyskinesia NUDS ➢ Disability while in an 'on' state remained unchanged between the two groups (7.7 IR vs. 7.8 CR) ➢ The mean disability score while in an 'off' state was significantly less for CR than with IR (21.0 SRD vs. 20.1 CR, $p<0.05$) Withdrawal rates ➢ 3 patients from each group dropped out during the initial titration phase (insufficient response (3), protocol deviation (2), adverse effects (1))
Source of Funding	None stated
Additional comments	➢ 19/25 patients completed the trial (76%) ➢ No methods of randomisation or allocation concealment stated ➢ No sample size calculations- very small sample size ➢ Not intention to treat analysis ➢ No clinical criteria for diagnosis stated

Citation	
NCC CC ID (Ref Man)	310

Evidence Table
Q TxCM8
What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?

Bibliographic reference	Wolters EC, Horstink MW, Roos RA, Jansen EN. Clinical efficacy of Sinemet CR 50/200 versus Sinemet 25/100 in patients with fluctuating Parkinson's disease. An open, and a double-blind, double-dummy, multicenter treatment evaluation. The Dutch Sinemet CR Study Group. *Clinical Neurology & Neurosurgery* 1992;**94**:205-11.
Study type	Randomised, double-blind, parallel group
Evidence level	1+
Study objective	To compare the efficacy and tolerability of sinemet controlled-release 50/200 (CR) and sinemet 25/100 (IR) in Parkinson's disease patients with motor fluctuations.
Number of patients	N=69 patients with Parkinson's disease (PD) N=34 sinemet IR N=35 sinemet CR Location: Holland Sites: 15 neurological departments
Patient characteristics	All patients had Hoehn and Yahr scores of II-IV, with motor fluctuations. Both groups were statistically comparable at the beginning of the study.

Variable	IR (n=34)	CR (n=35)
Male/ female	24/10	19/16
Mean Age, years (± SD)	60.8 ± 9.3	61.6 ± 8.4
Levodopa dose (mg/d) (± SD)	642 ± 285	632 ± 295
No. Doses/day (± SD)	5.5 ± 2.2	5.3 ± 2.7
PD duration, years (± SD)	10.6 ± 5.2	10.4 ± 4.6

Intervention	Sinemet controlled-release (CR) 50/200

Comparison	Sinemet immediate-release (IR) 25/100
Length of follow-up	None stated- trial duration 32 weeks
Outcome measures	NYUPDS (New York University Parkinson's disease scale), NUDS (Northwestern University disability scale), adverse events, withdrawal rates, on-off hours, off periods, sleep patterns, patient and physicians overall evaluations
Effect size	➢ The study lasted 32 weeks and was divided into 2 phases- the first phase was an 8-week open-label titration period and the second phase was a double-blind period of 24 weeks ➢ In the second phase the end-results were compared with week-8 (baseline-2) Clinical efficacy (NYUPDS) ➢ Mean (SD) total NYUPDS: no difference between sinemet IR and CR ➢ IR patients showed a significant increase at week 32 as compared with week 8 ($p<0.05$) ➢ The CR patients showed a small and non-significant decrease in scores ➢ Rigidity and bradykinesia was ameliorated but not gait and postural instability Disability score (NUDS) ➢ Mean (SD) total NUDS in SRD patients showed a significant increase from week 8 to 32 ($p<0.05$) ➢ CR showed a small and non-significant change from week 8 to 32 ➢ Dressing and speech gave the best responses Dose and frequency ➢ Mean (SD) total daily dose of LD in IR treated patients were: 847 $\pm$ 325 mg in 4.1 $\pm$ 1.1 mg doses at baseline (week-8) differing significantly from week-32 which was: 663 $\pm$ 276 mg in 6.0 $\pm$ 2.6 mg doses ➢ Daily dosage and doses did not show major changes during prolonged CR treatment over 24 weeks. Total LD intake was 797 $\pm$ 363 mg in 4.3 $\pm$ 1.9 mg doses at week 8 and 802 $\pm$ 345 mg in 4.5 1.6 mg doses at week 32 On-off hours ➢ No change in on-off hours in CR treated patients from week 8 to 32 ➢ Total on-off hours was significant in IR treated patients from week 8 to 32 ($p<0.01$) Off-periods

	➢ No change in CR treated patients between week 8 and 32 ➢ IR treated patients showed a significant increase in off-periods from week 8 to 32 9 ($p<0.01$) Sleep pattern ➢ There was no change in either group or between groups for number of hours spent in bed, actual sleeping time, quality-rating of sleep, and number of sleep interruptions Delay in clinical response ➢ Mean delay (SD) in levodopa-induced clinical effects was significantly ($p<0.001$) shorter after intake of sinemet IR (45.3 ± 24.8) than after sinemet CR (64.4 ± 26.2) Patient's overall evaluations ➢ Patient's perception of early morning akinesia, dystonia, and pain was recorded ➢ After week 24 33% of patients in both groups found early morning akinesia and dyskinesia to be improved ➢ Dystonia was found to be improved by 33% in CR treated patients and only 18% in IR-patients Adverse events ➢ Drug-related adverse events reported: dizziness, dyskinesia (IR) and gastrointestinal complaints and hypotension (CR) Withdrawals ➢ 84 patients were recruited but a total of 15 patients withdrew from the study- 7 during the titration period and 8 during the double-blind period ➢ 5 withdrawals were due to adverse events- 3 which were sinemet CR related ➢ 6 withdrawals were due to insufficient therapeutic response- of which 4 were in the sinemet CR titration period ➢ 3 patients were excluded because of protocol violation and 1 due to loss of follow-up
Source of Funding	Pharmaceutical
Additional comments	➢ Methods of randomisation or allocation concealment not stated ➢ Sample size calculations not provided ➢ No comparability between centres performed ➢ No intention-to-treat analysis ➢ No clinical criteria for diagnosis given

Citation	
NCC CC ID (Ref Man)	775

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	Wolters EC,.Tesselaar HJ. International (NL-UK) double-blind study of Sinemet CR and standard Sinemet (25/100) in 170 patients with fluctuating Parkinson's disease. *J Neurol* 1996;**243**:235-40.
Study type	Randomised, double-blind, parallel group
Evidence level	1+
Study objective	The efficacy and tolerability of sinemet controlled–release (CR) and Sinemet standard (IR) were compared in a large number of Parkinson's disease (PD) patients who suffered motor fluctuations
Number of patients	N=149 PD patients N=75 Sinemet IR N=74 Sinemet CR Location: International sites: 16 Dutch and 6 British centres
Patient characteristics	Patients were aged 35-75 years, presenting with Hoehn and Yahr stage II-IV Parkinson's disease and demonstrating major clinical signs of illness (rigidity, tremor, postural and or gait disturbances and predictable deterioration of motor behaviour that fluctuated with levodopa (LD) treatment.
Intervention	Sinemet CR (treatment began with optimal dose from titration period, but investigators were allowed to optimise (alter) the dosage at their discretion during the double-blind phase)
Comparison	Sinemet immediate-release (IR)
Length of follow-up	None stated
Outcome measures	*Only double blind phase clinical efficacy results reported (see paper for titration period results) Patient's diary (on-off periods and dyskinesias), Northwestern University Disability Scale (NUDS), New York University Parkinson's disease Scale (NYUPDS), patient's and physician's global evaluation, patient's sleep evaluation, doses per day, time to effect, adverse events, withdrawal rates
Effect size	➢ 32 week trial- 8 week titration phase and followed by 24 week double-blind phase

	➢ Efficacy and safety measures were taken at 4, 8, 12 and 24 weeks for double-blind phase Sleep ➢ At baseline patients slept an average of 32% of the day in both groups ➢ After 24 weeks of treatment: -1% for sinemet IR and +1% for sinemet CR (non-significant) ➢ No significant within or between-group (treatment) changes detected in distribution of answers for any questions related to the evaluation of sleep ➢ Baseline scores for hours of sleep at approximately 4.5 (on 6 point scale) were equal in both groups (a score of 4 refers to 4-6 hours of sleep, score 5 refers to 6-8 hours sleep) ➢ Mean changes in sleep score were small ion both groups (on average 0.2) ➢ The difference was significant ($p<0.05$) at all evaluation times only in sinemet CR group ➢ The difference between treatments was not significant at any time 'On' time ➢ Mean proportion of the waking day that the patient spent 'on' averaged 68% at baseline and 64% after 24 weeks in sinemet IR (non-significant) ➢ For sinemet CR the mean proportion of mean time increased from 68% to 73% at week 4 ($p<0.05$) and to 74% at week 8 ($p<0.01$) but waned to 69% by the end of the study ➢ A significant difference between the two groups only at week 4 ($p<0.05$) when % on time was significantly greater in sinemet CR group Off periods ➢ The mean daily number of off periods was 4 in both treatment groups at baseline ➢ Sinemet IR: mean number of off periods did not change in double-blind phase ➢ Sinemet CR: significant decrease ($p<0.01$) of almost one off period was observed at all assessment times during the double-blind phase ➢ There were significantly fewer off periods ($P<0.01$) in the sinemet CR than the sinemet IR group at all assessments during the double blind phase NUDS score ➢ The mean baseline line score was close to 10 in both treatment groups ➢ No significant change was demonstrated in either group during the double-blind phase NYUPDS ➢ Mean total score showed a non-significant decreasing trend in the sinemet IR group ➢ Whereas as a significant decrease ($p<0.01$) of almost 1 was observed in the sinemet CR group ➢ The reduction in score in sinemet CR group was mainly due to amelioration of rigidity, tremor, and bradykinesia and not to improvement in gait and postural stability ➢ The reduction in score with sinemet CR was significantly greater than with sinemet IR ($P<0.05$)

	after 6 months of treatment Time for effect ➢ Mean baseline score for time for fist pill to take effect was 2.0 in both groups (2=30-60 min) ➢ Mean changes were small in the sinemet IR group but significant ($p<0.01$) in the sinemet CR group ➢ Sinemet CR took more time to take effect throughout the double blind period ➢ The mean score at the end of the study was 2.6 in sinemet CR and 2.1 in sinemet IR ($p<0.01$) Doses ➢ There was a significant decrease in the mean number of doses per day relative to the end of titration with sinemet IR ➢ In sinemet IR the number decreased from 5.7 to 5.1 ($p<0.01$) in sinemet CR group from 5.8 to 4.9 ($p<0.01$) Patient's global evaluation ➢ Score of 2 implies patient feels the better than at baseline, score of 3 implies patient feels the same ➢ In sinemet IR mean score at week 24 was 3.1 ➢ Sinemet CR mean score at week 24 was 2.9 ➢ Significant difference in patient's global evaluation between groups in favour of CR at weeks 12 ($p<0.05$) and 24 ($p<0.05$) ➢ No significant difference was found between groups at any time in physician's global evaluation Adverse events ➢ During titration period with sinemet IR, 30 patients reported at least one adverse event, of which 25 were considered to be at least possibly related to study-drug ➢ During the double blind period 15 patients reported at least one adverse events- 12 of these considered to be related to study medication ➢ Treatment with sinemet CR- the number of patients reporting adverse events (36 during titration and 28 in double blind phase) was significantly higher ($p<0.05$) ➢ The frequency of drug-related clinical adverse events did not differ significantly between the two treatments ➢ Most common adverse events: dyskinesia, dystonia, headache, hallucinations, and nausea and vomiting (accounted for half of the adverse events recorded) Withdrawal rates ➢ 12 patients withdrew during titration periods due to adverse events (2 sinemet IR and 10 sinemet CR)

	➢ 6 patients withdrew during the double-blind phase due to adverse events (1 sinemet IR, 5 sinemet CR) ➢ No significant difference was found between groups for number of patients withdrawing during either phase due to drug-related adverse events ➢ During the study a total of 39 patients withdrew (21 titration phase and 18 double-blind phase) ➢ 18 due to adverse events, 9 due to insufficient therapeutic response, and 12 lack of compliance or through missing follow-up appointments
Source of Funding	None stated
Additional comments	➢ 170 recruited, 149 randomly assigned into groups (88%), 131 completed the study (77%) ➢ No randomisation or allocation concealment methods stated ➢ No sample size calculations ➢ No comparisons between centres ➢ Not intention to treat analysis
Citation	
NCC CC ID (Ref Man)	19640

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	Ahlskog JE, Muenter MD, McManis PG, Bell GN, Bailey PA. Controlled-release Sinemet (CR-4): A double-blind crossover study in patients with fluctuating Parkinson's disease. *Mayo Clinic Proceedings* 1988;**63**:876-86.
Study type	Randomised, double-blind, crossover study
Evidence level	1+
Study objective	Investigation of standard sinemet versus controlled-release sinemet in moderate to advanced stage Parkinson's disease patients.
Number of patients	N=28 Parkinson's disease (PD) patients Location: USA Sites: single

<table>
<tr><td>Patient characteristics</td><td>Patients had short-duration response to standard sinemet. 13 women and 15 men (ages 36 to 80 years) had stage 2 to 4 parkinsonism on Hoehn and Yahr scale.</td></tr>
<tr><td>Intervention</td><td>Sinemet controlled-release (CR) 50/200 mg</td></tr>
<tr><td>Comparison</td><td>Sinemet immediate-release (IR) 25/100 mg</td></tr>
<tr><td>Length of follow-up</td><td>Trial duration 24 weeks.</td></tr>
<tr><td>Outcome measures</td><td>Dosages, patient-ratings, fluctuations, Schwab and England scores, drug-response profiles, sleep, adverse events, withdrawal rates</td></tr>
<tr><td>Effect size</td><td>

8 week open-label titration phase (2x-4week arms) followed by 16 week double-blind treatment phase (2x-8week arms)
Comparison of number of doses and dosing intervals for IR and CR during treatment

<table>
<tr><th>Variable</th><th>IR</th><th>CR</th><th>P value</th></tr>
<tr><td>Mean no. of doses</td><td></td><td></td><td></td></tr>
<tr><td>Per 24h</td><td>9.8</td><td>7.0</td><td>0.0001</td></tr>
<tr><td>During daytime (6am-midnight)</td><td>9.1</td><td>6.4</td><td>0.0001</td></tr>
<tr><td>During nighttime (12.01am-5.59am)</td><td>0.8</td><td>0.7</td><td>NS</td></tr>
<tr><td>Mean interval between daytime doses (h)</td><td>2.2</td><td>2.9</td><td>0.0001</td></tr>
</table>

Comparison between median (and mean) LD doses at end of treatment

<table>
<tr><th>Variable</th><th>IR</th><th>CR</th><th>P value</th></tr>
<tr><td>LD dose (mg)</td><td></td><td></td><td></td></tr>
<tr><td>Total per 24h</td><td>1800 (1730)</td><td>2000 (1980)</td><td><0.01</td></tr>
<tr><td>First dose taken at start of day</td><td>200 (190)</td><td>350 (343)</td><td><0.01</td></tr>
<tr><td>Majority</td><td>175 (181)</td><td>275 (277)</td><td><0.01</td></tr>
<tr><td>Carbidopa dose per 24h (mg)</td><td>450 (424)</td><td>500 (495)</td><td><0.01</td></tr>
</table>

Patient ratings of IR and CR during treatment

<table>
<tr><th>Patient rating[$]</th><th>IR</th><th>CR</th><th>P Value</th></tr>
<tr><td>Overall benefit</td><td></td><td></td><td></td></tr>
<tr><td>Median (mean) rating</td><td>3 (2.8)</td><td>2 (2.4)</td><td></td></tr>
<tr><td>Helpful vs. same or worse</td><td>7 vs. 16</td><td>17 vs. 6</td><td><0.01</td></tr>
<tr><td>No. giving better rating than other</td><td>3</td><td>12</td><td><0.05</td></tr>
<tr><td>Fluctuations</td><td></td><td></td><td></td></tr>
<tr><td>Median (mean) rating</td><td>4 (3.6)</td><td>3 (3.0)</td><td></td></tr>
<tr><td>Improved vs. same or worse</td><td>9 vs. 14</td><td>14 vs. 9</td><td>NS</td></tr>
</table>
</td></tr>
</table>

No. giving better rating than during other double-blind phase	6	13	NS	

$= Overall benefit was rated on a 5-point scale: 1= much more helpful, 3=same, 5= much less helpful. Fluctuations were rated on a 7-point scale: 1= very much improved, 4= same, 7= much worse

- Diary card of patients during last 2 weeks of the treatment phase

Status	IR	CR
Hours 'off'	3.7	3.2
Hours 'on'		
Without dyskinesia	10.4	10.4
With dyskinesia	2.0	2.4
Hours 'off'/hours awake	0.23	0.20

- The median scores on the Schwab and England scale were identical during sinemet CR and IR for both 'off' periods (score of 60) and 'on' periods (score of 90)
- The activities of daily living battery scores also showed no statistical significance

Sleep

- No patient taking CR complained of major sleep disturbances when questioned at end of double-blind phase
- 4/23 reported sleep disturbances while on IR (non-significant)
- Separate ratings for depression and motivation showed no significant difference between groups

Drug response profiles

- Improved response (10 patients): a longer 'on' duration with CR without substantial reduction in peak effect
- Not improved (10 patients): none of the patients demonstrated substantial prolongation of a fully developed 'on' response- in 7/10 the peak response was less with CR than IR
- Equivocal response (2 patients): had a longer response from CR than IR but peak effect was less

Follow-up

- 6 months after completion of trial- 20/23 patients continued in the open-label phase using CR

Adverse events

- Patient ratings of duration of dyskinesia and related disability, the presence of painful dyskinesia, or presence of early morning dystonia were not significantly different
- Diary cards showed mean time spent 'on' with dyskinesia were not significantly different
- No significant difference in any other specific side effect between CR and IR

Withdrawal rates

	➢ 4 patients dropped-out while receiving CR (3 during open-label phase) because of an erratic anti-Parkinson response, dyskinesia, confusion, or personal reasons respectively ➢ One patient dropped out of the study during the open-label IR phase before receiving CR
Source of Funding	Not stated
Additional comments	➢ 23/28 (82%) completed the study ➢ Analysis for period effect showed no differences ➢ No methods of randomisation or allocation concealment ➢ No sample size calculations (small sample size n=23) ➢ Intention-to-treat not stated
Citation	
NCC CC ID (Ref Man)	248

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	Sage JI,.Mark MH. Comparison of controlled-release Sinemet (CR4) and standard Sinemet (25 mg/100 mg) in advanced Parkinson's disease: A double-blind, crossover study. *Clinical Neuropharmacology* 1988;**11**:174-9.
Study type	Randomised, double-blind, crossover trial
Evidence level	1+
Study objective	To compare controlled-release sinemet with standard sinemet in patients with Parkinson's disease who had motor fluctuations.
Number of patients	N=25 Parkinson's disease (PD) patients Location: USA Sites: single
Patient characteristics	10 women, 15 men who were experiencing motor fluctuations while receiving standard sinemet therapy. Their mean age was 64 years (range 50-77 years) onset of PD was 53 years (range 39-74 years), duration of PD was 11 years (range 3-20 years) and duration of fluctuations was 5 years (range 0.5-16 years). All patients were taking sinemet at least 4x per day and exhibited end-of-dose

	wearing off phenomenon.
Intervention	Controlled-release sinemet (CR) 50/200 mg
Comparison	Immediate-release sinemet (IR) 25/100 mg
Length of follow-up	Study duration was 24 weeks, initial 8-week open phase, followed by 16-week double blind phase.
Outcome measures	UPDRS, Hoehn and Yahr, Schwab and England activities of daily living, patient diaries
Effect size	➢ During the first 4-weeks of open phase patients were titrated to optimal dose of IR, then followed by 4 weeks of CR titration ➢ Patients then assigned randomly to SRD or CR in two 8-week double blind phases Significant increases in the number of patients doing better on CR: ➢ Hours 'on' without dyskinesias were better in 58% during CR phase and 29% during IR phase ($p<0.05$) ➢ Walking when 'off' was better in 29% of patients during CR phase and in no patients on IR phase ($p<0.05$) ➢ Sensory complaints when 'on' were improved in 17% of patients during CR phase and in no patients in during IR phase ➢ Duration of dyskinesias improved in 25% of patients during IR phase an in no patients in CR phase ($p<0.05$) ➢ More patients were better at cutting food when 'on' with IR (25%) than CR (4%) ($p<0.05$) Sleep ➢ During IR phase more patients slept more hours during recorded 24h period (58%) than CR (29%) ($p<0.05$) ➢ Total hours of sleep during the 24h period was no different on CR (8.2 ± 2.2 h) than IR (8.6 ± 2.1h) ($p<0.05$) Dosage ➢ 19 patients took fewer doses per day on CR (79%) whereas only one patient (4%) took fewer doses on IR ($p<0.05$) ➢ During CR phase patients took a mean of 5.3 doses per day (range 3-10) whereas the mean number of doses per day on IR was 7.8 (range 4-15) ➢ Total LD use (mg/d) was increased on CR 67% of patients whereas only 29% used more on IR ($p<0.05$) ➢ During CR phase, mean daily LD was 1544 mg (range 600-2800 mg) while mean daily LD use on

	IR was 1303 mg (range 250-2400 mg) ➢ Results of hourly examinations during the 6h visit did not show any significant differences for: ➢ Parkinson's disability score (12 improved on CR vs. 10 improved on IR) ➢ Dyskinesias (9 improved on CR vs. 7 improved on IR) ➢ Total disability score (12 improved on CR and 10 on IR) ➢ All p>0.05 Withdrawal rates ➢ One patient dropped-out – not due to study medication- death of family member
Source of Funding	Not stated
Additional comments	➢ Not intention-to-treat ➢ Methods of randomisation or allocation concealment not stated ➢ No sample size calculations ➢ 1/25 (4%) dropped-out of study
Citation	
NCC CC ID (Ref Man)	348

Evidence Table **Q TXCM8** What is the effectiveness of modified-release levodopa vs immediate release levodopa in the treatment of early Parkinson's disease?	
Bibliographic reference	Friedman, J. H. & Lannon, M. C. 1989, "An open trial of controlled release carbidopa/L-DOPA (Sinemet CR) for the treatment of mild-to-moderate Parkinson's disease", *Clinical Neuropharmacology*, vol. 12, no. 3, pp. 220-223.
Study type	Open label 1 year longitudinal study switching patients already on Sinemet to controlled release Sinemet (Sinemet CR)
Evidence level	2-
Study objective	To evaluate the efficacy of Sinemet CR for the treatment of mild to moderate PD in patients who are already taking Sinemet.

Number of patients	N=19 Mild to moderate Parkinson's disease (PD) patients Location: USA (no further details) Sites: not stated
Patient characteristics	Subjects with mild to moderate Parkinson's disease. Already on Sinemet (carbidopa/L-DOPA) Age 51-77 years (mean age 65.6 years) 16 males and 4 females Mean duration of PD 9 years (range 3-18 years) Mean Sinemet dose 50.8/642.5mg (range 25/100 to 150/1500) prior to starting Sinemet CR. Mean frequency of dosing 4.3 doses/day (range 1-7) Sixteen patients taking additional PD medications; 5 (bromocriptine), 10 (anticholinergics), 4 (tricyclic antidepressants), 1 (diphenhydramine), 1 (propanolol), 5 (amantadine). Mean Northwestern Disability score before the start of Sinemet CR was 7.25. Recruitment: No description of recruitment
Intervention	Controlled-release carbidopa/levodopa (Sinemet CR) containing 50mg carbidopa and 200mg levodopa. Dosage titrated as needed.
Comparison	Standard carbidopa/levodopa (Sinemet). Mean Sinemet dose 50.8/642.5mg (range 25/100 to 150/1500) prior to starting Sinemet CR. Mean frequency of dosing 4.3 doses/day (range 1-7)
Length of follow-up	1 year with patients seen at weeks 1,2,4,8,12,24, 36 and 52 for assessments and medication adjustments
Outcome measures	Northwestern University disability scale, Daily total L-Dopa intake (only reported for six patients), Dose frequency of Sinemet, Subjective patient experience of function on Sinemet CR after 1 year compared with function 1 year before on standard Sinemet, Physician-assessed improvement (general impression – not objectively measured on PD scales)
Effect size	➢ Mean Northwestern University disability scale score dropped from 7.25 to 6.4 (not statistically significant) ➢ Four patients reported themselves much better, seven patients reported themselves minimally better, seven unchanged and one worse. ➢ Physician found 2 patients much improved, 10 patients minimally improved, 6 unchanged and 1 worse.
Source of Funding	Pharmaceutical

Additional comments	➢ Clinical diagnostic criteria not stated ➢ Patients evaluated during first 4 weeks for gait, tremor, bradykinesia, tone and balance. ➢ Doses of drugs not stated; however when patients were switched from standard Sinemet to Sinemet CR, total daily L-DOPA was kept approximately the same, but the frequency of dosing was decreased. ➢ Protocol allowed for concurrent treatment with any PD medications commercially available. ➢ Number of sites not stated. Number of investigators not stated. ➢ Detailed methods of outcome measurement not stated. ➢ Selective reporting of positive data ('six patients reduced daily total L-Dopa intake by mean of 24%') ➢ No objective measurement of adverse effects ➢ 1 patient dropped out suffering from a severe myocardial infarction at week 36.
Citation	
NCC CC ID (Ref Man)	280

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	The U.K.Madopar CR Study Group. A comparison of Madopar CR and standard Madopar in the treatment of nocturnal and early-morning disability in Parkinson's disease. *Clin Neuropharmacol* 1989;**12**:498-505.
Study type	Double-blind crossover study
Evidence level	1+
Study objective	To compare the effects of Madopar CR with that of conventional Levodopa/benserazide (Madopar) on nocturnal and early morning disability in patients with Parkinson's disease.
Number of patients	N=103 patients with Parkinson's disease (PD) Location: UK Sites: 11 centres
Patient characteristics	Majority of patients had difficulty turning in bed or getting out of bed and suffered from cramps and pain at night; foot spasms and spontaneous jerks were also common. The mean age was 67.7 years

	and 67% of the population was male. Disease duration ranged from 1 to 29 years, with a mean of 8 years. Mean duration of levodopa therapy was 6.4 years. The majority of patients (52%) were rated as Hoehn and Yahr stage III, 26% were stage II, 19% were stage IV and 2% were stage I. Daytime fluctuations in response to levodopa and/or abnormal involuntary movements were reported by 42 of 103 patients (41%).
Intervention	Controlled-release Madopar 125 mg (CR) immediately before going to bed. If insufficient effect on symptoms was observed, the dose was increased by 125mg weekly to a maximum of 4 capsules at night. Once optimum night time dose was determined, patients remained at this dosage for 2 weeks. They then transferred to alternative treatment, starting at one capsule, the procedure was repeated.
Comparison	Standard Madopar 125 mg immediate-release (IR) immediately before going to bed
Length of follow-up	Trial duration: 6 weeks (3 weeks per arm). No follow-up stated.
Outcome measures	Patient diaries and opinion of investigator
Effect size	➢ 82/103 patients completed the study Dosage ➢ Mean optimum dosages for the treatments was similar (2.4 capsules for CR, 2.2 for IR) Sleep ➢ On entry to study mean time taken to fall asleep (recoded by investigator) was 47 min ➢ During optimum treatment periods this time was reduced to 38 min (CR) and 39 min (IR) ➢ Mean time taken to fall asleep (patient diaries) was little different between treatments ➢ Both CR and IR reduced total nocturnal and early-morning disability scores recorded by investigator compared with baseline to a statistically significant degree ➢ Little difference between total scores for two optimum treatment periods for either nocturnal or early-morning disability ➢ Nocturnal and early-morning disability scores taken from patient diaries and averaged over the periods of optimum treatment were also very similar for IR and CR ➢ Patient ratings of early morning condition also improved from baseline but not between treatments ➢ The majority of patients considered their overall nocturnal condition was better after optimum treatment with either IR or CR than on entry to study ➢ 62% of patients felt better after CR and 59% felt better after IR ➢ The number of patients who felt their nocturnal condition was worse from baseline was 4% CR and 10% IR ➢ Overall early-morning condition was rated as better than on entry to the study was 46% after CR and 45 after IR

	➢ Percentage of patients who felt overall condition was worse was 2% cr and 6% IR ➢ 2/3 of patients gave the same response for both treatments with respect to their effect on overall condition compared to baseline ➢ Only 27% felt the two treatments were the same in relation to their effect on nocturnal condition ➢ 41% felt CR was better 33% felt it was worse ➢ Corresponding percentages for early-morning condition are 41% the same, 33% felt CR was better and 26% felt CR was worse ➢ CR was considered to be advantageous by 61% of patients and IR by 60% ➢ Patients who found treatments to be disadvantageous: 23% CR and 28% IR ➢ After the optimum treatment period the investigator (patient) felt it was justified to continue treatment with CR 55% (63%) of cases and with IR in 50% (55%) of cases ➢ Good agreement between patient and investigatory opinions ➢ Despite many little differences between treatments investigator thought that there was a difference between the two treatments in 60% of cases ➢ Of these CR was felt to be preferable in 65% and IR in 35% Adverse effects ➢ 63 adverse events were reported by 37 patients (32 CR and 31 IR) ➢ Majority were consistent with levodopa profile ➢ Dyskinesia was the most commonly reported adverse event (8 CR, 7 IR) ➢ Other adverse events: disorders of movement, gastrointestinal, central effects such as confusion, expression, hallucinations etc was evenly distributed between the 2 treatments Withdrawal rates ➢ 21 patients withdrew ➢ Lack of effect was the reason given in 3 cases (one on IR and 2 on CR) ➢ Adverse side effects in 11 cases (4 on IR and 7 on CR) ➢ 7 due to other reasons
Source of Funding	Not stated
Additional comments	➢ There was no washout period between arms and no first arm results were reported ➢ Period and carry-over effects were analysed ➢ Differences from baseline to the end of the first treatment period were assessed within each treatment group separately, also using analysis of variance techniques ➢ Methods of randomisation or allocation concealment not stated ➢ No sample size calculations ➢ Intention-to-treat not stated

	➢ Centre comparisons were performed ➢ No details of blinding procedure ➢ No details of clinical diagnosis criteria
Citation	
NCC CC ID (Ref Man)	19641

TxCM9 – section 7.5.8 and 9

Evidence Table **TxCM9** What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?	
Bibliographic reference	Ostergaard L, Werdelin L, Odin P, Lindvall O, Dupont E, Christensen PB *et al*. Pen injected apomorphine against off phenomena in late Parkinson's disease: a double blind, placebo controlled study. *Journal of Neurology, Neurosurgery & Psychiatry* 1995; **58:681**-7.
Study type	Randomised, double-blind, placebo-controlled crossover study
Study objective	To evaluate the effect, therapeutic dose range, and pharmokinetics of apomorphine given as subcutaneous injection by single use pen was evaluated in the treatment of off phenomenon in patients with Parkinson's disease (PD).
Number of patients	N= 22 PD patients Location Denmark and Sweden Sites: four in Denmark and one in Sweden
Patient characteristics	12 women and 10 men with a mean age of 59.3 (range 44-76) years were included. Patients has idiopathic Parkinson's disease for an average of 9.8 (range 3.4 to 19.2 years) and when in on phase they were in Hoehn and Yahr stages 2.0 to 4.0. The mean duration of levodopa treatment was eight (range 3-19 years). Mean body weight was 69.9 (range 47.0 to 98.0) kg. All patients had daily, disabling off periods, defined as change in motor state with 5 minutes. The patients were on stable levodopa (LD) treatment 5-14 doses per day.
Intervention	Apomorphine (APO) 10 mg/mL (pH 3-4). Pre-filled single use pens with a push button release system

	were used to give injections. The test was performed by giving increasing doses of 1.6, 3.2, 4.8, and 6.4 mg apomorphine with a interval of at least 120 min. One placebo dose was added to the regimen as dose 2, 3 or 4 in a randomised manner. Patients were given 1 mg of APO at off periods. Doses were increased by 1 mg with at least 90 min intervals, until the optimal effect in off phenomenon was reached or intolerance occurred. The dose was maintained for a minimum of 2 days before entry to the crossover phase. Maximum single dose allowed was 12mg APO and max daily dose allowed was 100mg.
Comparison	Isotonic saline.
Length of follow-up	Trial duration 8 days (4 days APO and 4 days placebo)
Outcome measures	

Effect size	➢ Patients were admitted to hospital at study entry ➢ After an initial placebo-controlled test of dopamine responsiveness (APO test) on day 2 and screening phase (minimum 3 days), doses of APO were individually titrated in an open phase finding phase (maximum one week) ➢ 8 day treatment phase (4 days in each arm) then discharged from hospital and during an 8 week maintenance phase came fro visits to the clinic every second week ➢ During the crossover phase APO in individual optimal doses or placebo were given for four days each- every time the patient was 'off' and during the 8 week maintenance phase the patients continued to take optimal doses of APO at 'off' periods Results Withdrawal rates ➢ 19 patients completed the APO test, 17 completed the dose finding crossover phases ➢ 16 patients completed week 2 of the maintenance phase and 14 completed the whole study ➢ Eight patients dropped out altogether (14/22= 64%) due to: hypotension (3), unsatisfactory effect (2), exanthema, unclear off periods, and lack of motivation (one patient each) ➢ All 17 patients who participated in the crossover phase completed the 4 days with APO ➢ 6/10 who started on placebo and 3/7 who received placebo after APO- reported a lack of drug effect during placebo period and the duration was shortened to 24-72 hours for ethical reasons ➢ The maximal dose of apomorphine during the apomorphine test was on average 4.9 (range 1.6 to 6.4 mg)

	➢ During the dose finding phase max dose was 3.9 (range 1.0 to 8.0) mg and optimal dose was 3.4 (0.8 to 6.0) mg Off periods ➢ Mean daily duration of off periods (min/day) during crossover was reduced by 58% according to staff (difference –167; 95% CI –231 to –103, p<0.0001) and reduced by 51% according to patients (difference –313, 95% CI –469 to –156, p<0.002) compared to placebo ➢ Mean daily numbers of off periods during crossover phase was increased by 34% (difference 34; 95% CI 5 to 70, p<0.02) as assessed by staff and no significant change according to patients (difference 10; 95% CI –11 to 37, non-significant) compared to placebo ➢ Distribution of severity of off periods showed a significant effect (p<0.00001) in favour of APO ➢ Compared with the screening phase, the off variables for the maintenance phase showed changes in the same direction as crossover phase Clinical global impressions ➢ 12/14 patients who completed the maintenance phase reported 'much' or 'very much' improvement at the last visit, two patients reported minimal improvement ➢ No patients reported to have worsened during maintenance phase Efficacy ➢ Part I, II and IV of UPDRS showed minimal changes ➢ Part III (motor) seemed to be slight reduction in total score ➢ But for primary parkinsonian symptoms (tremor, rigidity, bradykinesia) only a slight reduction in bradykinesia was observed Adverse events ➢ 67% (p<0.02) increase in mean daily duration of involuntary movements with APO (164 ± 132 min/day compared with placebo 98 ± 102 ➢ The mean daily numbers of periods of involuntary movements were 2.19 with APO and 1.62 with placebo (increase of 35% in APO) (p<0.05) ➢ No significant effect in the severity of involuntary movements ➢ Most frequent adverse event was nausea with or without vomiting 16/22 patients ➢ Among 16 patients who participated in the 8-week maintenance phase 10 experienced mild or moderate local irritation at the injection sites ➢ Other adverse events reported by more than one patient include: dyskinesia and chorea, sweating and warmth, dizziness, headache, drowsiness, yawning and rhinitis ➢ The symptoms were mild or moderate expect in the case of dizziness which were characterised as

	severe in a few cases Suitability of the pen ➢ Questionnaire: 11/14 found feeling of freedom increased after they had started APO injections ➢ After 8 weeks use 13/14 were able to inject themselves ➢ 11/13 found it very easy, easy or rather easy to handle the pen ➢ 11/14 were not afraid of performing injections and only one found injection painful
Source of funding	Not stated
Additional comments	➢ Allocation concealment through the use of pre-filled pens ➢ Method of randomisation not stated ➢ Carry-over effects were not evaluated because APO is rapidly eliminated ➢ Analysis of patient, treatment, period and sequence of treatments
Citation	
NCC CC ID (Ref Man)	19628

Evidence Table **TxCM9** What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?	
Bibliographic reference	Dewey RB, Jr., Hutton JT, LeWitt PA, Factor SA. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events. *Archives of Neurology* 2001;**58**:1385-92.
Study type	Randomised, double-blind, placebo-controlled, parallel group
Evidence level	1+
Study objective	To assess the safety and efficacy of subcutaneous apomorphine administration for off-state periods in patients with Parkinson's disease (PD) with motor fluctuations.
Number of patients	N=29 PD patients N= 20 apomorphine N= 9 placebo-treated Location: US sites: four

<table>
<tr><td>Patient characteristics</td><td>Inclusion criteria: patients with advanced PD suffering from motor fluctuations. At least two hours of off time per day despite an optimised oral drug regimen, including levodopa and an oral dopamine agonist. A significant improvement in the UPDRS motor score after administration of oral levodopa was required (≥30% improvement).
<table>
<tr><th>Characteristics</th><th>Apomorphine</th><th>Placebo</th></tr>
<tr><td>Sex (%) male</td><td>60</td><td>89</td></tr>
<tr><td>Mean age (yr)</td><td>66 ± 2</td><td>62 ± 4</td></tr>
<tr><td>Duration of PD (yr)</td><td>9.2 ± 1.1</td><td>12.3 ± 2.1</td></tr>
<tr><td>Total no. of off hours per day</td><td>5.9 ± 0.5</td><td>5.9 ± 0.8</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Apomorphine hydrochloride (APO) 10 mg/mL. Upward titration was begun at 0.2 mL with 0.2 mL increments to a maximum of 1.0 mL (2-10 mg active) per dose. Titration was terminated at 1.0 mL or on demonstration of a UPDRS motor score reduction of at least 90% of that recorded during levodopa challenge. If a dose of apomorphine or placebo had not generated a levodopa-equivalent response, a second or third dose could be tested on a single day at intervals of not less than 2 hours. There were no significant differences between groups at baseline.</td></tr>
<tr><td>Comparison</td><td>pH 3.5 –matched vehicle placebo. Same titration regimen as above.</td></tr>
<tr><td>Length of follow-up</td><td>4 week trial duration</td></tr>
<tr><td>Outcome measures</td><td>Percentage of off-state events aborted,</td></tr>
<tr><td>Effect size</td><td>➢ Phase one: inpatient observation of upwardly titrated doses given to reverse a practically defined off state achieved by withholding antiparkinsonian drugs overnight
➢ Phase two: involved a one month period of out-patient observation of drug effectiveness when administered by patients or caregivers as needed for the reversal of off-states

In patient phase
➢ Distribution of therapeutically equivalent dose (or maximum dose achieved) was different between groups APO 5.4 ± 0.5 mg and placebo 1.0mL (p<0.001)
➢ The change in UPDRS motor scores was not significant following oral levodopa (p=0.29)
➢ UPDRS motor was significantly different following study drug injection
➢ APO resulted in change of 23.9 points (62% improvement) while placebo produced essentially no change (1%) (p<0.001)
➢ Dyskinesias were seen more in APO treatment (p=0.001) than placebo
➢ Hand-tapping score and Webster step-seconds score were not significant between groups following oral levodopa therapy but were significant following blinded test medication (p<0.001) for</td></tr>
</table>

	both outcomes measures (hand-tapping in favour of APO and Webster step in favour of placebo) Out patient phase ➢ Patient experiences (diary) found (out of 10 parameters two were significant): ➢ Off state events aborted per patient (%) was 95 ± 2.4 in APO and 23 ± 13 in placebo (p<0.001) in favour of APO ➢ Onset latency, min (no. of patients reporting the condition/total no. Of patients) 22 ± 2.4 (18/18) APO and 45 ± 5.7 (5/8) placebo (p<0.001) in favour of APO ➢ From a baseline of 6 hours of off time per day, APO-treated patients demonstrated a 2-hour reduction in off-time while placebo-treated patients demonstrated no reduction (p=0.02) ➢ This reduction in off time was seen without a reduction in the number of discrete off-state events suffered per day Correlation analysis ➢ Despite a response ratio of 96% morning levodopa dose (that single dose that produced the effect to which APO responses were matched) was not predictive of required APO dose (p=0.35) ➢ Total daily LD dose was also not predictive of APO dose (p=0.32) ➢ In 22/26 patients inpatient and outpatient results were concordant- thus in patient response was correlated with and predictive of outpatient efficacy (p<0.001) ➢ The 2 mg dose of APO (optimal for 3/20 patients) resulted in 32% improvement in UPDRS motor score for APO and only 6.3% change in placebo (p=0.02) ➢ Levodopa-equivalent dose of APO produced a 62% improvement in UPDRS motor score ➢ 2mg below LD equivalent dose (or 2mg in 3 patients titrated to only 2mg) still provided a 42% improvement p<0.001) Adverse events ➢ Occurred in 85% pf APO and 89% of placebo (mostly mild in severity) ➢ Injection site complaints were common ➢ Yawning was reported in 40% of APO and no placebo-treated patients (p=0.03) ➢ 35% of APO and no placebo-treated patients experienced drowsiness or somnolence (p=0.07) ➢ Dyskinesias were reported as an adverse event by 35% of APO and 11% placebo ➢ Nausea or vomiting occurred in 30% of APO and 11% of placebo ➢ In one APO patient a 6 mg dose resulted in nausea and vomiting severe enough for

	discontinuation ➢ There were no significant changes in other safety measures (blood tests, ECG, physical exam) Withdrawal rates ➢ Two patients dropped-out prior to in patient dosing because of failure to demonstrate a significant response to the levodopa challenge and once patient dropped-out after signing the consent form but prior to any inpatient dosing ➢ 3 patients from the inpatient phase failed to progress to the outpatient phase ➢ One placebo-treated patient discontinued participation in the study because of lack of effect after third level of inpatient dosing ➢ One apomorphine patient dropped-out due to adverse events (nausea and vomiting) during dose titration ➢ One additional apomorphine patient dropped-out because of chest pains during first week of treatment
Source of funding	Pharmaceutical
Additional comments	➢ Sample size calculations performed ➢ Methods of randomisation (patient presentation) and allocation concealment stated ➢ Intention-to-treat analysis
Citation	
NCC CC ID (Ref Man)	19655

Evidence Table **TxCM9** What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?	
Bibliographic reference	T. van Laar, E. N. Jansen, A. W. Essink, C. Neef, S. Oosterloo, and R. A. Roos. A double-blind study of the efficacy of apomorphine and its assessment in 'off'-periods in Parkinson's disease. *Clinical Neurology & Neurosurgery* 95 (3):231-235, 1993.
Study type	Randomised, double-blind, placebo-controlled crossover study (five N=1 studies, with each patient as their own control)
Evidence level	1+

Study objective	To evaluate the clinical benefit of subcutaneous (SC) apomorphine (APO) in the treatment of off-periods in patients with idiopathic Parkinson's disease (PD).
Number of patients	N= 5 PD patients Location: Netherlands Sites: one
Patient characteristics	Five patients, 3 males and 2 females, mean age 54.2 (range 29-68 years) with idiopathic PD with a mean duration of 12.4 years (range 7-23 years) were selected for study. Three patients were in Hoen and Yahr stage 4 and 2 in stage 3. All patients had used Levadopa (L-dopa) with a peripheral decarboxylase inhibitor for 9.6 years (range 2-20 years), and had response fluctuations for at least 6 months. Anti-PD medication was kept unchanged for at least 1 month prior to study. All conventional methods to improve response fluctuations had failed. Exclusion criteria: Other neurological or general internal diseases, mini mental state examination less than 24 points.
Intervention	Patients titrated up to an optimal dose of SC APO HCL (1%, 10 mg/ml) starting with 1 mg, with subsequent 1 mg increments up to a maximum dose of 10 mg. Optimal dose defined as maximum tolerated dose with best motor response combined with minimal adverse events. In the following ten 'off' periods, with intervals of at least 3 hours, APO was injected with a non-transparent injection pen, following a randomisation table, of which the key was kept by the pharmacist. Each patient acted as their own control.
Comparison	Patients titrated up to an optimal dose of SC APO HCL (1%, 10 mg/ml) starting with 1 mg, with subsequent 1 mg increments up to a maximum dose of 10 mg. Optimal dose defined as maximum tolerated dose with best motor response combined with minimal adverse events. In the following ten 'off' periods, with intervals of at least 3 hours, placebo (0.9% sodium hydrochloride solution) was injected with a non-transparent injection pen, following a randomisation table, of which the key was kept by the pharmacist. Each patient acted as their own control.
Length of follow-up	Patients were admitted to hospital for one week during the study period. Follow-up occurred over next 10 'off' periods after achievement of the optimal APO dose in each patient. For each patient 2 time-concentration profiles of serum concentration APO were made in the dose finding series. First data collected after injecting starting dose of 1 mg, and second set after giving optimal dose of APO. After injecting 1 mg, blood samples were taken at 0, 3, 6, 9, 12, 15, 30, 45, 60, and 120 min by intravenous catheter. After injection of optimal APO dose, 3 samples were taken and analysed.

Outcome measures	Before and at time of best motor response, or 0.5 h after injection the following outcomes were measured: Columbia rating (tremor, rigidity, gait, bradykinesia, stability); finger/foot-tapping score during 30s, time walking over 25 m, time pinboard test, blood pressure.
Effect size	➢ Mean optimal dose of APO was 2.7 (range 1-5 mg) ➢ Latency of onset mean value 7.3 min (range 1.5-15 min) ➢ Mean duration of response 96 min (range 20-120 min) ➢ Mean difference in Columbia scores showed significant improvement for individual items (tremor, rigidity, gait, bradykinesia, stability) for all patients on APO versus placebo (p<0.001) ➢ Mean difference in Columbia scores for the sum of all items were significant for 4/5 patients (p=0.03; p=0.29; p=0.01; p= 0.00; p=0.01), and significant when scores of all patients were combined (p=0.001) for APO versus placebo. ➢ Combined measures of pinboard, tapping and walking variables in all patients showed significant improvement after APO versus placebo (p=0.001). ➢ The following types of adverse events reported by number of patients included: Nausea without vomiting (1), dyskinesia combined with maximal response (4), short-lasting twinkling in legs (1), short-lasting worsening of tremor (1), warmth and perspiration (1), lower level of motor functioning at end of clinical effect compared to basic level before the test (2).
Source of funding	Not stated
Additional comments	➢ Allocation concealment through the use of non-transparent injection pen following a randomisation table ➢ Key to randomisation table kept by pharmacist rather than remote study centre off-site ➢ 3/50 trials (5 patients with 10 trials each) were excluded because the contents of the injection pen, according to the list of the pharmacist, did not correspond with the HPLC-analysis of the serum levels. Unclear how this affected the results for individual patients and for outcomes where results of patients were combined. ➢ Although study refers to five N =1 trials, the results from the five patients are combined for the main outcomes, so study is more akin to a crossover trial with multiple intervention and placebo phases coinciding with ‘off’ periods.
Citation	
NCC CC ID (Ref Man)	19992

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Evidence Table
TxCM9
What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?

<table>
<tr><td>Bibliographic reference</td><td>Poewe W, Kleedorfer B, Wagner M, Bosch S, Schelosky L. Continuous subcutaneous apomorphine infusions for fluctuating Parkinson's disease. Long-term follow-up in 18 patients. Advances in Neurology 1993;60:656-9.</td></tr>
<tr><td>Study type</td><td>Before and after study</td></tr>
<tr><td>Evidence level</td><td>3</td></tr>
<tr><td>Study objective</td><td>To present the long-term outcomes of a group of patients with complex refractory response oscillations treated with 24-hour continuous subcutaneous (s.c.) apomorphine (APO) infusions</td></tr>
<tr><td>Number of patients</td><td>N=18 Parkinson's disease (PD) patients

Location: Germany sites: single</td></tr>
<tr><td>Patient characteristics</td><td>Patients with idiopathic PD and complex refractory response fluctuations to oral L-dopa. Patients were hospitalised and oral medications were initially kept unchanged.
<table>
<tr><th>characteristics</th><th>Patient data</th></tr>
<tr><td>Male: female ratio</td><td>15:3</td></tr>
<tr><td>Age, yr (range)</td><td>60.2 (49-72)</td></tr>
<tr><td>Disease duration, yr (range)</td><td>12.4 (4-24)</td></tr>
<tr><td>Hoehn and Yahr stage</td><td></td></tr>
<tr><td>'on'</td><td>1.5 (1-3)</td></tr>
<tr><td>'off'</td><td>3.8 (3-5)</td></tr>
<tr><td>L-dopa</td><td></td></tr>
<tr><td>Duration, yr (range)</td><td>9.9 (2-18)</td></tr>
<tr><td>Dose, mg/d (range)</td><td>1230 (600-2400)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>After a minimum of one-week baseline observations patients were started on regular oral domperidone (20mg t.d.s.). Continuous 24-h s.c. APO infusion using a portable system driver was initiated one day later, beginning with infusion rates of 1mg/h.
Hourly infusion rated were gradually increased by 1mg/h per day until a clinical response became apparent (reduced 'off'' time and/or increased interdose dyskinesias).</td></tr>
<tr><td>Comparison</td><td>Baseline evaluations</td></tr>
</table>

Length of follow-up	Out-patient follow-ups initially every 2-weeks, monthly from month 2 to 6 and every 3 months thereafter.
Outcome measures	Individual fluctuation patterns were recorded using self-scoring 'on-off' diaries.
Effect size	➢ At the time of the latest follow-up 14/18 patients had been treated with APO for >6 months ➢ Daily hours 'off' had been reduced by an average of 60% and 4 patients had virtually continuous 'on' states with only rare interruptions for periods of less than 30 min at irregular intervals ➢ The reduction in 'off' time remained stable over the entire follow-up period ➢ The total daily dose of L-dopa could be progressively reduced in all patients to an average 20% of baseline levels and 4 were eventually taken off the drug completely ➢ 'Off' period foot dystonia disappeared (5 cases) or was markedly improved (4 cases) in 9 patients affected after 1 month APO treatment ➢ at the latest follow-up 7/9 originally affected were still on s.c. APO and 'off' period foot cramps still occurred (less than 3 episodes per week) in 3 of them ➢ all 4 patients suffering from biphasic dyskinesias lost those between month 3 and 6 s.c. APO infusions while the majority of 14 patients affected, interdose dyskinesias did not change significantly in severity over the time of follow-up- although their average daily duration increased in parallel to the increase in daily 'on' time ➢ 3 patients with severe and disabling interdose dyskinesias prior to APO treatment experienced a progressive reduction in the intensity over the first 12 months of APO infusions adverse events ➢ side effects reported by 14 patients on long-term continuous s.c. APO infusions: severe skin reaction (4), sedation (3), eosinophilia (3), increased appetite (2), increased libido (2), visual delusions (3), diurnal agitation (2), immune haemolytic anaemia (2) ➢ the mental side effects were common and could be controlled by APO dose reductions

<table>
<tr><td></td><td>withdrawal rates
➢ reasons for withdrawal after less than 3 months of treatment included: interdose chorea (2), insufficient response (1) and severe local skin allergy (1)
➢ 2/14 long-term responders had been taken off APO at the time of latest follow-up
➢ one patient was due to compliance problems, two others had developed reversible immune haemolytic anaemia after 14 and 15 months respectively

Treatment data summary
<table>
<tr><th>outcome</th><th>Patient data (n=14)</th></tr>
<tr><td>Follow-up period</td><td>20.6 (8-35)</td></tr>
<tr><td>Apomorphine dose (mg)</td><td></td></tr>
<tr><td>Hourly</td><td>7.0 (3.5-12.5)</td></tr>
<tr><td>Daily</td><td>160.0 (84-300)</td></tr>
<tr><td>L-dopa dose (mg/d)</td><td></td></tr>
<tr><td>Before APO</td><td>1260 (500-2400)</td></tr>
<tr><td>With APO</td><td>280 (0-750)</td></tr>
<tr><td>Hours ‘off’ per day</td><td></td></tr>
<tr><td>Before APO</td><td>5.7 (3-10)</td></tr>
<tr><td>With APO</td><td>2.4 (0-5)</td></tr>
<tr><td></td><td></td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Not stated</td></tr>
<tr><td>Additional comments</td><td>➢ before and after study
➢ non-randomised, uncontrolled, non-blinded evaluations
➢ long-term follow-up
➢ diagnostic criteria not stated
➢ method of recruitment not stated</td></tr>
<tr><td>NCC CC ID (Ref Man)</td><td>19651</td></tr>
</table>

Evidence Table
TxCM9
What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?

Bibliographic reference	Kanovsky P, Kubova D, Bares M, Hortova H, Streitova H, Rektor I *et al*. Levodopa-induced dyskinesias and continuous subcutaneous infusions of apomorphine: results of a two-year, prospective follow-up. *Movement Disorders* 2002;**17** :188-91.
Study type	Before and after study
Evidence level	3
Study objective	To assess the effects of smaller amounts of apomorphine (APO) in subcutaneous (s.c.) infusions, administered for 2 years in fluctuating Parkinsonian patients in whom the levodopa (L-dopa) daily dose was reduced.
Number of patients	n=12 Parkinson's disease (PD) patients location: Czech Republic sites: single
Patient characteristics	Patients suffering from fluctuating advanced PD were followed-up for a period of 2 years. All patients were suffering from frequent on-off fluctuations, and from all types of L-dopa induced dyskinesias.

characteristics	Patient data (n=12)
Male: female	4: 8
Mean age, yr (SD)	64.3 (9.2)
Mean age at onset of PD, yr (SD)	49.8 (7.7)
Mean disease duration, yr (SD)	14.4 (6.3)
Mean duration of L-dopa treatment, yr (SD)	12.6 (5.4)
Mean duration of fluctuating PD, yr (SD)	3.6 (1.8)
Mean total UPDRS score before APO	68.3 (12.7)
Mean Hoehn and Yahr stage value	4.5 (range 4-5)

Intervention	The APO daily dose titration lasted 3 weeks, when infusions were introduced during the stay at hospital ward. The mean time needed to stabilise the dose in all patients was 8 weeks (range 6-10 weeks).
Comparison	Onset evaluation (when titration APO was stabilised)
Length of follow-up	2 year follow-up
Outcome measures	Home self-scoring diaries for the self-assessment of on-off fluctuations, the duration of off periods, and the duration (and severity) of all types of dyskinesias.

Effect size

- The mean daily dose of APO remained essentially stable after the completion of the titration phase (which has been taken as the onset for the next comparison and analysis) for the rest of the follow-up period
- No statistically significant differences were found between the mean APO doses at onset, or at 6, 12 or 24 months
- There was a significant difference between mean daily L-dopa dose at onset and at months 12 ($p \geq 0.005$) and 24 ($p \geq 0.005$)
- The difference between the mean values of daily off hours at onset was significant for months 6, 12 and 24 at the level of $p > 0.005$; the difference between values at months 6,12, and 24 was non-significant
- The number of off periods were reduced at month 6 vs. onset ($p \geq 0.05$)
- Differences between mean values of the UPDRS total score and subscores at onset and month 6,12 and 24 were all significant ($p \geq 0.005$)
- All patients suffering from peak-of-dose dyskinesia showed the % of dyskinetic time at onset and at 6,12, and 24 months was significant ($p \geq 0.01$)
- The differences in the occurrence of biphasic dyskinesias at onset and at months 6,12, and 24 were all significant ($p \geq 0.05$)

Side effects:

- The following were reported by patients: sleepiness (8), vertigo (3), orthostatic hypotension (3), panniculitis at injection site (1), rash at injection site (1), hallucinations (1)

Summary of patient outcome data:

Outcome (SD)	onset	Month 6	Month 12	Month 24
Mean daily dose of APO s.c. infusions, mg	30.8 (10.4)	30.4 (11.9)	30.4 (11.9)	31.4 (12.2)
Mean daily dose of L-dopa, mg	1650 (570)	1250 (640)	1150 (600)	1270 (750)
Mean off hours during waking day, %	54.2 (18.3)	13.8 (8.3)	10.8 (5.2)	10.9 (4.6)
Mean UPDRS total score	68.3 (12.4)	39.5 (9.3)	37.9 (8.2)	38.1 (9.1)
UPDRS I and II scores	27.8 (6.6)	17.7 (5.7)	17.8 (5.9)	18.7 (6.8)
UPDRS III	29.7 (6.2)	16.3 (6.8)	15.6 (6.5)	16.5 (7.1)
UPDRS IV	10.8 (1.2)	5.4 (1.1)	5.3 (1.2)	5.4 (0.9)
Mean values of duration of dyskinesia % of waking day				

	Peak-of-dose (n =7)	40.0 (20.8)	17.7 (12.6)	18.6 (10.4)	15.6 (11.3)
	End-of-dose (n =3)	13.3 (5.4)	5.0 (3.4)	0	0
	Biphasic (n =5)	36.0 (18.8)	14.0 (7.1)	11.0 (4.7)	10.0 (5.0)
	Off-period (n =2)	8.5 (2.0)	4.5 (1.0)	0	0
Source of funding	Non-profit				
Additional comments	➢ Before and after study ➢ Uncontrolled and non-randomised ➢ No diagnostic criteria ➢ No recruitment details ➢ No intention-to-treat analysis				
NCC CC ID (Ref Man)	19656				

Evidence Table **TxCM9** What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?	
Bibliographic reference	Manson AJ, Turner K, Lees AJ. Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: long-term follow-up study of 64 patients. *Mov Disord* 2002;**17**:1235-41.
Study type	Retrospective database analysis of before and after results
Evidence level	3
Study objective	To present the long-term results of apomorphine (APO) subcutaneous (s.c.) infusions since the strategy of monotherapy was introduced 6 years ago.
Number of patients	N=64 Parkinson's disease (PD) patients N= 45 monotherapy N=19 polytherapy Location: UK sites: single
Patient characteristics	A departmental database was used to identify all patients who had been on APO infusions since 1995 (n=64). This included all patients who had started therapy since 1995, as well as any who had begun

	before 1995 and were still on treatment at follow-up in 2000. 45 successfully achieved long-term monotherapy. 19 continued APO in conjunction with other oral anti-PD medication (polytherapy). 54% had previously received APO in some form. APO infusion was indicated only for patients with severe motor fluctuations or severely disabling dyskinesias, refractory to optimum oral medication. Characteristics: average age 60.3 years, 58% male, mean duration of PD 15.7 years, mean years of levodopa treatment 14.5 years, mean baseline levodopa dose 928 mg/d.
Intervention	10mg/ml administered diluted with normal saline 5mg/ml via ambulatory infusion pump
Comparison	Pre-APO administration assessments
Length of follow-up	33.8 months (range 4-108 months)
Outcome measures	Dyskinesia, doses, adverse events, withdrawals
Effect size	➢ 45/64 (70%) achieved monotherapy ➢ Mean time from initiation to stabilization on monotherapy in these patients was 4.6 months ➢ Once stabilised there was a reduction in dyskinesias of 56% ➢ Mean maximum reduction of dyskinesia per patient was 64% in monotherapy group and 30% in polytherapy group (n=19) ($p<0.005$) ➢ There was an increase in on time from 55% of waking day to 84% ($p<0.002$) ➢ Polytherapy group reduced LD therapy by 48% and still exhibited a marked reduction in dyskinesias as well as increase in on time ➢ Mean time to achieve maximum dyskinesia improvement was 12.1 months ➢ No significant difference between the mean APO dose at initial follow-up and at second follow-up ➢ The mean individual change per patient was 2.7% in daily dose and –0.4% in hourly rate ➢ Mean duration of APO infusion was 16.5 hours ➢ 9 patients were on 24-h infusions ➢ 25% of patients managed treatment independently, 50% managed with family help, 25% required outside nurse input ➢ There was a significantly ($p<0.05$, 81%) greater success rate amongst patients managing the system independently or with help from family than those requiring outside help ➢ Improvement in neuropsychiatric problems (especially in patients with depressive-type symptoms) (40% improvement in monotherapy group, 16% in polytherapy group, $p<0.05$)) Adverse events ➢ Nearly all developed subcutaneous skin nodules ➢ 35% complained of pain or discomfort at needle insertion site ➢ Skin complications (23%), daytime somnolence (31%), weight increase (60%) (mean increase of

	13% in individual body weight) Withdrawals ➢ 3 patients failed long-term APO stopping treatment within 6 months of initiation ➢ 10 patients died (cancer 3, pneumonia 3, myocardial infarction, 4)
Source of funding	Hospital
Additional comments	➢ Non-randomised ➢ Uncontrolled ➢ Non-blinded
Citation	
NCC CC ID (Ref Man)	19730

Evidence Table **TxCM9** What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?	
Bibliographic reference	Frankel JP, Lees AJ, Kempster PA, Stern GM. Subcutaneous apomorphine in the treatment of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1990;**53**:96-101.
Study type	Retrospective before and after study
Evidence level	3
Study objective	To report experience in 57 patients with disabling levodopa related motor oscillations treated with subcutaneous apomorphine (APO) for periods up to 32 months. (only results from infusion study reported here)
Number of patients	N=57 Parkinson's disease (PD) patients N=32 received APO injections N=25 received continuous APO infusion Location: UK sites: single
Patient characteristics	25 (15 men and 10 women) levodopa treated patients with idiopathic PD. In all cases disabling 'on-off' fluctuations in motor performance remained despite attempts to improve control by redistribution of levodopa doses, concurrent use of dopamine agonists (57%) or selegiline (91%), controlled release levodopa preparation (10%) and dietary protein restriction. The mean age was 58.8 years and disease

	duration was 17.8 years, duration of levodopa therapy 15.6 years, and Hoehn and Yahr stage of 4.1.. Exclusion criteria: patients with significant cardiovascular, hepatic or renal pathology; no patient with current evidence of neuropsychiatric disturbance or dementia.
Intervention	APO and (domperidone 20 mg orally) administered by mini-pump inserted subcutaneously into abdominal wall and the site changed at least daily. Continuous infusion was started at a rate of 1 mg/h then increased according to the individual response each day.
Comparison	Pre-infusion evaluations
Length of follow-up	32 months
Outcome measures	Dosage, off hours, levodopa dose, dyskinesias, adverse events and withdrawals
Effect size	➢ 1 mg of APO was given subcutaneously during an 'off' period ➢ Incremental increases of 1 mg of APO every 20 min was given until unequivocal motor response occurred ➢ Patients whose overall control remained unsatisfactory but were known to have good 'on' period response to single intermittent dose of APO were transferred to continuous APO infusion by mini-pump (n=25) ➢ 21 continued on long-term treatment for up to 32 months with little change in total APO requirements ➢ Infusion rates ranged between 1.25 to 5.5 mg/h (mean 3.3 mg/h) equivalent to 0.02 to 0.08 mg/kg/h (mean 0.05 mg/kg/h) with the majority of patients requiring between 2-4 mg/h ➢ Patients supplemented the continuous infusion with an average of 9.5 bolus doses per day (range 0-32) at a mean dose of 2.4 mg per bolus (range 1.0- 7.5) ➢ Onset of action following a booster dose was slightly slower in this group compared with those on intermittent injections, the mean delay being 9.0 minutes ➢ Total dose for individual patients varied between 24 and 207 mg (mean 89 mg/d) ➢ 7 patients (33%) took apomorphine for 24 hours per day with no apparent loss of efficacy Off hours ➢ Diary records from the first 11 cases treated showed a fall in mean total off hours from 10.1 to 3.8 ($p<0.01$) at one year ➢ Review of 21 who received long-term treatment (mean 22 months, range 5-32 months) showed a fall in mean total daily off hours from 9.9 to 4.5 ($p<0.01$) Levodopa ➢ Levodopa requirements fell in over 60% of patients irrespective of duration of treatment, with a mean reduction of 21.87% (from 992 to 775 mg/d, non-significant)

	➢ When the data for cases on treatment for over 18 months were analysed separately this reduction was 32% (p<0.02) ➢ Three patients were able to discontinue levodopa ➢ Seven patients (33%) continued to require oral domperidone at a mean daily dose of 35mg- the remainder were able to withdraw from the drug without ill effect ➢ 10 remained on some form of oral antiparkinsonian medication other than levodopa ➢ One patient elected to change back from infusion to injection Dyskinesias ➢ Most patients had only moderately severe drug-induced involuntary movements during 'on' periods ➢ Biphasic dyskinesias responded favourably, but improvement was maintained for at most a few days after which dyskinesias broke through and eventually occurred almost continually during 'on' periods Adverse events ➢ All patients on continuous therapy developed nodules at needle sites- severity was related to total daily dose of APO ➢ Visual hallucinations and confusion occurred in 3 patients ➢ Most patients initially experienced mild drowsiness usually accompanied by yawning ➢ Many reported occasional nausea ➢ Peripheral blood eosinophillia of up to 10% occurred shortly after starting therapy in all patients- this returned to normal in about half of the patients treated for over one year Withdrawal ➢ 4 withdrew early due to unacceptable increase in biphasic dyskinesia and one because of hallucinations ➢ Two late withdrawals due to marked oscillations in motor function with severe inter-dose dyskinetic movement on levodopa- she was unable to cope with the pump technique and returned to conventional therapy; the second patient developed late hypotonia and mutism
Source of funding	Public sector
Additional comments	➢ Non-randomised ➢ Uncontrolled ➢ Unblinded
Citation	
NCC CC ID (Ref Man)	19731

Evidence Table **TxCM9** What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?	
Bibliographic reference	Stocchi F, Vacca L, De Pandis MF, Barbato L, Valente M, Ruggieri S. Subcutaneous continuous apomorphine infusion in fluctuating patients with Parkinson's disease: long-term results. *Neurological Sciences* 2001;**22**:93-4.
Study type	Retrospective before and after study
Evidence level	3
Study objective	To report the clinical data of 30 patients having at least 5 years of treatment with subcutaneous continuous apomorphine (APO) infusion.
Number of patients	N=30 Parkinson's disease (PD) patients Location: Italy Sites: single
Patient characteristics	The patients had previously been treated with oral levodopa and other antiparkinsonian medication. Exclusion criteria: patients over 70 years of age, patients with previous history of psychiatric side effects from dopaminergic agents, those without a good response to levodopa, those suffering from dementia, heart disease problems or other systemic disorder. At the beginning of APO infusion: 21 men and 9 women, mean age of 62.0 $\pm$ 8.5 years, duration of disease 14.8 $\pm$ 5.5 years, Hoehn and Yahr score of 4.2 $\pm$ 0.8. They were on pharmacological treatment for 14.6 $\pm$ 4.7 years, with a mean levodopa dosage of 708 $\pm$ 245 mg/d, titrated in 4.1 $\pm$ 2.3 administrations during the day.
Intervention	APO at an initial dosage of 2 mg/h (all patients received oral domperidone 60mg/d) administered by modified insulin pump programmable for varying infusion rates. The needle was placed subcutaneously into the abdominal wall and was changd every day.
Comparison	Pre-infusion evaluation
Length of follow-up	5 years
Outcome measures	Dosage, movement abnormalities, side effects
Effect size	➢ Infusion rate was gradually increased according to therapeutic requirements of the patients ➢ Subcutaneous apo was administered without any additional antiparkinsonian medication between 8am and 8pm and discontinued overnight

	➢ The regime was maintained for one week, increasing dose to obtain the best clinical response Dosage ➢ APO dose averaged 4.3 ± 2.9 mg/h during the 12-hour infusion in all 30 patients (range 2.5- 8.0) and did not significantly change with time ➢ Daily oral levodopa dosage fell by about 2/3 during period of infusions (P<0.0001) ➢ Oral levodopa dosage did not change significantly during the follow-up period on infusion Movement ➢ Abnormal involuntary movements were also reduced during the early time of lisuride(??) infusion ➢ Tendency for dyskinesias to return after some years but never to pre-infusion levels Side effects ➢ Acute: nausea and dizziness which disappeared after 7-10 days of treatment ➢ During chronic phase almost all patients developed distressing skin reactions at the injection site
Source of funding	None stated
Additional comments	➢ Unblinded ➢ Non-randomised ➢ Uncontrolled ➢ Typo in paper re: lisuride infusion??
Citation	
NCC CC ID (Ref Man)	19733

Evidence Table **TxCM9** What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?	
Bibliographic reference	Pietz K, Hagell P, Odin P. Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up. *Journal of Neurology, Neurosurgery & Psychiatry* 1998;**65** :709-16.
Study type	Before and after study
Evidence level	3
Study objective	To investigate the therapeutic response and range of side effects during long term treatment with apomorphine in advanced Parkinson's disease (PD).

Number of patients	N=60 advanced PD patients enrolled N=49 entered study phase (11dropped out during test phase) N=25 treated with subcutaneous **infusion** therapy Location: Sweden Sites: 1
Patient characteristics	25 patients; 14 men and 11 women; mean age 64.7 years and mean duration of disease 16.0 years.. Inclusion criteria: daily disabling 'wearing off', 'on-off' motor fluctuations, or diphasic dyskinesias despite optimised peroral antiparkinsonian treatment. Only patients fulfilling criteria for idiopathic PD, including positive levodopa and apomorphine responses were included. Exclusion criteria: cardiovascular, renal, haematological, or psychiatric diseases.
Intervention	Apomorphine (APO) infusions or injections (results below only pertain to infusions). APO portable infusion pumps. Infusion sets were changed at least once, often twice, a day.
Comparison	Pre-treatment
Length of follow-up	Median 44.0 months
Outcome measures	
Effect size	➢ Evaluation of most of the 49 patients was done at 2 time points ➢ The group who received APO infusions were evaluated after a mean of 20.2 or 54.0 months ➢ APO test was performed on all patients to determine responsiveness ➢ 12 to 24 hours before APO administration the patient was given domperidone (10-20 mg, 3x daily)- after initiation of APO treatment the domperidone dose could be reduced in most cases by 10 mg/d over first 2 weeks and finally stopped ➢ Levodopa doses were reduced by at least 30%, in most cases about 50% before APO infusions (given as continuous 24 h infusions) were started ➢ Other dopamine agonists and anticholinergic drugs were stopped, whereas selegiline remained unchanged ➢ The initial dose was 1 mg/h which was subsequently increased in a step-wise manner by no more than 1 mg/h/d until optimal effect or side effects occurred APO and LD doses ➢ Daily LD dose reduced in 24/25 patients (p=0.003) ➢ Of the 24 patients reducing LD- 8 were able to stop altogether ➢ 16 who did not stop still reduced (p<0.001) total LD daily intake Clinical effects ➢ Daily time 'off' was significantly reduced (p<0.001) from 50% to 25%

	➢ The number of off periods increased slightly but not significantly ➢ The median Hoehn and Yahr stages improved in both on (p=0.02) and off (p<0.001) states ➢ Schwab and England scores also improved in the on and off states (p<0.001) ➢ Dyskinesias scores remained largely unchanged for the intensity and duration ➢ Global impression rating: no patient described overall worsening of parkinsonism, 3 felt unchanged, 6 experienced slight improvement and 16 a clear improvement ➢ Physicians rating: no patient worsened, two patients were unchanged (the same who described themselves as unchanged), seven slightly improved and 16 clearly improved Adverse events ➢ Minor irritations (nodules) were present in all patients with APO but none led to termination of treatment ➢ One patient developed an abscess which was successfully treated ➢ One patient with diabetes mellitus developed necrotic areas at the infusion sites ➢ Four patients developed orthostatic hypotension ➢ 2 noticed increase in urinary urge, one developed diarrhoea ➢ One patient experienced nausea ➢ Psychiatric changes: 5 became psychotic, 3 had visual hallucinations, one had intermittent illusions, one was confused, and one had occasional nightmares Withdrawal rates ➢ After a test period of 2 months- it was decided whether the patient should continue ➢ 11/60 stopped treatment during this period and are not included in main results ➢ 5 patients dropped out of the infusion group ➢ 3 dropped out because of psychiatric side effects, 2 because of insufficient effect ➢ Due to disease progression 4 patients changed from injection to infusion- the data from these patients was included in the infusion group ➢ No patient changed from infusion to injection
Source of funding	Private and public funding
Additional comments	➢ Intention to treat analysis of the 49 patients ➢ Non-randomised ➢ Unblinded evaluation ➢ Uncontrolled evaluation
Citation	
NCC CC ID (Ref Man)	19734

Evidence Table **TxCM9** What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?	
Bibliographic reference	Hughes AJ, Bishop S, Kleedorfer B, Turjanski N, Fernandez W, Lees AJ *et al*. Subcutaneous apomorphine in Parkinson's disease: response to chronic administration for up to five years. *Movement Disorders* 1993;**8**:165-70.
Study type	Retrospective before and after study
Evidence level	3
Study objective	To report the long-term results using subcutaneous apomorphine (APO) with follow-up periods of up to 5 years, and compare these with the therapeutic response obtained after one year of sustained treatment.
Number of patients	N=108 patients with Parkinson's disease (PD) N=77 intermittent subcutaneous injections N=31 continuous s.c. infusions Location: UK Sites: single
Patient characteristics	Since 1986, 108 patients (64 men and 44 women) with idiopathic PD have been on APO, with 86 (52 men, 34 women) still receiving treatment in 1991. The mean age was 60.7 years (range 27-78), mean duration of disease 15.5 years (range 4-32), and mean duration of levodopa treatment was 13.8 years (range 4-24). All patients had developed disabling 'on-off' fluctuations after a mean period of 8 years (range 1-18) of sustained levodopa treatment and had already tried all standard approaches to management. 22 patients (12 male, 10 female) were treated with continuous infusions for >1 year. Mean age 60.6 years, mean duration of disease 19.2 years, mean duration of levodopa treatment 16.6 years, mean duration of motor fluctuations 9.3 years.
Intervention	Only continuous s.c. infusions (average 80.8 mg/d) will be discussed below. Patients were treated with domperidone 20 mg 3x daily (gradually reduced over the first 3-6 months and discontinued where possible).
Comparison	Pre-apomorphine assessments

<table>
<tr><td>Length of follow-up</td><td>Conducted every 2-3 months on an outpatient basis. Mean follow-up 36.5 months.</td></tr>
<tr><td>Outcome measures</td><td>On time, off time, levodopa dose, apomorphine dose, adverse events, withdrawal rates</td></tr>
<tr><td>Effect size</td><td>

31 patients were initially treated with continuous subcutaneous (s.c.) infusions of APO using a portable syringe pump (with the exception of 4 patients on steady-state 18-h APO and 2 on 24-h continuous pulsed APO)
Patients received continuous s.c. infusions supplemented by APO boluses throughout the waking day

Clinical efficacy

Mean % of daily on time achieved after stabilization on APO remained stable in most patients (despite slight reduction in APO dosage)
Mean initial reduction in off hours was >50% (p<0.01) was maintained at 1 year follow-up

<table>
<tr><th></th><th>Before APO</th><th>After APO</th><th>At review</th></tr>
<tr><td>Levodopa dose (mg/d)</td><td>986</td><td>850</td><td>1141</td></tr>
<tr><td>APO dose (mg/d)</td><td></td><td>80.8*/93.2**</td><td>70</td></tr>
<tr><td>Total off hours per waking day</td><td>9.5</td><td>3.5*/3.8**</td><td>3.9</td></tr>
</table>
* When initially stabilized; ** after 1 year of use

Adverse events (n=22, at mean follow-up of 36.5 months)

Cutaneous moderate to severe (n=9), persisting intermittent nausea (n=4), mild sedation (n=3), neuropsychiatric (mainly mild)(n=8), haemolytic anaemia (n=2)
N=9 described worsening of dyskinesias at 12 months (probably reflecting both an increase in both severity and duration)

Withdrawals

4 patients who had been treated successfully for 2-4 years by s.c. died
in none was APO infusion considered to be responsible for patient’s death
2 other patients were switched from continuous to intermittent injections due to local cutaneous adverse events
3 ceased using APO (one had undergone fetal/nigral implantation, one developed late hypotonia and mutism, the other developed increasingly severe on period dyskinesias)

</td></tr>
<tr><td>Source of funding</td><td>Public sector</td></tr>
<tr><td>Additional comments</td><td>Unblinded</td></tr>
</table>

	➢ Non-randomised ➢ Uncontrolled
Citation	
NCC CC ID (Ref Man)	19735

Evidence Table **TxCM9** What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?	
Bibliographic reference	Colzi A, Turner K, Lees AJ. Continuous subcutaneous waking day apomorphine in the long term treatment of levodopa induced interdose dyskinesias in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry* 1998;**64**:573-6.
Study type	Retrospective 12-month before and after study
Evidence level	3
Study objective	To determine whether continuous waking day dopaminergic stimulation with the dopamine agonist apomorphine (APO) can reduce levodopa increased dyskinesias in Parkinson's disease (PD).
Number of patients	N=19 PD patients N= 10 (group 1: APO monotherapy) N=9 (group 2: levodopa-induced motor complications) Location: UK Sites: single
Patient characteristics	Group 1: 3 women and 7 men with levodopa responsive Parkinson's disease who had been treated with waking day APO monotherapy for a mean duration of 4.3 years. These patients received no oral antiparkinsonian drug treatment from the time when the PO pump was started in the morning to when it was turned off at night. The mean age was 60.3 years, mean duration of PD was 18.8 years and median duration of APO therapy was 5.8 years. Group 2: Nine patients who were experiencing unpredictable refractory motor fluctuations and severe levodopa induced dyskinesias, were switched to continuous waking day APO monotherapy using syringe pump. Mean age was 57.1, mean duration of disease was 15.8 years, mean daily dose of LD was 758.85 mg/d, and median duration of levodopa therapy was 13.1 years.

	Patients with biphasic dyskinesias (known to be ineffectively managed by APO pump were excluded)
Intervention	Continuous waking day APO monotherapy using syringe pump. Group 2 were receiving a mean dose of 67.5 (range 0-300) mg/d before onset of levodopa reduction and stabilized on a dose of 77.6 (range 30-300) mg/d.
Comparison	Pre-APO therapy assessments
Length of follow-up	Mean duration of APO therapy was 34.8 months (range 9 months to 9 years)
Outcome measures	Dosage, off time, dyskinesias, adverse events, follow-up
Effect size	➢ In both groups levodopa was slowly reduced (on average 50mg a week) with concomitant increase in APO if needed ➢ Mean time needed to stabilize patients on waking day APO was 3.3 months ➢ All patients received subcutaneous APO challenge tests at the beginning to confirm that they had interdose dyskinesias Dosage ➢ Nine patients were able to stop levodopa therapy completely ➢ 4 continued to take an early morning dose of standard levodopa ranging from 62.5 to 500 mg (mean 289.5 mg) ➢ Another 5 continued to take a nocturnal dose of controlled-release formulation at a mean dose of 400 (range 250-500) mg ➢ One needed both and early morning and nocturnal controlled release doses ➢ 4 continued to take peripheral domperidone in a median daily dose of 35 (range 10-60) mg/d ➢ Mean dose of APO calculated after one year was not significantly increased (90.6 mg/d) ➢ No trend for the dose of APO to be continually increased was found Clinical efficacy ➢ APO led to a further reduction in the median daily duration of off time from 35.2% to 16% ($p<0.001$) ➢ UPDRS score for disability of dyskinesia: interdose dyskinesia disability was reduced by a mean of 65% and duration by 85% ($p<0.001$) ➢ Time course of reduction in dyskinesia severity was variable and showed a progressive decline over several months after patient was established on waking day APO (mean delay to reach optimum and anti-dyskinetic effects after establishing APO therapy was 18 weeks) Adverse events ➢ 15/19 experienced small abdominal cutaneous nodules at needle site ➢ 4 developed abdominal wall scarring with ulceration

	➢ Neuropsychiatric side effects seen in 3 patients (visual hallucinations and mild confusion) ➢ 2 patients developed a paranoid psychosis (did not have to discontinue APO therapy) Follow-up ➢ Analysis of clinical data from group 1 at time of review (mean 4.5 years) did not substantially differ from data obtained at 1 year ➢ 6 patients had virtually continued sustained on states with only an irregular and very rare return of parkinsonian disabilities for periods of less than 15 minutes at a time ➢ 3 patients developed neuropsychiatric side effects after a mean duration of treatment of 3.7 years
Source of funding	None stated
Additional comments	➢ Non-randomised ➢ Uncontrolled ➢ Unblinded
Citation	
NCC CC ID (Ref Man)	19736

Evidence Table **TxCM9** What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?	
Bibliographic reference	Gancher ST, Nutt JG, Woodward WR. Apomorphine infusional therapy in Parkinson's disease: Clinical utility and lack of tolerance. *Movement Disorders* 1995;**10**:37-43.
Study type	3-month retrospective follow-up of best and after results of treatment
Evidence level	3
Study objective	To investigate whether the response to apomorphine (APO) changed after chronic treatment by comparing the relationship between APO dose and motor response before and after a 3-month treatment period.
Number of patients	N=7 Parkinson's disease (PD) patients Location: USA sites: single
Patient characteristics	Seven patients with PD exhibiting disabling motor functions or dyskinesias despite multiple adjustments of oral antiparkinsonian medication. Average age 61 (range 36-73) years, average Hoehn

	and Yahr stage of disease is 4, average disease duration 17.6 years (range 6-36 years), average levodopa dose treatment 12 years, average levodopa dose 992.9 mg/d (range 150- 2200), average levodopa doses per day 7.4. Most disabling symptoms included dyskinesia (2), off dystonia (1), wearing off (2) unpredictable (2).
Intervention	Subcutaneous infusion of APO during waking hours. The initial infusion rate was selected by doubling the smallest test APO dose that improved parkinsonism for ≥10min and administering this dose over each hour. All patients were initially pre-treated with domperidone 60mg/d (5/6 discontinued during the study). Levodopa was taken in addition to APO if 'off' periods persisted despite increasing APO rate.
Comparison	Pre-APO assessments
Length of follow-up	3 months
Outcome measures	Dose-response, clinical efficacy (motor fluctuations), levodopa dose, side effects, withdrawals
Effect size	➢ Patients were followed at intervals over 3-months by telephone calls and clinic visits ➢ For 3 to 5 days before entry into the study and at monthly intervals, the patient or spouse kept an hourly record of periods of good mobility and of recurrent parkinsonism ('on','off') and of concomitant PD meds Dose-response ➢ Duration of anti-PD effect was correlated to dose of APO (P<0.001) ➢ Larger doses produced longer duration of action ➢ The magnitude of each measure of parkinsonism was largely 'all or none' and no significant dose-response relationship observed Clinical efficacy ➢ Motor fluctuations decreased during the period of APO infusion ➢ Number of off periods was reduced by 58% and corresponding 'on' hours per day increased accordingly (p<0.01) ➢ Daily dose of levodopa and number of doses per day were reduced by one half (p<0.02) Side effects ➢ All patients developed s.c. nodules ➢ No patient exhibited cutaneous necrosis or ulcerations ➢ Other side effects: rhinorrhea (2), serious otitis media (1), nausea and hiccups (1), recurrent diarrhea (1), confusion and emotional lability (1), euphoria and dysarthria (1), Withdrawals ➢ One patient developed recurrent diarrhea and discontinued APO after 6 weeks of treatment
Source of funding	Public sector

Additional comments	➢ Non-randomised ➢ Small sample size ➢ Unblinded ➢ uncontrolled
Citation	
NCC CC ID (Ref Man)	19737

Evidence Table
TxCM9
What is the effectiveness of apomorphine vs. standard oral treatment in complex Parkinson's disease?

Bibliographic reference	R. Katzenschlager, A. Hughes, A. Evans, A. J. Manson, M. Hoffman, L. Swinn, H. Watt, K. Bhatia, N. Quinn, and A. J. Lees. Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson's disease: a prospective study using single-dose challenges. *Movement Disorders* 20 (2):151-157, 2005.
Study type	Before and after study
Evidence level	3+
Study objective	To assess the effects of continuous subcutaneous (SC) apomorphine (APO) on drug induced dyskinesias administered for 6 months in fluctuating Parkinsonian patients, and to assess whether single-dose levodopa (L-dopa) and APO challenges before and after continuous APO therapy demonstrate a reduction in dyskinesias.
Number of patients	n=12 Parkinson's disease (PD) patients location: United Kingdom, Australia sites: two
Patient characteristics	Patients suffering from PD with motor fluctuations and disabling on period dyskinesias who were refractory to oral medication adjustments were given SC APO and followed-up for 6 months.

Baseline characteristics	Patient data (n=12)
Male: female	7: 5
Mean age, yr (range)	61.3 (51-80)
Number per study site	8 (UK); 4 (Australia)
Mean disease duration, yr (range)	14.5 (6-23)*
Mean duration of L-dopa treatment, yr (SD)	12.6 (5.4)

<table>
<tr><td></td><td>
<table>
<tr><td>Mean L-dopa dose</td><td>1.356 mg/day (UK); 2.175 mg/day (Australia)</td></tr>
<tr><td>Mean Hoehn and Yahr stage value</td><td>2.7 (on); 4.0 (off)</td></tr>
</table>
*11.8 (UK); 18.8 (Australia); p<0.05</td></tr>
<tr><td>Intervention</td><td>Pre-treatment with domperidone (20mg t.i.d) to block peripheral dopamine receptors, and thereafter optimum APO dose determined by challenges with increased SC doses. During inpatient stay, hourly APO flow rate increased and oral medication decreased, with further adjustments made during monthly outpatient visits and at 6 months re-assessment of treatment. Calculation of daily L-dopa equivalent unit (LEU) dose for other drugs based on theoretical equivalence to L-dopa. SC APO challenges given in increasing doses upto 9mg. L-dopa challenges carried out on same or following day once APO effect had worn off and UPDRS motor scores had returned to baseline.</td></tr>
<tr><td>Comparison</td><td>Single-dose L-dopa and APO challenges performed at baseline and 6 months later at same time of day and with identical doses.</td></tr>
<tr><td>Length of follow-up</td><td>Six months</td></tr>
<tr><td>Outcome measures</td><td>Patient diaries and self-assessment forms used to record off hours/day, on-time duration, UPDRS score, Lang and Fahn scale, Severity and duration of symptoms, and dosages of L-dopa, LEU and APO.

Video recordings of patient behaviour rated independently by two blinded assessors using modified Goetz and AIMS rating scales measured effects of L-dopa and APO challenges on dyskinesia measures at baseline and 6 months.</td></tr>
<tr><td>Effect size</td><td>Summary of patient measures of dyskinesias, PD, and dosages of L-dopa, L-dopa equivalent unit (LEU), and APO:
<table>
<tr><th>Outcome</th><th>Baseline</th><th>6 months</th><th>Change baseline – 6 months</th><th>Statistical difference (6 months versus baseline)</th></tr>
<tr><td>Off hours/day</td><td>6.3 (2.7)</td><td>3.9 (2.1)</td><td>-38%=2.4 hrs</td><td>p<0.05</td></tr>
<tr><td>On-time duration (% waking day)</td><td>66.2 (13.1)</td><td>79.1 (10.0)</td><td>+20%</td><td>p<0.01</td></tr>
<tr><td>UPDRS 32 (dyskinesia duration)</td><td>2.1 (0.8)</td><td>1.3 (0.7)</td><td>-40%</td><td>p<0.01</td></tr>
<tr><td>UPDRS 33 (dyskinesia severity)</td><td>2.4 (1.1)</td><td>1.7 (0.8)</td><td>-31%</td><td>p<0.05</td></tr>
<tr><td>Lang & Fahn (ADL)</td><td>15.1 (3.6)</td><td>12.0 (3.4)</td><td>-21%</td><td>p<0.05</td></tr>
</table></td></tr>
</table>

Severity + duration in diaries (cm on VAS)	39.0 (25.5)	16.1 (9.4)	-58%	p<0.01
L-Dopa (mg/day)	1629 (750-3700)	735 (100-1850)	-55%	p<0.01
LEU (mg/day)	1867 (900-3834)	794 (125-1884)	-58%	p<0.01
APO (infusion mg/day)	-	75.2 (45.0-127.5)	-	-

Summary of objective dyskinesia measures during L-dopa and APO challenges at six months:

	Baseline	6 months	Change	Statistical difference (6 months versus baseline)
L-dopa challenges				
AIMS	8.9 (4.6)	4.9 (2.8)	-44%	p<0.01
Goetz	2.2 (0.7)	1.3 (0.8)	-40%	p<0.01
APO challenges				
AIMS	9.7 (4.9)	5.9 (2.9)	-39%	p<0.01
Goetz	2.2 (0.8)	1.4 (0.8)	-36%	p<0.01

Side effects:

- Type of adverse event and number of patients reporting included: Positive direct antiglobulin test without associated haematological changes (5), mild self-limiting leg edema (2), mild to moderate skin nodules reflecting focal panniculitis (9), mild cognitive dysfunction (1), mild treated depression before pump treatment (5).

Source of funding	Conflicts of interest statement: Two of the authors received fees for speaking, and one received fees for consulting and organising education for the pharmaceutical company that manufactures APO in the UK.
Additional comments	➢ Before and after study ➢ Uncontrolled and non-randomised ➢ Patient behaviour rated independently by two blinded assessors ➢ Patients from the Australia study site had more advanced disease, and showed less changes in medication and dyskinesia reduction that those from the UK study site.

	➢ AIMS scale designed to assess involuntary movements in psychiatric patients, rather than dyskinesias in PD patients.
NCC CC ID (Ref Man)	19993

Surg1 – section 8.2

Evidence Table ***SURG 1*** What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	
Bibliographic reference	Tavella A, Bergamasco B, Bosticco E, Lanotte M, Perozzo P, Rizzone M *et al*. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: Long-term follow-up. *Neurological Sciences* 2002;**23**:S111-S112.
Study type	24-month follow-up before and after study
Evidence level	3
Study objective	To evaluate the effectiveness of high frequency electrical stimulation in patients affected by idiopathic PD, who underwent surgery for the implantation of a bilateral stimulating system of STN.
Number of patients	N= 47 PD patients Location: Italy Sites: single
Patient characteristics	PD patients, 18 women, 29 men; mean age 62.8 years; mean disease duration 15.6 years; average duration of levodopa therapy 14.5 years; mean score on Hoehn and Yahr scale in off phase was 4. Inclusion criteria/exclusion not stated.
Intervention	Bilateral STN deep brain stimulation (no details given)
Comparison	Pre-operative assessments
Length of follow-up	24 months
Outcome measures	UPDRS, levodopa dose, stimulation parameters, adverse events, predictive factors
Effect size	➢ A clinical evaluation of stimulation effectiveness was performed in 39 patients at 3 months, 21

	patients at one year and 7 patients at 2 years post-op ➢ Patients were evaluated in the off phase pre-op after a 12 hour withdrawal of all antiparkinsonian medication and after the administration of a supramaximal dose of levodopa (150-400mg) (on phase) ➢ After surgery the clinical assessment was evaluated in 4 conditions: stim on-med off, stim off-med off, stim off-med on (with the same dose of levodopa) and stim on-med on Stim on-med off: ➢ STN DBS was responsible for a 58% improvement in UPDRS part II score (ADL) at 3- month follow-up, 57% at one year and 55% at 2 years (vs. pre-op off state) ➢ Differences between pre-op UPDRS part II and post-op values were significant ($p<0.05$) ➢ No differences were observed between the 3 post-op stim on-med-off conditions ➢ UPDRS part III (motor) improved 56.4% improvement at 3 months, 58.2% at one year and 63.4% at 2 years ➢ Differences between med off condition and stim on-med off post-op conditions in absence of statistical differences between post-op controls (3 months, 1 year, 2 years) ➢ Improvement of motor fluctuations and drug-induced dyskinesias (UPDRS IV, complications of the therapy) was 80% at 3 months and 1 year and 90% in 2 years Drug dosages ➢ The clinical effectiveness of STN DBS was responsible for a reduction in the mean daily levodopa dosage from 850 mg/day to 172 mg/day (80%) at 3 months of follow-up, to 232 mg/d (73%) at one year and 160.7 mg/d (81%) at 2 years after surgery ➢ These values showed a significant difference between pre-op and post-op (p value not stated) but no differences between the 3 post-op values ➢ At 3 month follow-up, 12 patients (31%) no longer took levodopa and 6 of them took no dopaminergic therapy, 9 patients were taking only and 18 assumed levodopa and small doses of dopamine agonists ➢ At one year follow-up 6 patients (29%) no longer took levodopa and 3 took only dopamine agonists; 4 took only levodopa and 11 took levodopa and dopamine agonists Stimulation parameters ➢ Voltage progressively increased from a mean value of 2.56V immediately after surgery to 2.96V at 3 months, 3.21V at 1 year and 3.34V at 2 years Adverse events ➢ After surgery 7/47 patients evaluated showed transitory mental confusion, 2 patients showed hypophonia and 1 patient had transitory eye opening apraxia

	➢ There was one case of thrombophlebitis and 1 case of subcutaneous infection Predictive factors ➢ Younger age at the moment of operation and a short duration of complicated phase of disease are related to a better clinical outcome ➢ Patients were divided into two groups: older and younger than 60 years at time of operation ➢ No significant differences between the two groups for UPDRS II, III, and IV scores ➢ Two groups showed same degree of clinical improvement ➢ Mean daily levodopa dosage taken by patients older than 60 years was 30% greater at the 3-month follow-up and 40% greater at 1 year (non-significant) ➢ No differences in voltage values utilized were observed
Source of funding	None stated
Additional comments	➢ No details of surgical procedure ➢ No details of outcome methods (definitions) ➢ Only outcome % given- no raw data (ranges, means) ➢ No indication of how patient's were selected/recruited ➢ No inclusion/ exclusion criteria state patient population ➢ Non-controlled ➢ Unblinded
NCC CC ID (Ref Man)	389

Evidence Table ***SURG 1*** What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	
Bibliographic reference	Herzog J, Volkmann J, Krack P, Kopper F, Potter M, Lorenz D *et al*. Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. *Movement Disorders* 2003;**18**:1332-7.
Study type	2-year follow-up before and after study
Evidence level	
Study objective	To assess the long-term outcome of deep brain stimulation of subthalamic nucleus (STN) in

	Parkinson's disease patients who are affected by long-term complications of dopaminergic therapy such as motor complications and severe dyskinesias.
Number of patients	N=48 PD patients Location: Germany Sites:
Patient characteristics	48 patients with idiopathic PD (30 men, 18 women; 60 ± 6 years of age; disease duration of 15 ± 5 years) who suffered from severe motor fluctuations and dyskinesias unresponsive to medical treatment. Patients diagnosed according to the UK PDS brain bank criteria. No patient showed any signs of dementia.
Intervention	STN deep brain stimulation (see paper for full details)
Comparison	Pre-operative assessments
Length of follow-up	2 years
Outcome measures	UPDRS motor score (part III), medication reductions, activities of daily living (ADL), stimulation parameters, adverse events and withdrawal rates
Effect size	Pre-operative (pre-op) ➢ Motor assessment was performed in the off-state after 12 hours withdrawal of antiparkinsonian medication ➢ Response to levodopa was evaluated after taking 1.5-fold of the usual morning dose ➢ UPDRS score was assessed when patient achieved their best on-state score (usually one hour after medication) ➢ Before operation all patients showed an improvement of 30% in part III of the UPDRS by administration of levodopa Post-operatively (post-op) ➢ Patients were assessed in all 4 possible treatment conditions: without medications (med-off) and without stimulation (stim-off), med-off and stimulation on (stim-on), med-on and stim-off, and med-on and stim-on UPDRS III (motor) ➢ Post-op all patients showed an improvement in UPDRS III in med-off and stim-on ➢ At 6 months follow-up score was reduced by 50.9% vs. pre-op ($p<0.001$) ➢ The effect by stimulation did not differ significantly from the best pre-op improvement by levodopa ➢ Additional levodopa led to a further improvement of UPDRS III by 32% (on med and on stim) ($p<0.001$) ➢ Tremor (mean of item 20 and 21) was improved the most by stim on with a reduction of 71.6% vs.

	pre-op (p<0.001) ➢ Additional administration of levodopa caused a nearly complete abolition of tremor stim on and (med on)(p<0.001) ➢ Stim on also reduced subscores of rigidity, limb bradykinesia, and axial symptoms by 59.2%, 52.8% and 54.6% respectively ➢ Levodopa resulted in a further reduction of these items (less pronounced than tremor) ➢ Facial expression and speech (pre-op off med vs. post-op off med and on stim) showed an improvement of only 31.9% and 19.7% ➢ Amelioration of motor symptoms remained stable at subsequent visits ➢ Pre-op vs., post-op UPDRS III total score was reduced by 57.5% after 12 months (off med and on stim) and by 57.3% after 24 months (p<0.001 for both) ➢ Levodopa caused an additive reduction of 33.3% and 35.1% respectively ➢ At 24 months in on med and on stim- patients were without tremor ➢ Dyskinesias were remarkably reduced post-op ➢ 83% reduction after 6 months (p<0.001), 87% after 12 months (p<0.001) and 85% after 24 months (p<0.001) ➢ Pre-op 29 patients were suffering from off dystonia (item 35) vs. post-op where only a few complained of early morning dystonia Medications ➢ In the majority of patients- dopaminergic medication could be reduced within the first days post-op ➢ This caused a reduction in pre- and post-op levodopa equivalent daily dose (LEDD) ➢ LEDD was reduced 48.8% after 6 months (p<0.001), 42.4% after 12 months, and 67.8 after 24 months ➢ 5 patients were managed post-op without any medication (11%) (attributed to placement of electrodes) ADL ➢ In med off was improved slightly post-op versus pre-op ➢ At 6 months follow-up an improvement of 52.5% (p<0.01) ➢ Improvement persisted with a reduction of ADL score by 49.2% and 43.2% at 12 and 24 months ➢ Hoehn and Yahr staging was improved in med off by 48.6%, 48.2% and 42.8% at 6,12, and 124 months ➢ Schwab and England score was improved from 47% pre-op to 79% post-op- nearly identical values were observed in subsequent visits Stimulation parameters

	➢ 43/48 (90%) of patients had a continuous monopolar stimulation ➢ 5 patients were treated by bipolar stimulation on at least one side ➢ Most changes in stimulation took place in the first post-op weeks ➢ After 6 months only 2 patients had active contacts changed because of better stimulation effect ➢ At 6 months parameters for both left and right electrodes averaged: amplitude 2.9 ± 0.6 V, frequency 134 ± 12 Hz, pulse width 62 ± 9 μsec ➢ At subsequent visits no significant changes were observed ➢ After 24 months there was a slight tendency for increases in frequency and pulse width Adverse events ➢ Serious adverse events were rare ➢ Relevant side effects, necessitating surgical intervention included: intraoperative subdural haematoma without any neurological sequelae (n=1), minor intracerebral bleeding at the side of the trajectory lead, dislocation of the impulse generator from site of implantation ➢ Transient psychiatric symptoms were the most common therapy-related side effect including: transient perioperative confusional state (n=7) or psychotic syndromes (n=2), hypomanic behaviour (n=2), and depression (n=5) ➢ In all patients side effects improved quickly without any specific therapy ➢ Nearly all patients reported transient paresthesias associated with adjustment of stimulation parameter ➢ Permanent side effects by stimulation to adjacent structures were rare: dysarthria (n=2) and apraxia of one eyelid opening (n=3) ➢ Disabling dyskinesia beyond the first 3 months after beginning of stimulation occurred in 2 patients Withdrawals ➢ All patients were followed-up for 6 months ➢ 32 (68%) patients were followed-up for 12 months and 20 (43%) patients for 24 months
Source of funding	None stated
Additional comments	➢ Consecutive series of patients treated between January 1999 to March 2002 ➢ Rating physician was informed of status of stimulation and medication (unblinded) ➢ Non-controlled
NCC CC ID (Ref Man)	19698

Evidence Table

SURG 1

What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?

Bibliographic reference	Limousin P, Speelman JD, Gielen F, Janssens M, Benabid A, Pollak P *et al*. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *Journal of Neurology, Neurosurgery & Psychiatry* 1999;**66**:289-96.
Study type	12-month follow-up before and after study
Evidence level	3
Study objective	To evaluate the efficacy and the morbidity of thalamic stimulation in a large number of patients with parkinsonian or essential tremor.
Number of patients	N=111 patients N=74 parkinsonian N=37 essential tremor Location: France, UK, Amsterdam, The Netherlands Sites: 13
Patient characteristics	Inclusion criteria: idiopathic PD or essential tremor with pharmacotherapy resistant tremor, present during the major [part of the day; tremor score rated 3 or 4 on the 5 point tremor scales (0= no tremor to 4= very severe tremor) for the limb intended for treatment, ability to abide by protocol and operate stimulator. Parkinsonian and essential tremor medications had been prescribed to the maximum tolerated doses for at least 3 months before enrolment. Included patient characteristics:

	Parkinson's disease	Essential tremor
N=	73	37
Unilateral/ bilateral implant (n=)	57/16	28/9
Sex (M:F)	47 : 26	24 : 13
Mean age at surgery (years ± SD)	61.5 ± 10.8	63.1 ± 12.7
Mean duration of disease (years ± SD)	10.0 ± 5.6	26.6 ± 14.5

Intervention	Ventrointermediate (Vim) thalamic nucleus deep brain stimulation- see paper for details
Comparison	Pre-operative assessments

Length of follow-up	12 months
Outcome measures	UPDRS, Activities of daily living (ADL), dyskinesias and drug modifications, adverse events, stimulation parameters
Effect size	Pre-operative (pre-op) assessment ➢ All parkinsonian patients were evaluated using the UPDRS rating scale in the defined 'off' condition (12 hours without medication) ➢ Patients were scored less than one month pre-operatively for baseline assessment and 1 week and 3,6 and 12 months post-operatively (post-op) Post-op assessment ➢ The effect of stimulation (on stimulation versus off stimulation), the effect of the procedure (before surgery versus on stimulation), and the effect of implantation (before surgery versus on stimulation) on clinical score was assessed ➢ ADL, dyskinesias and drug dosage were compared to baseline Tremor ➢ At 3 and 12 months follow-up both upper and lower limb tremor were significantly reduced by stimulation and by the procedure ($p<0.001$) ➢ No significant effect by the implantation alone was shown ➢ Rest tremor of the contralateral upper limb was reduced at least 2 points in 85% of the electrodes ➢ Analysis was repeated for a subgroup of unilaterally implanted patients (n=57) to assess ipsilateral effects ➢ Significant reduction of contralateral tremor by stimulation and procedure was confirmed in this subgroup at 3 and 12 months ($p<0.001$) ➢ Before surgery patients had generally very mild tremor on the hemibody ipsilateral to surgery ➢ At 3 months, off stimulation ipsilateral tremor was non-significantly increased in comparison with baseline and was significantly reduced by stimulation ($p<0.001$) ➢ At 12 months, off stimulation ipsilateral tremor was back to baseline and the effect of the stimulation was not significant UPDRS motor (part III) ➢ Procedure and stimulation significantly reduced UPDRS III scores for total population (n=73) ➢ Reduction mainly related to effect of stimulation as off stimulation score remained the same ➢ Symptoms other than tremor were mild pre-op ➢ Stimulation significant reduced contralateral akinesia and rigidity at 3 and 12 months follow-up ($p<0.001$) ➢ Stimulation had the same effect on contralateral akinesia and rigidity in the group of unilaterally

	treated patients- whereas ipsilateral akinesia and rigidity remained unchanged ➢ Axial symptoms, speech, postural stability, and gait were not affected by unilateral or bilateral surgery ➢ Levodopa induced dyskinesias were slightly but non-significantly reduced 12 months after surgery ➢ Off dystonia was unchanged after surgery ADL ➢ Schwab and England score and UPDRS part II scores were improved after surgery as a consequence of improvement in motor function ($p<0.001$) ➢ Item 8 (handwriting) and item 16 (invalidity related to tremor) of UPDRS II were significantly reduced ($p<0.001$) Drug modifications ➢ 7 patients had no antiparkinsonian drugs at time of surgery ➢ 5 had tried levodopa at max dose and stopped because tremor was not controlled ➢ 2 other patients had decided not to try levodopa ➢ 65 were still taking levodopa at surgery ➢ The number of patients taking medication was not changed and mean doses were non-significantly reduced at 12 months after surgery Adverse events ➢ 4 patients had major adverse events unrelated to surgery or stimulation ➢ 3 died from causes unrelated to surgery or stimulation and one patient had a stroke in the contralateral hemisphere 3 months after surgery ➢ Two patients had subdural haematomas which resorbed without intervention and left no sequelae ➢ Third patient had subdural and thalamic haematoma inducing transient left hemibody neglect which resolved without sequelae ➢ Two patients had an infection of the system ➢ Two other patients developed subcutaneous haematomas which were evacuated ➢ Electrode was replaced in 5 patients because of unsatisfactory results ➢ A transient attentional and cognitive deficit has been described in one patient ➢ Other adverse events (n=): dysarthria (7), disequilibrium (3), dystonia (1) were mild, related to stimulation and reversible with change in electrical parameters ➢ Some patients complained of local pain at the implantation site of the pulse generator Electrical parameters ➢ Voltage was slightly but significantly increased over one year ➢ Changed in pulse width and frequency were small

	➢ Frequencies over 130 Hz were usual ➢ Most patients were stimulated at 130Hz at implant and 185 Hz at 12 months ➢ Monopolar stimulation (one contact negative, the case of the pulse generator positive) was used in most patients ➢ Bipolar stimulation (at least one contact negative and one contact positive) was used when tremor reduction was obtained with less adverse effects than monopolar stimulation ➢ Stimulated contact was changed over time ➢ At 12 months stimulation was stopped at night in 48 electrodes (out of 79) in PD group Withdrawals ➢ One PD patient was withdrawn before surgery because he had difficulty breathing
Source of funding	Private sector
Additional comments	➢ Patients recruited from August 1992 to November 1994 ➢ Assessments performed by a neurologist specialising in movement disorders ➢ Not intention to treat ➢ Unblinded ➢ Uncontrolled ➢ Comparability between sites not discussed
NCC CC ID (Ref Man)	19703

Evidence Table What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	
Bibliographic reference	Welter ML, Houeto JL, Tezenas du MS, Mesnage V, Bonnet AM, Pillon B *et al*. Clinical predictive factors of subthalamic stimulation in Parkinson's disease. *Brain* 2002;**125**:575-83.
Study type	6-month follow-up before and after study
Evidence level	
Study objective	To identify which preoperative clinical variables were predictive of the best post-operative clinical improvement in Parkinson's disease (PD) patients treated by bilateral STN stimulation.
Number of patients	N=41 PD patients Location: Paris, France Sites: single
Patient characteristics	Inclusion criteria: under 70 years of age at time of surgery (except two women aged 71 and 74),

	advanced form of disease (Hoehn and Yahr scores), disease duration of <25 years, 40% response of motor symptoms to levodopa (LD) treatment, occurrence of severe levodopa-related motor complications despite optimal adjustment of antiparkinsonian medication, absence of severe cognitive impairment, absence of depression (assessed in only 36 patients), and absence of severe corticosubcortical lesions. Patient characteristics: 26 men and 15 women, mean age 56.4 ± 8.6 years, mean Hoehn and Yahr 4.3 ± 0.8, mean disease duration 16 ± 5 years, mean motor improvement to LD treatment 72 ± 15%, and mean daily dose of LD equivalent 1459 ± 600 mg/day
Intervention	Bilateral placement of stimulating electrodes within the STN. Procedure previously described and referenced.
Comparison	Pre-operative assessments
Length of follow-up	6 months
Outcome measures	Unified Parkinson's disease rating scale (UPDRS) parts II (ADL) and III (motor), axial motor score, levodopa-equivalent dose and correlation analyses
Effect size	➢ Patients were evaluated one month prior to and 6 months after surgery ➢ UPDRS ADL score was assessed scored during 'on' and 'off' drug conditions and percent improvement was determined with respect to pre-op 'off' drug condition ➢ Evaluation of motor disability score (UPDRS part III) pre-op was in 'off' condition ➢ Evaluation post-op was evaluated in 4 conditions: I) 'off' stimulation and 'off' drug, ii) 'on' stimulation and 'off' drug, iii) 'off' stimulation and 'on' drug, and iv) 'on' stimulation and 'on' drug ➢ The 'axial 'score (sum of the following motor subscore: speech, gait, posture, postural stability (items 18,28,29, and 30 of UPDRS Part III) was assessed at 'on' and 'off' times ➢ Levodopa-related complications were evaluated using UPDRS Part IV UPDRS II- activities of daily living (ADL) ➢ 6 months post-op ADL score improved 61% when patients were 'on' stimulator and 'off' drug ➢ Combination of 'on' stimulation and 'on' drug treatment produced an improvement of +77% than that obtained pre-op and 'on' drug UPDRS III (motor) ➢ 6 months post-op motor disability score improved 64% following 'on' drug with stimulator 'off' and 65% with stimulator 'on' and drug 'off'

	➢ The combination of 'on' drug and 'on' stimulator produced and improvement of +80% than that obtained with either levodopa alone (pre-op or post-op) or with stimulator alone Axial motor score ➢ 6 months after surgery scores improved 73% when patient was 'off' stimulator and 'on' levodopa ➢ Combination of 'on' levodopa and 'on' stimulator induced an improvement of +83% Levodopa-equivalent doses ➢ Post-op stimulation induced a decrease in LD doses by 68% ➢ Whereas, the scores for the duration of motor fluctuations, levodopa-induced dyskinesias, and UPDRS IV were improved by 87, 69 and 78% respectively Predictive factors ➢ No significant correlation was found between age at time of surgery or disease duration and post-op clinical outcome ➢ Correlation was found between motor disability score in the 'on' stimulation, 'on' drug condition, and age or disease duration ($p<0.005$ and $p<0.007$ respectively) ➢ 6 months post-op residual ADL ('on' stimulation and 'off' drug), motor disability ('on' stimulation and 'on' drug) and axial scores ('on' stimulation and 'off' drug) were lower and percentage of improvements in ADL ('on' stimulation and 'off' drug) and motor disability ('on' stimulation, 'off' and 'on' drug) were greater in younger patients ➢ Post-op residual ADL, motor disability and axial scores ('on' stimulation and 'on' drug) was significantly lower and percentage improvement in ADL and motor disability ('on' stimulation and 'on' drug) scores were significantly greater in patients with shorter disease durations Influence of patients' preoperative clinical characteristics on ADL evaluated after surgery ➢ No correlation between either the residual ADL score or the percentage improvement ADL ('on' stimulation, 'off' and 'on' drug) post-op ➢ The residual ADL scores ('on' stimulation) post-op were positively correlated with the pre-op residual motor disability and axial scores ('on' drug) and negatively correlated with frontal score ➢ The percentage improvement in the ADL score under STN stimulation alone ('on' stimulation, 'off' drug) was negative correlated with the levodopa-equivalent doses ➢ The percentage improvement in the ADL score under the combination of STN stimulation with drug treatment ('on' stimulation, 'on' drug) was negatively correlated with the pre-op residual motor

	disability score ('on' drug), the pre-op percentage improvement in motor disability score and the pre-op levodopa-equivalent dose Influence of patients' pre-op clinical characteristics on parkinsonian motor disability evaluated after surgery (summary- see paper for full details) ➢ The lower the parkinsonian motor disability during the best 'on' period (in particular gair disorders) and the higher neuropsychological status (in particular frontal aptitudes) were before surgery, the greater the improvement in parkinsonian motor disability after surgery Influence of patients' pre-op clinical characteristics on parkinsonian axial motor symptoms evaluated after surgery (summary- see paper for full details) ➢ The less severe the axial motor symptoms assessed under levodopa treatment before surgery (in particular gait disorders and postural instability), the greater the improvement in axial motor disability after surgery Influence of patients' pre-op clinical characteristics on levodopa-related complications and levodopa treatment evaluated after surgery (summary- see paper for full details) ➢ The efficacy of STN stimulation on levodopa-related motor complications was independent of the severity and duration of these motor complications evaluated before surgery
Source of funding	Private and non-profit funding
Additional comments	➢ No controls ➢ Unblinded ➢ Assume all patients completed follow-up assessments- no mention of drop-outs in follow-up
NCC CC ID (Ref Man)	19700

Evidence Table	
SURG 1 What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	
Bibliographic reference	Lagrange E, Krack P, Moro E, Ardouin C, Van Blercom N, Chabardes S *et al*. Bilateral subthalamic nucleus stimulation improves health-related quality of life in PD. *Neurology* 2002;**59**:1976-8.

Study type	12-month before and after study (uncontrolled)
Evidence level	3
Study objective	To assess the impact of bilateral subthalamic nucleus (STN) stimulation in Parkinson's disease (PD) patients on quality of life.
Number of patients	N=60 PD patients Location: France Sites: single
Patient characteristics	Sixty consecutive patients with PD (18 women and 42 men) with a mean age of 56 (±10 SD) years at the time of surgery and a mean duration of disease of 14 (±8 SD) years.
Intervention	STN stimulation (methods described in previous publication)
Comparison	Pre-operative assessments
Length of follow-up	12 months
Outcome measures	UPDRS I, II, III, Schwab and England Scale (S&E), Dyskinesias, Levodopa-equivalent dose, Beck Depression Inventory (BDI)
Effect size	Clinical evaluation of 60 patients before and after stimulation: ➢ UPDRS I non-significant (NS) ➢ UPDRS II 'on' medication NS, 'off' medication p<0.002 ➢ UPDRS III 'on' medication NS, 'off' medication p<0.002 ➢ S&E 'on' medication NS, 'off' medication p<0.002 ➢ Dyskinesias p<0.001 ➢ Levodopa-equivalent dose p<0.001 ➢ BDI p<0.002 Quality of life scores: ➢ PDQL total score improved 43% (p<0.001) ➢ Parkinsonian symptoms improved 48% (p<0.001) ➢ Systemic symptoms improved 34% (p<0.001) ➢ Emotional functioning improved 29% (p<0.001) and social functioning improved 63% (p<0.001) ➢ Some items dramatically improved such as 'doing hobbies' (100%) during ''off'' periods (90%) ➢ Others were not improved such as 'shuffling' or 'exhaustion' ➢ The improvement in the score of the UPDRS III was correlate with the improvement in the total PDQL score (p<0.001) but not with the improvement in the BDI (p=0.34)

	Adverse events ➢ 5 neurosurgical complications: 2 haematomas and 3 focal cerebral contusions ➢ Only one patient had a residual permanent deficit consisting of mild aphasia ➢ 5 transient psychiatric complications: mania (1), delusion (1), depression (3) (including suicide attempts (2))
Source of funding	Private sector
Additional comments	➢ Uncontrolled ➢ Unblinded assessments ➢ Same patient populations as ID's 19699 and 19707
NCC CC ID (Ref Man)	386

Evidence Table What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	
Bibliographic reference	Funkiewiez A, Ardouin C, Caputo E, Krack P, Fraix V, Klinger H *et al*. Long term of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry* 2004;**75**:834-9.
Study type	3-year prospective before and after study (uncontrolled)
Evidence level	
Study objective	To evaluate the cognitive, mood and behavioural effects of bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) in patients with Parkinson's disease (PD) followed-up for 3 years.
Number of patients	N=77 Parkinson's disease patients Location: Grenoble, France Sites: single
Patient characteristics	The initial consecutive series of 77 PD patients (34 women) who had been operated on at least 3 years previously, 70 have been followed up for 3 years. The mean age at surgery was 55 (± 8 SD) and the mean disease duration was at surgery was 15 (±5 SD) years.
Intervention	STN DBS (assume same techniques as previous publications by this trial group)
Comparison	Pre-operative assessments. Most patients were assessed without levodopa before surgery (83%). One year after surgery all patients evaluated with stimulator 'on' without levodopa (94%) at one year and (69%) at three years post-surgery.

Length of follow-up	3 years
Outcome measures	Neuropsychological, mood and behavioural assessments
Effect size	➢ 5 variables changed significantly between pre-operative and post-operative (post-op) assessments significance at p<0.01 Lexical Fluency (category, literal, total) ➢ Category fluency diminished from pre-op to one (p<0.0001) and three years (p=0.001) post-op ➢ Non-significant change between one and three years post-op ➢ Literal fluency did not change significantly pre-op to post-op ➢ Total number of words cited by patients (category and literal fluency) were worse from pre-op to post-op at one year (p=0.0011) and three years (p=0.0006) ➢ Non-significant change between one and three years Beck depression Inventory ➢ Improved from pre-op to assessments at one year (p<0.0001) and three years (p=0.004) ➢ The number of patients with severe depression at the end of three years was the same as at baseline UPDRS I ➢ Thought disorder worsened with years (p<0.001) ➢ Differences significant only for pre-op to 3 years (p=0.001) and between one to three years (p=0.007) ➢ However only a few patients had clinically relevant thought disorders (n=6) at three years ➢ The increasing score represents an increase from 0 to 1- no score of 4 (psychosis) was noted ➢ Apathy scores changed (p=0.005) showing an increase in the proportion of apathetic patients with time ➢ Only score changes between pre-op and 3 years was significant (p=0.001) ➢ The proportion of patients with a score of ≥ 2 doubled one year after surgery from 8.7% before surgery to 17.4% one year after surgery and 24.6% 3 years after surgery ➢ Three other variables showed a tendency to be impaired after surgery: Mattis dementia and rating scale (attention (p=0.017) and initiation scores (p=0.036)) and frontal score (p=0.042) Wisconsin card-sorting Test, Mattis dementia rating scale, Series (graphic and motor), frontal score, Grober and Buschke verbal learning test did not change significantly

	Correlation ➢ Between the decrease in frontal score (p<0.001), the initiation subset of Mattis DRS (p=0.007) and pre-op age of patients ➢ Between pre-op age of patients and item 2 of UPDRS thought disorders tended to be significant (p=0.023) ➢ None of these variables correlated with pre-op Mattis scores ➢ Between apathy and fluency (category) scores was significant one year after surgery (p=0.002) and tended to be significant at three years (p=0.023) Adverse events ➢ 9/66 (14%) had Mattis DRS scores below 130 (threshold for dementia) three years after surgery ➢ 5/9 (56%) already had pre-op scores below 130 ➢ 4 suicide attempts post-op (one died) ➢ This occurred at different time points (2,3,5,6, and 36 months) ➢ Hypomania occurred in 5 patients always in the first 3 months ➢ 4 recovered spontaneously and one patient persisted periodically with this behaviour during three 3 year post-op ➢ Two patients had an episode of aggressive behaviour in first few post-op days ➢ At different times post-op 4 patients suffered from psychosis ➢ One patient had transient florid psychosis six weeks post-op that required hospitalization ➢ Another had permanent psychosis and two others experienced hallucinations or delusions without insight (2/3 patients were demented) ➢ Severe depression requiring transient hospitalization occurred in one patient Withdrawals ➢ Of the 7 who withdrew: two died (one suicide, one death from unrelated disease), one patient developed large frontal haematoma during surgery and could not be evaluated, a systematic postoperative MRI showed four haematomas and three contusions ➢ All seven had cognitive deterioration either transient (2) or permanent (5)
Source of funding	Private sector (bio med company)
Additional comments	➢ Consecutive recruitment of patients ➢ Some patient population as ID19699 (different outcome measures) ➢ Behaviour was not assessed prospectively using psychiatric scales ➢ But the same neuropsychologist saw all patients at all follow-up times

	➢ Possibility of learning effects from re-testing at different time points ➢ Outcome measures were detailed ➢ No details on surgical techniques mentioned or referenced?? Assume it is the same as other ST DBS from the same centre and investigators)
NCC CC ID (Ref Man)	19707

Evidence Table
What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?

Bibliographic reference	Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C *et al*. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease.[see comment]. *New England Journal of Medicine* 2003;**349**:1925-34.
Study type	5-year prospective before and after study (uncontrolled)
Evidence level	
Study objective	To investigate the long-term outcomes of advanced Parkinson's disease (PD) patients treated with bilateral stimulation of the subthalamic nucleus (STN)
Number of patients	N=49 consecutive PD patients Location: Grenoble, France Sites: single centre
Patient characteristics	Selection criteria: clinically diagnosed PD, severe levodopa (LD)- related motor complications despite optimal adjustment of antiparkinsonian medication, an age under 70 years, no surgical contraindications, and no dementia or major ongoing psychiatric illness.

Characteristic	
Sex (male: female)	24:25
Age, yr (mean, range)	55.0± 7.5, 34-68
Duration of disease, yr	14.6 ± 5.0
Dose of levodopa (mg/d)	1100 ± 567

Intervention	Quadripolar electrodes were implanted bilaterally in a single operation in all but the first three patients, in whim the second electrode was implanted from 1 to 12 months after the first. A few days after implantation of electrodes, a programmable pulse generator was implanted subcutaneously on each side of the brain while the patients were under general anaesthesia. Stimulation settings and medication were progressively adjusted.

Comparison	Preoperative assessments
Length of follow-up	5 years
Outcome measures	UPDRS, Schwab and England scale of global activities of daily living, Mattis Dementia Rating Scale, Beck Depression Inventory,
Effect size	➢ Patients were evaluated pre and post-operatively ➢ Pre-operatively: unblinded assessments were performed when patients had taken no medication for 8 to 12 hours (off medication) and during periods of maximal clinical benefit after the administration of a dose of liquid levodopa that was 50% higher than the usual morning dose (on medication) ➢ Post-operatively: patients were assessed during stimulation Stimulation in off-medication state ➢ Total score on part III (motor) of UPDRS improved from baseline values by 66% at one year, 59% at 3 years and 54% at 5 years (5 years vs. baseline, p<0.001) (5 years vs. 1 year, p<0.001) ➢ Compared to baseline the score for tremor improved by 75% at 5 years, rigidity improved by 71% and akinesia by 49% (all p<0.001) ➢ Postural stability and gait also improved (both p<0.001 at 5 years vs. baseline) ➢ The score for speech improved only during the first year and then worsened, returning to baseline score at 5 years ➢ The total score for part II (activities of daily living, ADL) of UPDRS improved by 66% at 1 year, 51% at 3 years, and 49% at 5 years (5 years vs. baseline, p<0.001) ➢ Worsening between year one and five was significant (p<0.001) ➢ All changes from baseline to year one indicated improvement and all changes from year one to year five indicated worsening ➢ Schwab and England score improved (baseline vs. years 1,3,5; p<0.001): ➢ 5 years after surgery most patients were independent in their ADL in off-medication state (mean score 73%, where 100% indicated normal functioning) before surgery most patients were fully dependent on care givers (mean score 33%) ➢ before surgery 71% of patients had painful dystonia, while off-medication 19% had dystonia at one year and 33% had dystonia at 5 years Stimulation in on-medication state ➢ a levodopa test could not be performed in 2 patients at 3 years and 3 patients at 5 years who stopped dopaminergic treatment- these patients could not tolerate a levodopa challenge ➢ remaining patients: motor function and ADL in on-medication state did not improve after

	stimulation of STN ➢ between 1st and 5th year there were not significant changes in individual scores for tremor and rigidity, but scores for akinesia, speech, postural instability, and freezing of gait worsened (p<0.001) resulting in worsening of total score for motor function (p<0.001) and scores for ADL (p<0.001) as assessed by UPDRS ➢ Schwab and England ADL were unchanged ➢ The severity of disability related to dyskinesia decreased 58% and duration by 71% (p<0.001) Neuropsychological evaluation ➢ No significant changes on Beck Depression Inventory ➢ The average score on the Mattis Dementia Rating Scale was worse at 5 years, reflecting progressive dementia in 3 patients according to DSM-IV criteria but changes were not significant (p=0.07) ➢ The average score for frontal lobe function tended to be worse at 5 years (p=0.03) Medication and stimulation settings ➢ Post-operatively requirement for levodopa (or equivalent medication) decreased (p<0.001) from 1409 ± 605 mg/d at baseline to 584 ± 366 mg/d at year one, 526 ± 328 mg/d at 3 years and 518 ± 333mg/d at 5 years ➢ At 5 years 11/42 (26%) patients were no longer taking levodopa and 3 were not taking any dopaminergic drugs ➢ After five years there were no significant changes in voltage, frequency, or pulse width ➢ Monopolar stimulation with the use of a single contact from the Quadripolar electrode was applied in 90% of patients at one and 5 years ➢ With these settings the stimulators had to be replaced in the first 5 years in only one patient Adverse events ➢ 3/42 (7%) deaths ➢ surgical complications were frequent but mostly temporary ➢ Permanent side effects included dementia (2 patients) ➢ Transient postoperative delirium, ranging from temporospatial disorientation to psychosis during the first few days after surgery (12 patients, 24%) ➢ Device-related complications were rare ➢ Treatment-related side effects changed with time during follow-up: 4 patients at 3 months and 2 patients at 5 years indicated they still had disabling dyskinesia out of 29 patients at baseline ➢ 15/49 (31%) had eye-lid opening apraxia in first 3 months and this remained a problem for 8 patients (19%) for the duration of follow-up

	➢ in first 3 months, reversible stimulation-induced dyskinesias commonly developed in patients after an increase in voltage (in the long-term baseline dyskinesias improved) ➢ during first 3 months after surgery, 41 patients gained weight (mean 3 kg), patients on average gained another kilogram within the first year and then weight remained stable ➢ in immediate post-operative periods 8% developed transient hypomania ➢ in longer follow-up other psychiatric disorders occurred including: transient depressive episodes (17%), and transient apathy (5%) which were responsive to antidepressants, increase in dopaminergic medication or both ➢ Apathy that did not respond to dopaminergic medication occurred in 5 patients (12%) as did dementia in 3 patients (7%) between 3rd and 5th year of follow-up
Source of funding	Private sector, government and University funding
Additional comments	➢ No control group ➢ Consecutive patient recruitment ➢ Unblinded assessment
NCC CC ID (Ref Man)	19699

Evidence Table

SURG 1

What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?

Bibliographic reference	Russmann H, Ghika J, Villemure JG, Robert B, Bogousslavsky J, Burkhard PR *et al*. Subthalamic nucleus deep brain stimulation in Parkinson disease patients over age 70 years. *Neurology* 2004;**63**:1952-4.
Study type	48 month follow-up before and after study
Evidence level	3
Study objective	To better delineate the potential risk-to-benefit ratio of STN DBS in older patients (compared the effects of STN DBS in patients above and below age 70 in a cohort of 53 patients).
Number of patients	N=52 Parkinson's disease (PD) patients Location: Switzerland sites: single
Patient characteristics	52 consecutive PD patients. All had a dopa-responsive PD, without atypical signs and witout dementia

<table>
<tr><td></td><td>and depression. Age was not a selection criterion. Pre-operatively (pre-op) all patients showed at least 25% improvement in UPDRS motor score in response to levodopa tests.
<table>
<tr><td></td><td>< 60 years</td><td>60-70 years</td><td>>70 years</td></tr>
<tr><td>N=</td><td>15</td><td>24</td><td>13</td></tr>
<tr><td>Sex (M:F)</td><td>11: 4</td><td>13: 11</td><td>7: 6</td></tr>
<tr><td>Age, years</td><td>55 ± 4</td><td>65 ± 2.5</td><td>74 ± 3</td></tr>
<tr><td>Duration of disease, y</td><td>14 ± 5</td><td>15 ± 5</td><td>14 ± 5</td></tr>
<tr><td>Follow-up duration</td><td>22.4 ± 11.2</td><td>17.5 ± 8.5</td><td>15.5 ± 9.63</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Bilateral STN DBS implantation (surgical protocol cited to other study by same authors)</td></tr>
<tr><td>Comparison</td><td>Pre-operative assessment</td></tr>
<tr><td>Length of follow-up</td><td>6 to 48 months</td></tr>
<tr><td>Outcome measures</td><td>UPDRS, medication changes, adverse events</td></tr>
<tr><td>Effect size</td><td>➢ 13 patients older than 70 years of age were compared with 15 patients under the age of 60 and 24 patients aged 60 to 70 years
➢ Medication was reintroduced if patients did not reach pre-op ‘on’ score despite optimal stimulation
➢ UPDRS I to IV and Hoehn and Yahr scores were assessed at 3,6,12,18,24,36 and 48 months after operation
➢ 42 patients (12 <60 years, 21 60-70 years, and 9 > 70 years) accepted to have the stimulation turned off in the practically defined ‘off’ medication state after 8.3 ± 4.1 months
> 70 years
➢ Differed from other subgroups only by lower daily levodopa equivalent dose (p<0.03)
➢ Medication reduction of 49% at last follow-up
➢ 5 had no anti-PD medication, 8 had levodopa (three in association with dopamine agonists)
< 70 years
➢ Medication reduction of 74% (p<0.01)

➢ In all groups dyskinesia and fluctuations were significantly (p<0.001) and similarly reduced (p=0.3 to 0.7)
➢ All UPDRS motor scores off medication were improved (p<0.001 to 0.02) but less in patients over 70 than other two groups (p<0.02)
➢ Changes in UPDRS motor scores on medication worsened in patients over 70 and improved in patients under 70 (p<0.05)
➢ Pre-operative activities of daily living (ADL) scores on medication were similar between 3 groups</td></tr>
</table>

	(p=0.3 to 0.9) ➢ The two younger groups had unchanged postoperative ADL (p>0.9) whereas the oldest group had a 40% worsening (p<0.001) Correlations ➢ The STN DBS were linearly correlated with those of the pre-operative levodopa challenge (p<0.02) ➢ After correction by linear regression for the pre-op levodopa results all differences above were still significant ➢ Pre-op major signs subscores were the similar in all groups In 'on' and 'off' conditions (p=0.2 to 0.9) ➢ Post-op, off medication, bradykinesia and rigidity subscores were improved in all subgroups ➢ Tremor subscores were improved in the two younger subgroups, whereas axial signed were unchanged ➢ On medication, bradykinesia, rigidity and tremor subscores had not significantly changed ➢ Axial signs only worsened in patients over age of 70 (inversely correlated to drug reduction, p<0.01) Drug dosage ➢ Post-op 5 patients over 70 did not require antiparkinsonian medication ➢ Their pre-op scores were similar to other patients over 70- except trend toward lower pre-op axial scores (p=0.036) with scores for gait medication of ≤ 2 (no help to walk) contrasting with scores of 3 or 4 in five of the eight others (p<0.03) Adverse perioperative events ➢ > 70 years: leads repositioning (1), transient confusional states (3), connection wound dehiscence (1), delayed infection (1) ➢ < 70 years leads reposition (1), air embolus (1), seizure (1), panic attack (1), transient confusional states (4), connect wound dehiscence ➢ There was neither haemorrhage nor any permanent neurologic deficit ➢ Three patients over age 70 and 4 younger patients developed post-op neuropsychological deficit impairing daily life
Source of funding	Non-profit foundations
Additional comments	➢ Unblinded ➢ Uncontrolled

	➢ Details of protocol in separate publication ➢ No inclusion criterion stated ➢ Follow-up of 6- 48 months – no numbers of drop-outs per time period mentioned
NCC CC ID (Ref Man)	19727

Evidence Table

SURG 1

What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?

Bibliographic reference	Charles PD, Van Blercom N, Krack P, Lee SL, Xie J, Besson G *et al*. Predictors of effective bilateral subthalamic nucleus stimulation for PD. *Neurology* 2002;**59**:932-4.
Study type	5-year follow-up before and after study
Evidence level	3
Study objective	To identify factors predictive of effective bilateral subthalamic nucleus (STN) stimulation for PD with severe motor complications.
Number of patients	N=56 PD patients Location: France Sites: 1
Patient characteristics	56 consecutive PD patients, 29 men and 27 women, with a mean age of 56.0 ± 7.7 years at time of surgery. Mean disease duration at time of surgery was 15.7 ± 4.9 years. Average pre-op daily dose of levodopa 1102 ± 576 mg). Inclusion criteria: clinically diagnosed idiopathic PD, disabling motor fluctuations despite all drug strategies, good general health, brain MRI within normal range, and no severe dementia.
Intervention	Bilateral STN stimulator implantation (see paper for details)
Comparison	Pre-operative assessment
Length of follow-up	5 years
Outcome measures	UPDRS, predictive formulae, adverse events
Effect size	Protocol ➢ Patients were evaluated pre-op and 3 months post-op ➢ At 3 months post-op most patients demonstrated a chronic stable condition that was sustained for

	up to 3 years and required very little electrical adjustment ➢ UPDRS was assessed pre-op in both on and off drug states ➢ Post-op UPDRS was evaluated in 4 conditions: off-drug/off stimulation (stim); off-drug/on-stim; on-drug/off-stim; on-drug/on-stim ➢ Levodopa challenge was calculated as 120% of regular morning dose plus additional levodopa dose equivalent to the dopamine agonist dose that would usually have been taken in the morning Efficacy ➢ Improvement from levodopa, as measured by change in the UPDRS-III score, correlated positively with post-op improvement from stimulation ($p<0.00001$) ➢ The R^2 value indicating that this factor accounts for 32% of post-op improvement ➢ Age correlated negatively with post-op improvement from stimulation ($p<0.01$) ➢ A pre-op levodopa response in an individual symptom correlated with a post-op stimulation response for that same symptom: akinesia ($p<0.001$), tremor ($p<0.001$), rigidity ($p<0.001$), composite score for postural instability gait disorder ($p<0.001$), gait ($p<0.001$) and pull test ($p<0.001$) ➢ Improvement from levodopa in Hoehn and Yahr and Schwab and England global ratings was predictive of a similar improvement from stimulation in the same rating (both $p<0.001$) ➢ To predict the post-op improvement from pre-op levodopa response (multiple regression analysis) the following formula was obtained (after discarding factors with low predictive power): ➢ Predicted post-op improvement relative to pre-op UPDRS III off score= 38 – (age x 0.36)+ (duration of illness x 0.33) + (rigidity response to levodopa x 1.3) + (pull test response to levodopa x 3.9) – (freezing response to levodopa x 2.4) ➢ This was simplified by retaining only the 3 most powerful factors: ➢ Predicted post-op improvement relative to pre-op UPDRS III off score= 34 – (age x 0.29) + (rigidity response to levodopa x 1.3) + (pull test response to levodopa x 3.8) Withdrawals ➢ Two patients were not available for the 3-month assessment (one suffered from a severe frontal haematoma at time of surgery the other living far away reported great benefit but refused to return for formal assessments)

Source of funding	None stated
Additional comments	➢ Uncontrolled ➢ Unblinded ➢ No intention-to-treat ➢ Young patient population
NCC CC ID (Ref Man)	19726

Surg2 – section 8.4

Evidence Table **SURG 2** Which is the most effective form of deep brain stimulation in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	
Bibliographic reference	Obeso JA, Guridi J, Rodriguez-Oroz MC, Agid Y, Bejjani P, Bonnet AM *et al*. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *New England Journal of Medicine* 2001;**345**:956-63.
Study type	6 month, prospective, multicentre trial
Evidence level	3
Study objective	To evaluate the results of bilateral pallidal or subthalamic stimulation in patients with advanced Parkinson's disease.
Number of patients	N= 143 patients (of which 134 received bilateral implants) Location: Sites: 18
Patient characteristics	The ages of patients ranged from 30 to 75 years. The criteria for inclusion was the presence of at least cardinal features of parkinsonism (tremor, rigidity, and bradykinesia), a good response to levodopa, a minimal score of 30 points on the motor portion of the UPDRS (off medication), motor complications that could not be controlled with medication. The criteria for exclusion were major psychiatric illness, cognitive impairment, other substantial medical problems or laboratory abnormalities, presence of cardiac pacemaker, and previous intracranial surgery.

<table>
<tr><td></td><td>Baseline characteristics of patients with bilateral implants
<table>
<tr><th>Variable</th><th>STN</th><th>GPi</th></tr>
<tr><td>Sample size (n=)</td><td>96</td><td>38</td></tr>
<tr><td>Sex (M:F)</td><td>60 : 36</td><td>27: 11</td></tr>
<tr><td>Mean age at surgery (yr)</td><td>59.0 ± 9.6</td><td>55.7 ± 9.8</td></tr>
<tr><td>Mean age at illness onset (yr)</td><td>44.6 ± 8.9</td><td>41.2 ± 9.5</td></tr>
<tr><td>Dose of LD or equivalent (mg/d)</td><td>1218 ± 575</td><td>1090 ± 543</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Subthalamic nucleus (STN) deep brain stimulation (DBS)- see paper for details</td></tr>
<tr><td>Comparison</td><td>Internal globus pallidus (GPi) DBS- see paper for details</td></tr>
<tr><td>Length of follow-up</td><td>6 months</td></tr>
<tr><td>Outcome measures</td><td>Primary: difference between UPDRS motor scores in the double-blind crossover phase; secondary: unblinded assessment of UPDRS scores and subscores and levodopa dose</td></tr>
<tr><td>Effect size</td><td>➢ The double-blind crossover study was performed after both medication and stimulation (stim) had been discontinued overnight
➢ Patients were randomly assigned to undergo motor assessments in one of two treatment sequences
➢ Sequence 1: the first evaluation was performed after stim had remained off for an additional two hours and the second was performed after stim had been turned off for two hours
➢ Sequence 2: the order was reversed
➢ The investigators and patients were unaware of whether stim had been on or off
➢ Unblinded pre- and post-op evaluations
➢ Evaluations with stim were performed after the stimulator had been turned on for approximately 30 min
STN
➢ 102 patients were enrolled, 96 received bilateral implants, 91 participated in double-blind crossover study and completed 6 months follow-up
Double-blind study
➢ There was treatment effect (stim on vs. stim off, p<0.001)
➢ There were no carryover or treatment effects
➢ Stim produced the same result regardless of the order in which patients were evaluated
➢ Stim was associated with a mean improvement of 43% and a median improvement of 49% in the UPDRS motor score in comparison with the stim off evaluation (p<0.001)
➢ Significant benefits were also observed with stim on both sequences</td></tr>
</table>

	➢ A median improvement of more than 25% was noted at 15/`6 centres that performed STN DBS Unblinded evaluations: ➢ Baseline vs. stim/off-med UPDRS improved at each visit ➢ Smaller but significant effects were observed in on-med state (p<0.001) ➢ Stimulation status was associated with motor score (p<0.001) ➢ Significant interaction effects between medication and stimulation- suggests stimulation and medication act synergistically in predicting motor scores ➢ Follow-up visits did not predict motor scores (p=0.58)- indicating the beneficial effect of stimulation was stable over time ➢ Stim in off-med state was also associated with improvement in tremor, rigidity, bradykinesia, gait, postural instability, and activities of daily living (p<0.001) ➢ Home-diary assessments: % of time with good mobility and without dyskinesia during the waking day increased from 27% to 74% between baseline and 6 months (p<0.001) ➢ Paralleled by a decrease in % of time with poor mobility, from 49% to 19% (P<0.001) ➢ Mean (SD) dyskinesia score improved from 1.9 ± 1.1 at baseline to 0.8 ± 0.8 at 6 months (p<0.001) ➢ Global assessments by physicians and patients noted severe disability at baseline in 74% and 77% respectively as compared with 15% and 23% at 6 months ➢ Daily levodopa dose equivalents were reduced from a mean of 1218.8 ± 575 mg at baseline to 764 ± 507 mg at 6 months (p<0.001) GPi ➢ 41 patients were enrolled, electrodes implanted bilaterally in 38; 35 participated in blinded study ➢ 36 completed 6 months follow-up Double-blind crossover ➢ At 3 months demonstrated treatment effect in favour of stimulation (p<0.001) ➢ No significant carry-over effect or period effect ➢ Stimulation associated with a mean improvement of 32% and a median improvement of 37% in UPDRS motor score (p<0.001) ➢ Median improvement greater than 25% observed in 9/10 centres ➢ Benefit of stimulation was seen regardless of sequence assignment Unblinded evaluations: ➢ Vs. baseline significant improvement in UPDRS motor score at each visit with stim/ off-med (p<0.001)

	➢ Smaller but significant benefits in stim/on-med state (p=0.003) ➢ Stim was associated with improvement in the motor score (p<0.001) ➢ Interaction between med and stim was observed (p<0.001) and beneficial effect of stim was stable over time (p=0.72) ➢ Effects on ADL and cardinal features of PD: significant benefits particularly in off-med state (P<0.001) for ADL, tremor, rigidity, bradykinesia, gait and (p=0.02) for postural stability ➢ Home diary assessments indicated that between baseline and 6 months % of time with good mobility and without dyskinesias during the waking day increased from 28% to 64% (p<0.001) ➢ % Of time with poor mobility was correspondingly reduced from 37% to 24% (p=0.01) ➢ Dyskinesia score improved from a mean of 2.1 ± 1.5 at baseline to 0.7 ± 0.8 at 6 months (p<0.01) ➢ Physician and patient global estimates of severe disability improved from 76% and 82% respectively at baseline to 11% and 14% at 6 months ➢ The men daily dose of levodopa equivalents was unchanged between baseline (1090 ± 543 mg) and 6 months (1120 ± 537 mg) Adverse events ➢ Intracranial haemorrhage (n=7) (4 required surgical decompression), neurological deficits associated with haemorrhage (n=6) (4 of these had persistent dysfunction) ➢ The number of microelectrode passes used to determine target location correlated with risk of haemorrhage ➢ Patients without haemorrhage had a mean of 2.9 ± 1.8 passes vs. 4.1 ± 2.0 among those who did (p=0.05) ➢ Seizures (n=4), infection (n=2) stimulation-induced dyskinesia (n=5) ➢ One patient died of oesophageal carcinoma
Source of funding	Private sector
Additional comments	➢ Unblinded evaluations of motor function ➢ The choice of target site was determined at each centre according to experience and preference of investigator ➢ Method of assessment randomisation stated ➢ Within each centre all assessments were performed by the same investigator ➢ Study conducted from July 1995 to July 1999
NCC CC ID (Ref Man)	417

Evidence Table
SURG 2
Which is the most effective form of deep brain stimulation in the treatment of motor fluctuations and complications in patients with Parkinson's disease?

<table>
<tr><td>Bibliographic reference</td><td>Vesper J, Klostermann F, Wille C, Funk T, Brock M. Long-term suppression of extrapyramidal motor symptoms with Deep Brain Stimulation (DBS). German Journal of Neurosurgery 2004;65:117-22.</td></tr>
<tr><td>Study type</td><td>12 months follow-up before and after study (comparison of intervention results)</td></tr>
<tr><td>Evidence level</td><td>3</td></tr>
<tr><td>Study objective</td><td>To investigate the use of chronic deep brain stimulation in the treatment of patients with extrapyramidal disorders refractory to conservative management.</td></tr>
<tr><td>Number of patients</td><td>N=113 patients with extrapyramidal disorders
N=72 PD patients
N= 7 GPi
N=55 STN
N=10 Vim Thalamus</td></tr>
<tr><td>Patient characteristics</td><td>The patient group all suffered from extrapyramidal disorders unresponsive to conventional management. Patients with PD were eligible if the residual action of L-dopa still had a noticeable effect on motor symptoms in the on-state (mean Hoehn and Yahr state: pre-op 3.8, post-op 2.8, 2.6 (6 months) 2.5 (12months). Patients with severe dementia were excluded. 62 patients suffering from akinesia rigid forms of PD were included.</td></tr>
<tr><td>Intervention</td><td>Bilateral implantation was performed in 52/55 STN DBS patients- see paper for details</td></tr>
<tr><td>Comparison</td><td>Bilateral implantation was performed in 6/43 Vim DBS patients- see paper for details</td></tr>
<tr><td>Length of follow-up</td><td>12 months</td></tr>
<tr><td>Outcome measures</td><td>Tremor suppression, UPDRS, activities of daily living (ADL), levodopa equivalent daily dose (LEDD), dystonia and adverse events</td></tr>
<tr><td>Effect size</td><td>Parameter settings:
<table>
<tr><td></td><td>Vim</td><td>STN</td><td>GPi</td></tr>
<tr><td>Frequency (Hz)</td><td>135 (130-185)</td><td>130 (130-145)</td><td>160 (145 – 185)</td></tr>
<tr><td>Pulse width (µsec)</td><td>180 (60-400)</td><td>90 (60-120)</td><td>400 (270 – 450)</td></tr>
<tr><td>Amplitude (V)</td><td>2.8 (1.7 – 5.2)</td><td>2.7 (1.6- 5.0)</td><td>3.6 (1.8 – 4.1)</td></tr>
</table>
➢ Patients with generalised primary types of dystonia refractive the medical therapy, were selected for bilateral DBS of the GPi according to their resistance to drug treatment</td></tr>
</table>

	➢ However reduction in medication was not possible- therefore STN became major target Vim ➢ Suppression of tremor by Vim DBS was successful for resting and postural tremor as well as action-intention tremor ➢ Tremor scale according to Fahn showed significant differences between pre-op and post-op ($p<0.001$) for PD patients ➢ Aetiology of the tremor dud not affect the effectiveness of DBS of the Vim STN/ GPi ➢ DBS of STN and GPi were evaluated for the reduction of motor symptoms and medication ➢ Preliminary investigations had shown better results for STN and so became target of choice for akinetic rigid conditions in patients with PD ➢ STN stimulation significantly alleviated the motor symptoms in patients with PD ($p<0.001$) ➢ Patients with PD were assessed with 'on' and 'off' stimulation (STN and GPi) ➢ Dyskinesias were improved slightly by STN stimulation (pre-op on 2.9, off 3.4; 12 months post-op stim on med on 0.52, $p<0.001$) ➢ ADL in patients with PD also markedly improved ($p<0.05$)- corresponding to the effect of DBS on motor complaints ➢ Reduction of L-dopa medication ($p<0.05$) only possible with STN DBS (mean L-dopa pre-op dose 553 mg, post-op dose 458 mg, 12 months post-op dose 353 mg) ➢ Symptoms of dystonia showed overall improvement ($p<0.05$) during stimulation of GPi- however the 2 patients with secondary dystonia had only a marginal benefit from DBS Adverse events ➢ Related to surgery: transient disorientation during bilateral STN stimulation (n=6, 5.8%), symptoms persisted for some time (n=2, 1.8%) and required antipsychotic drugs; infections (n=5, 4.9%), so stimulations systems were removed and reimplanted after 6 months (all of the patients had a restored positive effect of stimulation); intacerebral haemorrhages (n=2, 1.8%); permanent contralateral hemiplegia, the other suffered from permanent neuropsychological deficit
Source of funding	None stated
Additional comments	➢ Non-randomised ➢ Unblinded ➢ GPi group below cut-off (n=10)
NCC CC ID (Ref Man)	400

Evidence Table
SURG 2
Which is the most effective form of deep brain stimulation in the treatment of motor fluctuations and complications in patients with Parkinson's disease?

Bibliographic reference	Ardouin C, Pillon B, Peiffer E, Bejjani P, Limousin P, Damier P *et al*. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: A consecutive series of 62 patients. *Annals of Neurology* 1999;**46**:217-23.
Study type	6-month follow-up before and after study (comparison o interventions)
Evidence level	3
Study objective	To assess the influence of bilateral stimulation of the subthalamic nucleus or internal globus pallidus on memory and executive functions in Parkinson's disease (PD).
Number of patients	n=62 PD patients n=49 subthalamic nucleus (STN) stimulated patients n=13 internus globus pallidus(GPi) stimulated patients location: France (Grenoble (STN1, GPi1) and Paris (STN2 and GPi2)) sites: two
Patient characteristics	All patients had a severe form of the disease, with a clear response to levodopa (demonstrated by differenced in 'on' and 'off' stated). Severe motor fluctuations were observed in all patients despite optimal medication. No other neurological impairment was found and MRI scans were normal. Patients had no significant cognitive or mood impairment before surgery, and were relatively young.

	STN1	STN2	GPi1	GPi2
Sample size (n=)	41	8	8	5
Sex (M:F)	19: 22	5: 3	6: 2	3: 2
Mean age (yr)	54.9 ± 7.6	53.4 ± 12.5	51.5 ± 6.5	55.2 ± 10.2
Disease duration (yr)	15.0 ± 5.2	15.5 ± 7.1	16.2 ± 3.4	12.6 ± 2.7
Hoehn and Yahr (off)	4.4 ± 0.8	4.4 ± 0.9	4.1 ± 0.6	3.5 ± 1.0
Hohen and Yahr (on)	2.4 ± 0.8	2.6 ± 1.1	2.9 ± 0.6	2.1 ± 0.9

Intervention	Internus globus pallidus deep brain stimulation- see paper for details
Comparison	Subthalamic nucleus deep brain stimulation- see paper for details
Length of follow-up	3 (Grenoble) to 6 months (Paris)
Outcome measures	Motor scores, levodopa dose, neuropsychological tests, adverse events
Effect size	➢ At the time of the study, the mean (SD) voltage of stimulation was 2.4 (0.7)V for STN and 3.1

(0.6)V for GPi; the mean pulse width was 60.5 (10.9) msec for STN and 78.5 (28.8)m sec for GPi; the mean frequency was 137.0 (27.6)Hz for STN and 139.6 (20.6) Hz for GPi

- Electrical parameters were progressively adjusted by telemetry using console programmer, until optimal effect was reached in both 'on' and 'off' drug conditions
- Parkinsonian motor features improved in all patients
- Hoehn and Yahr 'off' scores, UPDRS I, II 'off', III 'off', IV, and dose of levodopa improved ($p<0.01$) after electrode implantation for the whole population

Table: comparison of before and after motor scores (after stimulation)

	STN 1		STN 2		GPi 1		GPi 2		P value
	before	after	Before	after	Before	after	before	After	0.0001
H&Y	4.4	2.6	4.4	1.8	4.1	3.4	3.5	1.9	0.02
UPDRS I	2.4	1.8	0.9	1.1	1.1	0.6	1.2	0.6	0.0001
II (off)	31.5	12.8	31.4	11.2	25.8	15.7	22.4	11.8	0.0001
III (off)	56.2	20.2	59.0	29.2	55.4	37.1	41.6	27.0	0.0001
IV	11.4	3.4	11.6	2.5	12.4	6.0	11.6	3.4	0.0001
LD dose	1112	434	1125	487	744	874	850	725	0.0001

- The improvement was more pronounced in STN patients and antiparkinsonian medication could be reduced in these patients
- Analysis of group effect showed only one significant comparison from 26 cognitive and mood variables: Mattis Dementia rating Scale total score ($p=0.015$)
- This score was higher for the STN2 than the STN1 group ($p<0.01$) or GPi1 ($p<0.01$)
- Literal ($p=0.0018$) and total ($p=0.0002$) fluency decreased under stimulation
- The Trail Making test ($p=0.0013$) and test B ($p=0.0015$) and the BDI ($p<0.0001$) improved under stimulation
- These repetition effects were significantly in the whole population and in patients with STN (STN1 + STN2) stimulation, but not in patients with GPi (GPi1 + GPi2) stimulation
- The repetition by group interactions was significant only for category fluency ($p=0.009$) and graphic series ($p=0.005$)
- In category fluency a significant repetition effect was observed only for the group STN1
- In graphic series , post-hoc analysis showed no significant repetition effect for any individual group of patients
- Apart from the group effects, individual results showed that no patient became demented after

	surgery ➢ Overall the mean percentage of patients who declined was similar to the mean percentage of patients who improved ➢ Decline was observed for one cognitive domain in 39% of patients, for two cognitive domains in 18% of patients, for 3 cognitive domains in 5% of patients and 4 cognitive domains in 3% ➢ Conversely an improvement was observed for one category domain in 34% pf patients ➢ 33% of patients showed both improvement in some domains and decline in others ➢ authors conclude- declines or improvements were overall sprinkled haphazardly throughout the patients
Source of funding	Private sector
Additional comments	➢ Nonrandomised ➢ Unblinded ➢ No inclusion/exclusion criteria stated
NCC CC ID (Ref Man)	19702

Evidence Table **SURG 2** Which is the most effective form of deep brain stimulation in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	
Bibliographic reference	Volkmann J, Allert N, Voges J, Weiss PH, Freund H-J, Sturm V. Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. *Neurology* 2001;**56**:548-51.
Study type	1 year follow-up before and after study (comparison of results between interventions)
Evidence level	
Study objective	To report a retrospective analysis of efficacy and safety of deep brain stimulation (DBS) on either GPi or STN.
Number of patients	N=27 Parkinson's disease (PD) patients N=11 GPi implants N=16 STN implants Location: Germany sites: single
Patient characteristics	Between October 1996 and April 2000- 57 patients were treated with bilateral DBS for advanced PD.

	The first 11 patients were implanted within GPi (mean age: 56.6 ± 9.4 years, duration of disease 10.5 ± 2.7 years), and a selection of 16/46 patients treated with STN stimulation (mean age 60.2 ± 9.8 years, disease duration 13.1 ± 5.9 years) selection and exclusion criteria for surgery were identical in both groups.
Intervention	Globus pallidus (internal) deep brain stimulation- see paper for details (stimulation parameters not stated)
Comparison	Subthalamic nucleus deep brain stimulation- see paper for details (stimulation parameters not stated)
Length of follow-up	1 year
Outcome measures	UPDRS scores, 'off' time, levodopa equivalent daily dose (LEDD), electrical power, adverse events
Effect size	➢ Comparison is pre- to post-op changes within groups ➢ Both GPi and STN stimulation improved off-period motor symptoms ➢ None of the parameters differed significantly between groups (UPDRS ADL, UPDRS motor, Schwab and England, dyskinesia rating scale, UPDRS sub scores and LEDD) for before and after results ➢ Post-op UPDRS III scores in on/stimulation barely differed between groups, except for mild but significant worsening of speech and swallowing subscale in STN patients ➢ The reduction of 'off' time (UPDRS item 39) was significant in the STN group ($p<0.0001$), with only one patient reporting 'off' periods in less than 25% of the day, and 'off' periods no longer perceived by the other patients ➢ In the GPi group, 9/11 (81.8%) patients reported less than 25% 'off' time after surgery ($p=0.029$) ➢ The levodopa equivalent daily dose (LEDD) was reduced by 65.3 ± 20.2 % after one year in STN group, whereas only insignificant changes in GPi group (-16.1 ± 27.4%) ➢ Electrical stimulation power was on average more than threefold higher in GPi stimulation (13.8 ± 17.3 µW) than in STN stimulation (3.7 ± 6.9 µW) ($p<0.001$) Adverse events ➢ No operative mortality or permanent operative morbidity ➢ Transient increase in dyskinesias was common after STN stimulation, which usually subsided after a reduction of LEDD and replacement of levodopa by dopamine agonists ➢ 4/16 STN patients with low pre-op LEDD and severe hyperkinesias-however- had disabling choreoballistic dyskinesias for more than 1 month after surgery because of an extrememly narrow therapeutic window between 'off' and 'on' with dyskinesias ➢ the adjustment period of increasing stimulation in small steps after complete withdrawal of levodopa lasted more than 3 months in 2 patients and required almost weekly outpatient visits

	➢ transient depression, anhedonia, abulia, increased fatigue, and persisting hypophonia in STN-stimulated patients were attributed to levodopa withdrawal because they improved with increasing LEDD but not changing stimulation parameters ➢ mild hypophonia or hypersalivation had to be accepted as permanent side effects in 9/16 STN stimulated patients because of limits of increasing LEDD ➢ Neuropsychiatric testing in a subgroup (GPi n=10/8; STN n= 14/12) revealed a tendency toward reduced Hamilton depression scores in both groups in the intermediate term after surgery ➢ Mini-Mental State Examination, Cambridge Examination for Mental Disorders of the Elderly, Cognitive Subscale, State and Trait Anxiety Scale, and Minnesota Multiphasic Personality inventory Scores remained unchanged
Source of funding	Public sector
Additional comments	➢ Selection criteria for 16/46 STN patients? (biased) ➢ Non-randomised ➢ Unblinded ➢ No direct prospective comparison
NCC CC ID (Ref Man)	19701

Evidence Table **SURG 2** Which is the most effective form of deep brain stimulation in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	
Bibliographic reference	Minguez-Castellanos A, Escamilla-Sevilla F, Katati MJ, Martin-Linares JM, Meersmans M, Ortega-Moreno A *et al*. Different patterns of medication change after subthalamic or pallidal stimulation for Parkinson's disease: target related effect or selection bias? *Journal of Neurology, Neurosurgery & Psychiatry* 2005;**76**:34-9.
Study type	Before and after surgery study (retrospective analysis)
Evidence level	3
Study objective	To analyse outcomes after one year of bilateral GPi or STN DBS, with consideration of influence of selection bias on the pattern of post surgical medication change
Number of patients	N=20 PD patients N=10 STN

<table>
<tr><td></td><td>N=10 GPi

Location: Spain Sites: single</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria: diagnosis of idiopathic PD according to ‘Core Assessment Program for Intracerebral Transplantations (CAPIT) protocol, age between 35 and 75 years, history of the disease for more than 5 years, presence of motor complications causing functional disability and not satisfactorily controlled by pharmacological treatment, levodopa test with an improvement of at least 33% in part III (motor subscale) of UPDRS.
<table>
<tr><td></td><td>GPi patients (n=10)</td><td>STN patients (n=10)</td></tr>
<tr><td>Sex (male: female)</td><td>7: 3</td><td>5: 5</td></tr>
<tr><td>Age, years</td><td>59.0 ± 7.23</td><td>62.0 ± 5.27</td></tr>
<tr><td>Duration of disease, years</td><td>15.20 ± 4.19</td><td>14.80 ± 5.01</td></tr>
<tr><td>Hoehn and Yahr state in ‘’off’’ (no. ≤ 3/ >3)</td><td>0/10</td><td>0/10</td></tr>
<tr><td>CAPIT dyskinesia rating scale score</td><td>3.00 ± 0.71</td><td>1.85 ± 0.97</td></tr>
<tr><td>Levodopa dose equivalent (mg/d)</td><td>762 ± 294</td><td>1394 ± 500</td></tr>
</table>
STN and GPi patients differed in CAPIT score (p=0.013) and levodopa dose equivalent (p=0.004)</td></tr>
<tr><td>Intervention</td><td>GPi DBS or STN DBS (see paper for details)</td></tr>
<tr><td>Comparison</td><td>Pre-surgical evaluation</td></tr>
<tr><td>Length of follow-up</td><td>One year</td></tr>
<tr><td>Outcome measures</td><td>Unified Parkinson’s disease rating scale (UPDRS) total, UPDRS ADL, UPDRS motor, UPDRS item 39, Schwab and England scale, CAPIT dyskinesia rating scale, LD dose equivalent, adverse events</td></tr>
<tr><td>Effect size</td><td>➢ The one-year outcomes of the first patients who underwent bilateral GPi or STN DBS were retrospectively analysed

<table>
<tr><td>Outcomes</td><td colspan="2">GPi patients (n=10)</td><td colspan="2">STN patients (n=10)</td></tr>
<tr><td></td><td>Change*</td><td>P value</td><td>Change*</td><td>P value</td></tr>
<tr><td>UPDRS total (off)</td><td>-38% (19.64)</td><td>0.005</td><td>-38% (20.80)</td><td>0.005</td></tr>
<tr><td>UPDRS ADL (off)</td><td>-32% (18.80)</td><td>0.007</td><td>-33% (21.32)</td><td>0.007</td></tr>
<tr><td>UPDRS motor (off)</td><td>-35% (21.08)</td><td>0.005</td><td>-39% (20.72)</td><td>0.005</td></tr>
<tr><td>UPDRS motor (on)</td><td>+11% (67.73)</td><td>NS</td><td>+14% (70.05)</td><td>NS</td></tr>
<tr><td>Time in off (UPDRS item 39)</td><td>-1.30% (0.82)</td><td>0.006</td><td>-1.20% (0.63)</td><td>0.006</td></tr>
<tr><td>Schwab & England scale (off)</td><td>+33% (16.36)</td><td>0.005</td><td>+42% (15.49)</td><td>0.005</td></tr>
</table></td></tr>
</table>

	<table><tr><td>CAPIT dyskinesia rating scale</td><td>-56% (30.46)</td><td>0.007</td><td>-42% (51.28)</td><td>0.034</td></tr><tr><td>LD dose equivalent (mg/d)</td><td>+9% (24.22)</td><td>NS</td><td>-24% (21.80)</td><td>0.017</td></tr></table> ➢ *Change refers to the mean (SD) of the individual changes in paired comparisons between baseline and one year evaluations Efficacy summary ➢ Both groups show a significant reduction in UPDRS off medication scores, in time spent in the off state and in CAPIT scores ➢ The mean reduction in UPDRS III off medication score was 35% (95%CI 20% to 51%) in GPi and 39% (95%CI 25% to 54%) in STN with no statistically significant difference between them ➢ There were no differences between the groups in terms of improvement in tremor, rigidity, akinesia, and gait subscales ➢ CAPIT scores were reduced by 56% (95%CI 35% to 78%) in GPi and 42% (95%CI 5% to 79%) in STN- the absolute scores were significantly different with a greater reduction in GPi (p=0.046) but the percentage differences were not significant ➢ Levodopa dose equivalent did not change significantly in GPi but was reduced by 24% in STN (95%CI 9% to 40%; p=0.017) ➢ The intensity of motor complications was greater in GPi DBS group but non-significant (p=0.063) Adverse events ➢ Related to surgical procedure: intracranial haemorrhage (one STN), epileptic seizure (one GPi) ➢ Related to devices: infection (n=2) or electrode fracture (n= 1) ➢ Long-term follow-up (range 1-8 years) skin erosions (n= 2) ➢ Adverse events related directly or indirectly to the electrical stimulation appeared only in the STN DBS group (p=0.086): dyskinesias (1), paresthesias (1), apraxia of lid opening (1), mood change with apathy (1)
Source of funding	Non-profit
Additional comments	➢ Small sample size ➢ Unblinded and uncontrolled ➢ Retrospective analysis ➢ Patients no diagnosed according to UK PDS brain bank criteria
NCC CC ID (Ref Man)	19885

Evidence Table What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	
Bibliographic reference	Ondo W, Dat VK, Almaguer M, Jankovic J, Simpson RK. Thalamic deep brain stimulation: effects on the nontarget limbs. *Movement Disorders* 2001;**16**:1137-42.
Study type	3-month before and after study
Evidence level	
Study objective	To evaluate ipsilateral tremor characteristics and the effects of device inactivation in patients with Parkinson's disease (PD) who were evaluated at least one month after unilateral thalamic ventral intermediate (VIM) deep brain stimulation (DBS) placement.
Number of patients	N= 70 PD and essential tremor (ET) patients N=41 ET patients N=32 PD patients Location: USA sites: two
Patient characteristics	Patients with ET and tremor-dominant PD were recruited. All PD patients reported at least transient improvement with levodopa and in each case tremor was considered to be the most troublesome symptom. Patients were excluded if they had symptomatic dementia, a prior brain surgery, relevant co morbid disease or were older than 80 years. PD patients: 27/32 male, average age 70.5 ± 9.0 years
Intervention	Surgical procedures have been described in previous publication. See paper for more detail on methods. PD patients: all patients were implanted with a single electrode. The settings averaged from 2.8 ± 1.0 volts (range 1.5 – 5.3); pulse width 219.7 ± 64.4 μsec (range 120 -450), and frequency 149.4 ± 24.8 Hz (range 100-185). Electrode settings were bipolar for 27/32 patients.
Comparison	Pre-operative assessments
Length of follow-up	On average 97.0 ± 28.9 days (10 patients examined 1-2.5 months, the rest 3-6 months post surgery)
Outcome measures	UPDRS part III, posture and kinetic leg tremor score, kinetic arm tremor, mini-mental state examination (MMSE)
Effect size	➢ 62 patients (36/41 ET and 26/32 PD) were rated with a blinded assessment with the stimulator activation status randomised to either ON or OFF, using the device settings from the previous visit ➢ Only PD patient results discussed below ➢ After initial implantation all blinded and unblinded measures of contralateral tremor significantly improved

	➢ ON state: face tremor P<0.005, observed tremor (arm and leg ratings combined) contralateral P<0.0001), bradykinesia (UPDRS motor #23-26) contralateral P<0.05, rigidity (ratings are combined upper and lower extremity rigidity) contralateral P<0.005, ADL score (UPDRS total 'on' part II) P<0.0001 ➢ OFF state: all non-significant ➢ Blinded ON (n =15): observed tremor contralateral P<0.0001, rigidity contralateral P<0.05 ➢ Blinded OFF (n =11): rigidity contralateral P<0.05 ➢ Patients rated themselves as 'markedly improved' (n=21), 'moderately improved' (n=4), 'no change' (n=2), and 'mildly worse' (n=1) ➢ MMSE scores did not change throughout the study ➢ After deactivation all measures of tremor returned to baseline ➢ There were no differences or trends toward either residual improvement or rebound worsening after deactivation on either side ➢ On the ipsilateral side to DBS placement, PD patients demonstrated no changes or strong trends toward either worsening or improvement of tremor or other measures of PD Adverse events ➢ Usually mild and included: dysarthria (n=4), disequilibrium (3), paresthesia (1), increased drooling (1), nausea (1), insomnia (1), dysphagia 91), depression (1) and wire tightness (1)
Source of funding	Hospital, Public and Private sector funding
Additional comments	➢ Uncontrolled ➢ Blinded and unblinded ratings ➢ Reasons for exclusion or withdrawal stated ➢ Diagnoses criteria stated
NCC CC ID (Ref Man)	19704

Surg – section 8.5

Evidence Table

SURG 1

What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?

Bibliographic reference	Krauss JK, Simpson RK, Jr., Ondo WG, Pohle T, Burgunder JM, Jankovic J. Concepts and methods in chronic thalamic stimulation for treatment of tremor: technique and application. *Neurosurgery* 2001;**48**:535-41.
Study type	24-month follow-up before and after study
Evidence level	3
Study objective	To rationalize the technique and reduce the costs associated with chronic deep brain stimulation of the thalamus for treatment of refractory tremor
Number of patients	N=94 patients N= 45 Parkinson's disease (PD) N=42 essential tremor N=7 had kinetic tremor Location: US, Switzerland, Germany Sites: 3
Patient characteristics	Tremor was disabling or a source of social embarrassment in all patients and was not controlled satisfactorily by medication. Mean age was 68.7 years (range 31-83) at the time of operation and included 26 women and 68 men. Kinetic tremor in 7 patients was due to multiple sclerosis, head injury, stroke, or degenerative disease.
Intervention	Chronic thalamic DBS system implantation- see paper for details
Comparison	Pre-operative assessments
Length of follow-up	Mean follow-up was 11.9 months
Outcome measures	Tremor rating
Effect size	➢ The transient improvement of the contralateral tremor was judged as marked (arrest or near cessation of the tremor during a longer period) in 16 cases, moderate (transient but considerable relief) in 38 cases, and mild in 51 cases ➢ In all patients, paresthesias of the contralateral face and hand were evoked with high-frequency stimulation ➢ The electrode was repositioned intra-operatively in 22 cases

	➢ The electrode was repositioned twice in 5 patients and 3 times in one patient ➢ Post-op CT scans confirmed the appropriate position of electrodes in all patients Efficacy ➢ The mean formal follow-up was 11.9 months (range 3-24 months) ➢ At the last available follow-up the improvement in tremor was rated as excellent in 47 patients (50%), marked in 37 (39%), moderate in 8 (9%) and minor in 2 (2%) ➢ Success rated varied with casues of tremor ➢ Symptomatic improvement was rated as excellent in 51%, marked in 36%, moderate in 11% and minor in 2% of patients with PD Adverse events ➢ 6 patients experienced transient intraoperative or post-operative adverse events: one patient had a cortical or subcortical venous infarction with temporary aphasia, one patient had intraventricular haemorrhage and 4 had cardiovascular problems intraoperatively ➢ No persistent surgical complications ➢ Upon chronic stimulation 40 patients experienced some stimulation-related side effects ➢ Side effects were considerably more frequent in patients with bilateral implants (15/29, 52%) as compared with unilateral (21/67, 31%) ➢ They were generally mild and reversible with change of electrical parameters ➢ They disappeared when stimulator was turned off ➢ Stimulation-induced side effects included: dystonia (n=3), diplopia (2), sleepiness (2), altered mental status (2), paresthesias (6), mild distrurbace of gait and balance (22), and mild dysarthria (16) ➢ There were no infections ➢ Wire breakage occurred in 2 patients
Source of funding	None stated
Additional comments	➢ Patients received implants between November 1995 to March 1999 ➢ Assessment were performed by neurological team members or by trained study nurses employed by the neurological departments ➢ Blinded assessments were obtained from patients in Houston ➢ No before and after statistical analysis ➢ uncontrolled
NCC CC ID (Ref Man)	19705

Evidence Table What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?	
Bibliographic reference	Ondo W, Dat VK, Almaguer M, Jankovic J, Simpson RK. Thalamic deep brain stimulation: effects on the nontarget limbs. *Movement Disorders* 2001;**16**:1137-42.
Study type	3-month before and after study
Evidence level	
Study objective	To evaluate ipsilateral tremor characteristics and the effects of device inactivation in patients with Parkinson's disease (PD) who were evaluated at least one month after unilateral thalamic ventral intermediate (VIM) deep brain stimulation (DBS) placement.
Number of patients	N= 70 PD and essential tremor (ET) patients N=41 ET patients N=32 PD patients Location: USA sites: two
Patient characteristics	Patients with ET and tremor-dominant PD were recruited. All PD patients reported at least transient improvement with levodopa and in each case tremor was considered to be the most troublesome symptom. Patients were excluded if they had symptomatic dementia, a prior brain surgery, relevant co morbid disease or were older than 80 years. PD patients: 27/32 male, average age 70.5 ± 9.0 years
Intervention	Surgical procedures have been described in previous publication. See paper for more detail on methods. PD patients: all patients were implanted with a single electrode. The settings averaged from 2.8 ± 1.0 volts (range 1.5 – 5.3); pulse width 219.7 ± 64.4 μsec (range 120 -450), and frequency 149.4 ± 24.8 Hz (range 100-185). Electrode settings were bipolar for 27/32 patients.
Comparison	Pre-operative assessments
Length of follow-up	On average 97.0 ± 28.9 days (10 patients examined 1-2.5 months, the rest 3-6 months post surgery)
Outcome measures	UPDRS part III, posture and kinetic leg tremor score, kinetic arm tremor, mini-mental state examination (MMSE)
Effect size	➢ 62 patients (36/41 ET and 26/32 PD) were rated with a blinded assessment with the stimulator activation status randomised to either ON or OFF, using the device settings from the previous visit ➢ Only PD patient results discussed below ➢ After initial implantation all blinded and unblinded measures of contralateral tremor significantly improved

	➢ ON state: face tremor P<0.005, observed tremor (arm and leg ratings combined) contralateral P<0.0001), bradykinesia (UPDRS motor #23-26) contralateral P<0.05, rigidity (ratings are combined upper and lower extremity rigidity) contralateral P<0.005, ADL score (UPDRS total 'on' part II) P<0.0001 ➢ OFF state: all non-significant ➢ Blinded ON (n =15): observed tremor contralateral P<0.0001, rigidity contralateral P<0.05 ➢ Blinded OFF (n =11): rigidity contralateral P<0.05 ➢ Patients rated themselves as 'markedly improved' (n=21), 'moderately improved' (n=4), 'no change' (n=2), and 'mildly worse' (n=1) ➢ MMSE scores did not change throughout the study ➢ After deactivation all measures of tremor returned to baseline ➢ There were no differences or trends toward either residual improvement or rebound worsening after deactivation on either side ➢ On the ipsilateral side to DBS placement, PD patients demonstrated no changes or strong trends toward either worsening or improvement of tremor or other measures of PD Adverse events ➢ Usually mild and included: dysarthria (n=4), disequilibrium (3), paresthesia (1), increased drooling (1), nausea (1), insomnia (1), dysphagia 91), depression (1) and wire tightness (1)
Source of funding	Hospital, Public and Private sector funding
Additional comments	➢ Uncontrolled ➢ Blinded and unblinded ratings ➢ Reasons for exclusion or withdrawal stated ➢ Diagnoses criteria stated
NCC CC ID (Ref Man)	19704

Evidence Table

SURG 1

What is the effectiveness and safety of any deep brain stimulation procedure vs. standard medical therapy in the treatment of motor fluctuations and complications in patients with Parkinson's disease?

Bibliographic reference	Benabid AL, Pollak P, Seigneuret E, Hoffmann D, Gay E, Perret J. Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. *Acta Neurochir Suppl (Wien)*

	1993;**58**:39-44.
Study type	Before and after study
Evidence level	3
Study objective	To report on the author's experience over 5 years and the differential effects of Vim thalamic stimulation on various types of tremor.
Number of patients	N=87 patients suffering from disabling and drug-resistant tremor N= 61 Parkinson's disease (PD) patients N=13 essential tremor (ET) patients N=13 action tremor (mainly related to mesencephalic lesions) Location: Grenoble, France sites: single
Patient characteristics	87 patients suffering from disabling and drug-resistant tremor, 61 Parkinson's disease (PD) patients, 13 essential tremor (ET) patients, and 13 action tremor (mainly related to mesencephalic lesions- including 4 with multiple sclerosis). Eleven patients had previously undergone contralateral thalamotomy and 39 (45%) had bilateral Vim stimulation at the same time, making a total of 50/87 (57%) with bilateral thalamic surgery. No details on demographics, diagnosis, inclusion/exclusion criteria or disease severity.
Intervention	Chronic ventral intermediate (Vim) thalamic stimulation- see paper for details
Comparison	Pre-operative assessments
Length of follow-up	Not stated (5 year experience but no detail on time period from surgery to results listed below)
Outcome measures	Tremor suppression, morbidity/ mortality and side effects
Effect size	➢ The effect on tremor was scored independently by the neurologist on a 5-point scale ➢ (4= complete disappearance of tremor in all circumstances, 3= reappearance of slight tremor on rare occasions, for instance under stress, 2= moderate benefit, 1= slight benefit without real improvement in daily life, 0= no benefit at all or worsening of tremor) Tremor suppression ➢ Immediately after surgery a thalamotomy-like effect was responsible for a transitory tremor suppression for a few days ➢ During the test period- various combinations of stimulation parameters were evaluated ➢ The best effect/side effects ratio was observed for pulse width of about 60 μsec ➢ The threshold intensity versus frequency necessary to suppress totally the tremor was assessed: the minimum was a plateau from about 100 to 2000 Hz ➢ The stimulators are therefore set at 130 to 185 Hz

	➢ Voltage value was actually set according to patient choice based on his compromise between benefit and side effects ➢ Voltage increased during first 6 weeks ➢ The average voltage at the last follow-up for each patient was 2.7 volts (range 0.4 to 5.5V) ➢ A good result (scores of 3 or 4) was obtained in 71% of the operated sides ➢ **Major benefit was obtained in 88% of cases with PD** ➢ (68% of cases with ET and 18% of cases related to other causes) ➢ Rest tremor was better controlled than action tremor ➢ Distal limb tremor better controlled than proximal or axial tremor ➢ Upper better controlled than lower limb tremor ➢ In all cases the effect was strictly simulataneous with stimulation without significant delay of onset or post-effect at arrest ➢ Tremor was the only parkinsonian sign influenced by Vim stimulatuion ➢ **In 1/3 PD patients - L-dopa doses could be reduced by more than 30%** Morbidity and mortality ➢ No mortality in this series of patients ➢ Two patients had secondary skin ulceration of the scalp in front of the electrode-to-extension connection ➢ Two patients had asymptomatic intracranial micro-haematomas Side effects ➢ Were mild and immediately disappeared when stimulation was decreased or turned off ➢ Included: contralateral paresthesias (9%), limb dystonia (9%), disequilibrium (7.6%), and dysarthria (15% on the whole: 6% with bilateral stimulation, 7.5% with previous unilateral thalamotomy and contralateral stimulation, and 1.5% with unilateral stimulation) ➢ Dysarthria was therefore observed in 14% of the bilaterally stimulated patients and in 50% of the patients previously thalatomised ➢ No spontaneous psychological disturbance was reported ➢ Suddenly switching on the stimulator could induce transient (a few seconds) and not disabling contralateral parathesiae ➢ Switching off the stimulator induced a transient rebound tremor in about half of the patients which made them use the stimulator at night ➢ Continuous stimulation (mainly those with action tremor) a kind of ‘tolerance’ with decreasing efficacy of stimulation

Source of funding	Private and university funding
Additional comments	➢ Unblinded ➢ Uncontrolled ➢ No details of patient recruitment ➢ Lack of patient characteristic details ➢ Combination of results from patients of various diseases
NCC CC ID (Ref Man)	19728

Psych 1 – section 9.2.1

Evidence Table **Psych 1** What is the effectiveness of antidepressant therapies vs. placebo or active comparator in the treatment of depression in Parkinson's disease?	
Bibliographic reference	Shabnam G, Chung TH, Deane KHO, Rickards H, Clarke CE. Therapies for Depression in Parkinson's Disease.(Cochrane Review). *The Cochrane Library* 2003.
Study type	Cochrane review of randomised controlled trials
Evidence level	1++ (applied to Cochrane methodology and not studies included in the review)
Study objective	To assess the efficacy and safety of antidepressant therapies in idiopathic Parkinson's disease (PD).
Number of patients	N=106 PD patients N=22 (Andersen) N=37 (Wermuth) N=47 (Rabey) Location: Denmark (Andersen, Wermuth), Israel (Rabey) Sites: 2 (Andersen), 6 (Wermuth), 1 (Rabey)
Patient characteristics	Andersen: 22 patients recruited but only demographic data on 19 patients who completed the study provided (seven women, 12 men; aged 48 to 75 years with a median of 59 years). They had been diagnosed with PD (defined by trial authors) for a median of 6.5 years (range 1-17). They were diagnosed with depression if they scored at least 13 points on the author's unique 31-item scale. Levodopa dose was kept constant for all patients throughout the study. Rabey: recruited 47 patients with a mean of 75 years. They had been diagnosed with PD (defined by trial authors) for a mean of 7 years. Depression was diagnosed by DSM-IV criteria. 17 patients were

	demented according to DSM-IV criteria. Levodopa was given with a mean dose of 500 mg/d. Wermuth: 37 patients, 16 male, total mean age of 64 years (range 44-79). They had been diagnosed with PD as defined by trial authors. Depression was diagnosed by DSM-III-R (major depression). Demented patients were excluded from trial. The dose of levodopa was not stated and dopamine agonists were allowed.
Intervention	Andersen: Nortriptyline (TCA) 25-150 mg/d for each individual throughout the study Rabey: Fluvoxamine (SSRI) 78 mg/d (range unclear) Wermuth: citalopram (SSRI) (depended on age and clinical response) 20mg <65 yr and 10mg >65 yr)
Comparison	Placebo (Andersen, Wermuth) Amytriptyline (TCA) (Rabey) 69 mg/d (range unclear)
Length of follow-up	**Trial duration:** Andersen: 16 weeks, 8 week crossover period, no washout period stated (Andersen), Rabey: not stated (Rabey) Wermuth: 52 weeks, acute phase (first 6 weeks) and a continuation phase (the last 46 weeks)
Outcome measures	Depression rating scales (unique to authors), Hamilton Depression Rating Scale (HDRS), Melancholia Scale, UPDRS
Effect size	Andersen: double blind crossover study ➢ Stated nortriptyline reduced depression ($p<0.001$) when analysed on a per protocol basis and combining the results of both arms of the crossover trial ➢ Nortriptyline showed a larger improvement of median depression score over placebo in first arm of the crossover trial (baseline median 26 for both groups, nortriptyline group 13 and placebo group 9 after treatment)- statistical significance not stated ➢ No significant difference in posture, gait, general motility, finer movements, rigidity, akinesia, or tremor ➢ Adverse events: Mean systolic blood pressure (when standing)was found to be significantly lowered with Nortriptyline treatment, mean systolic and diastolic pressure did not significantly alter in recumbent position; cardiac arrhythmia was not present in any of the patients and ECG results did not change ➢ Withdrawals: three patients dropped out of study; two complained of dizziness and drop attacks at beginning of nortriptyline treatment probably due to orthostatic hypotension due to combined medications, and one after the crossover from active to placebo period (stopped because of ''lack of effect'')

	Rabey: open-label study ➢ 50% of amytriptyline group (15/27) and 60% of fluvoxamine group (12/20) showed a 50% decrease in Hamilton score after a mean treatment period of 16 and 17 months respectively ➢ This paper was only published as an abstract ➢ Adverse events: eight patients (40%) treated fluvoxamine and 12 (45%) treated with amytriptyline dropped out- due to confusion and hallucinations in 7 fluvoxamine and 10 amytriptyline patients, somnolence in 1 amytriptyline patient, tremor in 1 fluvoxamine and mouth dryness in 1 amytriptyline patient Wermuth: double blind parallel study ➢ Only reported a small but significant reduction ($p<0.05$) in the Hamilton Depression Scale and Melancholia Scale scores in both citalopram and placebo groups between baseline and acute phase ➢ No significant difference between placebo arm and citalopram arm either from baseline to acute phase or to continuation phase ➢ True for both per protocol and intention-to-treat analysis ➢ No significant difference observed for PD symptoms assessed by UPDRS from baseline to acute phase or to the end of the trial on either per protocol or intention-to-treat ➢ Adverse events: used Udvalg for Kliniske Undersogelser (UKU) side effect scale only in the acute phase of the trial. Inner unrest (7/17), reduced duration of sleep (3/17) and headache (4/17) were more frequently observed in patients in the placebo group than in the citalopram group ➢ In comparison diarrhoea (1/13) increased sweating (4/13) diminished sexual desire (2/13) and nausea and vomiting (3/13) were more prominent in the citalopram group ➢ No studies on electroconvulsive therapy or behavioural therapy were found which met criteria ➢ Reviewer's conclusions: insufficient data on the effectiveness and safety of any antidepressant therapies in Parkinson's disease are available on which to make recommendations for their use. Further large scale randomised controlled trials are urgently required in this area.
Source of funding	None stated
Additional comments	➢ Wermuth and Rabey did not state methods of randomisation or allocation concealment ➢ Small sample and no power calculations provided ➢ Baseline characteristics missing: gender, range of age, length of time after the diagnosis of PD, detailed exclusion criteria, dose range of levodopa (Rabey); length of time after diagnosis of PD

	(Wermuth), demographic data of withdrawal patients (Andersen) ➢ Comparison of patient's baseline data between different treatment groups was not possible- selection bias possibility ➢ None of the trials stated the criteria for the diagnosis of PD ➢ Lack of washout period in Andersen study- possibility of carryover effect ➢ Only Wermuth used intention-to-treat analysis
Citation	
NCC CC ID (Ref Man)	78

Evidence Table **Psych 1** What is the effectiveness of antidepressant therapies vs. placebo or active comparator in the treatment of depression in Parkinson's disease?	
Bibliographic reference	Leentjens AF, Vreeling FW, Luijckx GJ, Verhey FR. SSRIs in the treatment of depression in Parkinson's disease. *International Journal of Geriatric Psychiatry* 2003;**18**:552-4.
Study type	Double-blind, randomised, placebo-controlled trial
Evidence level	1+
Study objective	To investigate the effectiveness of sertraline (SSRI) in patients with Parkinson's disease and major depressive disorder.
Number of patients	N=12 Parkinson's disease (PD) patients N=6 sertraline N=6 placebo Location: The Netherlands Sites: single
Patient characteristics	Consecutively referred PD patients with major depressive disorder were recruited from the neurological outpatient department at a University hospital. The diagnosis of PD was established according to the clinical criteria of the UK-PDS-BB clinical criteria. The diagnosis of depression was made according to the 4th ed of the Diagnostic and Statistical Manual (DSM) of the American Psychiatry Association (APA), making use of the structured clinical interview for DSM-IV Depression (SCID-D). Four women and eight men with an overall average age of 67 years (SD 7.8) entered the trial. The

	average MMSDE score was 27.8 (SD 2.3) . Most were suffering from moderately severe PD. There were no significant differences between groups at baseline.
Intervention	Sertraline 25 mg, increased to 50mg after 1 week, if there was no response within 6 weeks dose was doubled to 100mg
Comparison	Placebo
Length of follow-up	Trial duration of 10 weeks
Outcome measures	Montgomery-Asberg Depression Rating Scale (MADRAS), UPDRS, side effects
Effect size	➢ In spite of recruitment efforts on 12 patients were included in the study in 30 months (aim was 40) ➢ Because of the low recruitment it was decided to terminate the trial ➢ The first analysis compared the number of responders in the sertraline group and the placebo group; response was defined as at least 50% reduction of the pre-treatment MADRAS score ➢ The second analysis compared the magnitude of response by comparing the changes in MADRAS scores during treatment in both groups ➢ 3/6 patients from sertraline group (50%) and 4/6 (67%) from placebo group responded (p=1.000) ➢ The effect of treatment on MADRAS scores showed a significant treatment effect in both groups- however no significant difference in effect between groups ➢ UPDRS motor scores of both groups did not change significantly from baseline ➢ There was no significant between-group change in post-treatment scores
Source of funding	Pharmaceutical
Additional comments	➢ Method of randomisation stated ➢ Method of allocation concealment not stated ➢ All types of antiparkinsonian medication was allowed ➢ No drop-outs (therefore intention to treat analysis)
Citation	
NCC CC ID (Ref Man)	19762

Evidence Table

Psych 1

What is the effectiveness of antidepressant therapies vs. placebo or active comparator in the treatment of depression in Parkinson's disease?

Bibliographic reference	Fregni F, Santos CM, Myczkowski ML, Rigolino R, Gallucci-Neto J, Barbosa ER *et al*. Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry* 2004;**75**:1171-4.
Study type	Randomised, parallel group study, blinded rater
Evidence level	1+
Study objective	To study the efficacy of 15Hz repetitive transcranial magnetic stimulation (rTMS) in treating depression in patients with Parkinson's disease.
Number of patients	N=42 patients with Parkinson's disease (PD) N=21 RTMS group N=21 fluoxetine group Location: USA Sites: single
Patient characteristics	Patients with idiopathic PD diagnosed according to the UK PDS brain bank criteria, and major or minor depression according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Ed (DSM-IV). Patients were excluded if they had been using antidepressants within two months of the study or had ferromagnetic metallic implants, a history of seizures, major head trauma, dementia or depression with psychotic symptoms.

	rTMS (group 1)	Fluoxetine (group 2)
Age (years)	65.3 ± 7.8	66.0 ± 8.5
Age at onset (years)	58.8 ± 8.5	57.5 ± 8.9
Male: female (n)	11:10	15:6
MMSE	24.8 ± 4.5	24.1 ± 3.6
Major depression (n)	17	16
Minor depression (n)	4	5

Intervention	rTMS and placebo-drug treatment. Focal rTMS of the left dorsolateral prefrontal cortex was undertaken using a figure-of-eight coil and a stimulator. Forty trains of 5 seconds each, using an intensity of 110% of motor threshold and 15Hz frequency, were applied in each patient for 10 days during a two-week period.
Comparison	Sham rTMS and 20mg/d fluoxetine (for sham surgeries, stimulation parameters were the same but a

	sham coil was used)
Length of follow-up	Trial duration: 8 weeks
Outcome measures	Hamilton Rating Scale for Depression (HRSD), Beck Depression Inventory (BDI), Mini-Mental state examination (MMSE), Hoehn and Yahr (H&Y) scale, Unified Parkinson's Disease Rating Scale (UPDRS), and Schwab and England activities of daily living scale (SEALD), adverse events
Effect size	➢ Evaluations at 2 and 8 weeks treatment HDRS ➢ Two-factor repeated measures ANOVA showed a significant effect of time for HDRS and BDI scores ($p<0.001$ both) ➢ Post-hoc analysis showed a significant difference between baseline and 2 weeks, but not between 2 and 8 weeks- suggesting a long lasting anti-depressive effect in both groups ➢ Mean decrease in HDRS and BDI after 2 weeks of treatment was 38% and 32% for group one and 41% and 33% for group 2 ➢ In each group 9 patients could be classified as 'responders' (50% reduction in HDRS scores) after 2 weeks of treatment ➢ No significant differences between the sexes in anti-depressant response UPDRS ➢ Repeated measures ANOVA showed no differences in group, time or group x time ➢ Although the effect did not achieve significance, group 1 tended to be stable during the treatment, while scores in group 2 tended to worsen after 8 weeks ADL ➢ For ADL repeated measures ANOVA showed a time effect ($p<0.001$) ➢ On post-hoc analysis, only group 1 had significantly higher scores of ADL at eight weeks compared with the initial value ($p=0.002$) MMSE scores ➢ Repeated measures ANOVA showed a significant effect of time ($p=0.023$) ➢ On post-hoc analysis there was a significant difference between the 2 groups at week 2 ($p=0.029$) ➢ Group 1 showed greater improvement in MMSE scores than group 2 ➢ After 8 weeks there was no difference between groups- suggesting that group 1 improved faster but not overall more than group 2 Adverse events ➢ More common in group 2 than in group 1 ($p=0.03$)

	➢ Total numbers of complaints related to treatment were 40 and 53 after 2 weeks and 14 and 40 after 8 weeks in group 1 and 2 ➢ Specific events not stated Withdrawals ➢ All patients completed the study
Source of funding	None stated
Additional comments	➢ Computer randomisation (1:1) ➢ Blinded raters ➢ Inter-rater reliability tested ➢ Intention-to-treat analysis ➢ Small sample size and no power calculations provided
Citation	
NCC CC ID (Ref Man)	19761

Psych 2 – section 9.2.2

Evidence Table **PSYC 2** What is the effectiveness of atypical antipsychotic therapies vs placebo or active comparator in the treatment of psychosis in Parkinson's disease?	
Bibliographic reference	Pollak P, Tison F, Rascol O, Destee A, Pere JJ, Senard JM *et al*. Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. *Journal of Neurology, Neurosurgery & Psychiatry* 2004;**75**:689-95.
Study type	Randomised, double-blind, placebo-controlled study
Evidence level	1+
Study objective	To assess the efficacy and tolerability of clozapine in drug-induced psychosis in Parkinson's disease.
Number of patients	N=60 patients with Parkinson's disease (PD) N=32 clozapine N=28 placebo

	Location: France Sites: 13
Patient characteristics	Patients suffering from idiopathic PD according to UK PD brain bank criteria and experiencing a drug-induced psychosis of at least two weeks duration. Patients had no or mild dementia (MMSE $\geq$ 20) and psychosis despite discontinuation of anticholinergic drugs, amantadine and selegiline, and showing no improvement in psychotic symptoms or unacceptable motor deterioration on attempted withdrawal of dopaminergic agonists or decreased daily levodopa doses. Doses of antiparkinsonian drugs were unchanged. Patient characteristics were practically identical in both groups: mean age 72$\pm$ 8, duration of disease 12 $\pm$ 5, PANSS positive subscore 16.6 $\pm$ 5.0, UPDRS motor score 33.5 $\pm$ 14.0, Hoehn and Yahr stage 3.2 $\pm$ 1.1, levodopa dose 774 $\pm$ 462 mg/d and dopamine agonist drug intake in 23% of patients.
Intervention	Clozapine 6.25 mg/d (titrated over at least 10 days to a maximum of 50 mg/d)
Comparison	Placebo
Length of follow-up	Trial duration: 4 weeks double-blind, 12-week open, followed by one month after drug withdrawal
Outcome measures	Clinical Global Impression Scale (CGI), Positive Subscore of Positive and Negative Syndrome Scale (PANSS), mini-mental state examination (MMSE), UPDRS, Hoehn and Yahr, Schwab and England activities of daily living
Effect size	➢ Antipsychotic efficacy was assessed weekly ➢ Baseline MMSE score was significantly higher in the clozapine group (26.1 vs. 24.1, p=0.01) Efficacy: ➢ At the end of the study the mean daily dose of clozapine was 36 $\pm$ 14 mg ➢ Significant changes in favour of clozapine from the first week for CGI score (p=0.001 at end point) and for the PANSS positive subscore (p<0.001) ➢ The scores for 6/7 items of the PANSS positive subscore (except item grandiosity) were significantly reduced ➢ MMSE score did not changed significantly in either group as well as UPDRS mean motor score which decreased by 3.5 and 3.0 in clozapine and placebo groups respectively Adverse events ➢ Frequency was similar in both groups (32 in clozapine and 28 in placebo) ➢ Somnolence and worsening of parkinsonism were significantly more frequent in clozapine group ➢ 7 patients in clozapine group reported worsening of PD (usually mild or transient) which was confirmed by an aggravation in Schwab and England score by 10% to 10% in 3 patients- no patient discontinued study for this reason

	➢ No case of agranulosytosis Withdrawals: ➢ 14 patients discontinued the treatment prematurely mainly for treatment failure ➢ 3 in clozapine groups and 6 in placebo group withdrew due to inefficiency ➢ 2 in each group due to adverse events ➢ 1 was withdrawn in placebo group
Source of funding	Pharmaceutical
Additional comments	➢ Study was conducted between January 1996 and October 1997 ➢ No methods of allocation concealment reported ➢ Methods of randomisation were reported ➢ Intention-to-treat analysis ➢ No mention of investigator-treatment interaction or centre interaction ➢ No power calculations
Citation	
NCC CC ID (Ref Man)	19779

Evidence Table **Psychosis** What is the effectiveness of atypical antipsychotic therapies vs placebo or active comparator in the treatment of psychosis in Parkinson's disease?	
Bibliographic reference	Friedman J, Lannon M, Cornelia C, Factor S, Kurlan R, Richard I *et al*. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *New England Journal of Medicine* 1999;**340**:757-63.
Study type	Randomised, double-blind, placebo-controlled trial
Evidence level	
Study objective	To determine whether clozapine, administered at low doses, is an effective treatment for drug-induced psychosis in patients with PD and to determine its effect on motor function in such patients.
Number of patients	N= 60 Parkinson's disease (PD) patients N=30 clozapine N=30 placebo

<table>
<tr><td></td><td>Locations: Sites: 6</td></tr>
<tr><td>Patient characteristics</td><td>Patients were enrolled between April 1995 to October 1996, and were included if they had idiopathic PD and psychosis induced by antiparkinsonian drugs. Parkinson's disease was diagnosed when at least three of the four cardinal features were present. Psychosis was severe enough to have warranted treatment with a standard neuroleptic drug if the patient had not had PD and a score of 3 or higher on the clinical global impression scale (CGI) for severity of psychosis. Each patient had to have a history of psychosis of at least 4 weeks duration before enrolment. All were taking levodopa.
Patients were excluded if they had taken clozapine or another neuroleptic drug before the start of the trial (for others see paper).

<table>
<tr><th>Baseline characteristics</th><th>Clozapine (n=30)</th><th>Placebo (n=30)</th></tr>
<tr><td>Females (n=)</td><td>10</td><td>16</td></tr>
<tr><td>Caucasian</td><td>30</td><td>28</td></tr>
<tr><td>Age (yr)</td><td>71.9 ± 8.1</td><td>70.8 ± 8.6</td></tr>
<tr><td>Duration of PD ((yr)</td><td>10.4 ± 75</td><td>10.8 ± 6.1</td></tr>
<tr><td>Hoehn and Yahr stage</td><td>2.8 ± 0.8</td><td>2.6 ± 0.9</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Clozapine 6.25 to 50 mg/d</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow-up</td><td>Trial duration: 14 months (double-blind evaluation lasted for 4 weeks)</td></tr>
<tr><td>Outcome measures</td><td>Clinical Global Impression Scale (CGIS), Brief Psychiatric Rating Scale (BPRS) (original and modified (M) scale), Scale for the Assessment of Positive Symptoms (SAPS), withdrawals</td></tr>
<tr><td>Effect size</td><td>➢ Randomisation of patients was made according to site and age of patients (under 70 yrs or over)
➢ At baseline patients receiving clozapine had less severe psychosis than placebo
Efficacy
➢ The mean daily dose of clozapine prescribed at the end of the study was 24.7mg (range 6.25 to 50)
➢ The mean daily dose of placebo was equivalent to 35.2 mg (range 62.5 to 50)

➢ Changes in psychiatric measures (n=27 in both groups) from baseline to follow-up, as measures by the clinical global impression scale, favoured clozapine treatment over placebo (p=0.002)
➢ BPRS score (p=0.002), BPRS-M score (p=0.003), CGIS score (p<0.001), SAPS score (p=0.01)
➢ MMSE score (p=0.90)

➢ 13 patients in clozapine group and 3 patients in placebo group the severity of psychosis decreased to a level that, if present at baseline, would have made them ineligible for the study</td></tr>
</table>

	➢ Hallucinations, almost entirely visual, improved by 1.9 points for the patients receiving clozapine and 0.7 for placebo (p=0.002) on the Brief Psychiatric Scale (BPS) ➢ No differences between groups with respect to sleep questionnaire ➢ There was no worsening of motor symptoms in either group according to measures of parkinsonism ➢ There was a statistically significant beneficial effect of clozapine on UPDRS tremor (p=0.02) ➢ No significant differences between two groups with respect to other parkinsonian measures Withdrawals ➢ 54 patients completed the trial (6 withdrew- 3 on clozapine and 3 on placebo) ➢ The psychiatric condition of 2/3 patients on placebo worsened- the third patient was hospitalised for pneumonia ➢ One clozapine patient discontinued the drug because of leukopenia, one because of myocardial infarction and one because of sedation ➢ No significant changed in the mean neutrophil or white-cell counts in either group ➢ No significant differences between groups for orthostatic blood pressure- but a small significant increase form baseline in mean resting heart rate (3.9 beats/min) of patients receiving clozapine (p=0.046) no increase in patients receiving placebo ➢ Weight increased by 0.7 kg in patients receiving clozapine and 0.1 kg in patients on placebo (p=0.005)
Source of funding	Government and non-profit
Additional comments	➢ 54/60 (90%) completed the trial ➢ Method of randomisation and allocation concealment not stated ➢ Intention-to-treat analysis ➢ Power calculations provided ➢ Investigator-treatment interactions were assessed
Citation	290
NCC CC ID (Ref Man)	19775

Evidence Table **PSCH 2** What is the effectiveness of atypical antipsychotic therapies vs placebo or active comparator in the treatment of psychosis in Parkinson's disease?	
Bibliographic reference	Breier A, Sutton VK, Feldman PD, Kadam DL, Ferchland I, Wright P *et al*. Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease. *Biological Psychiatry*

<table>
<tr><td></td><td>2002;52:438-45.</td></tr>
<tr><td>Study type</td><td>Randomised, double-blind placebo-controlled trials (2 trials)</td></tr>
<tr><td>Evidence level</td><td>1+</td></tr>
<tr><td>Study objective</td><td>To report the findings from two placebo-controlled, double blind studies of the use of olanzapine for control of dopamimetic psychosis when added to a fixed dose of dopamimetic agent.</td></tr>
<tr><td>Number of patients</td><td>
<table>
<tr><td></td><td>US study</td><td>European study</td></tr>
<tr><td>N= total</td><td>83</td><td>77</td></tr>
<tr><td>N=olanzapine</td><td>41</td><td>49</td></tr>
<tr><td>N=placebo</td><td>42</td><td>28</td></tr>
</table>
Location US and Europe Sites: each a multi-centre trial</td></tr>
<tr><td>Patient characteristics</td><td>Patients with idiopathic Parkinson’s disease (PD) experiencing treatment-associated psychosis, as defined by the Diagnostics and Statistics Manual-IV, were enrolled.

Inclusion criteria: patients must have had a diagnosis of idiopathic PD, been responsive to dopamimetics for motor symptoms, experienced hallucinations, delusions, or both in the 2-week period before entry, and a had an individual Hallucinations and Delusions item score of ≥ 2on the neuropsychiatric Inventory (NPI).

Exclusion criteria: any prior treatment with atypical antipsychotic within last 3 months before study.
<table>
<tr><td></td><td colspan="2">US Study</td><td colspan="2">European Study</td></tr>
<tr><td></td><td>Olanzapine</td><td>Placebo</td><td>Olanzapine</td><td>Placebo</td></tr>
<tr><td>Sample size</td><td>41</td><td>42</td><td>49</td><td>28</td></tr>
<tr><td>Age (yr)</td><td>73.5 ± 8.7</td><td>71.7 ± 6.8</td><td>70.9 ± 6.3</td><td>70.5 ± 8.2</td></tr>
<tr><td>Sex (m % : f %)</td><td>63.4: 36.6</td><td>76.2 : 23.8</td><td>67.3 : 32.7</td><td>64.3 : 35.7</td></tr>
<tr><td>Age at onset (yr)</td><td>60.6 ± 14.1</td><td>61.1 ±v 10.3</td><td>60.8 ± 8.0</td><td>55.4 ± 16.1</td></tr>
<tr><td>Demented %</td><td>46.3</td><td>33.3</td><td>34.7</td><td>28.6</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Olanzapine 2.5 mg/d (2.5 mg/d increases allowed every 3 to 4 days up to max of 15mg/d)</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow-up</td><td>Trial duration of 4-weeks double blind phase</td></tr>
<tr><td>Outcome measures</td><td>Primary measure: positive symptoms cluster subscore of the Brief Psychiatric Rating Scale (BPRS)
Secondary measures: BPRS total and negative symptoms cluster scores, the clinical global impression-severitry (CGI-S), and NPI total score and individual item subscores, mini-mental state examination (MMSE), UPDRS total, motor with tremor subscore, ADL, and complications.</td></tr>
<tr><td>Effect size</td><td>➢ Baseline demographic and clinical data did not differ between groups in either study and were roughly equivalent between the two studies</td></tr>
</table>

- The mean modal dose of olanzapine in the US and European studies were 4.2 (± 2.6) mg/d and 4.1 (± 2.0) mg/d respectively

Efficacy

	US study	**European Study**
Psychiatric performance	P value vs. placebo	P value vs. placebo
BPRS total	0.677	0.735
BPRS positive	0.962	0.612
BPRS negative	0.481	0.095
BPRS hallucinations	0.400	0.368
CGI-S psychosis	0.341	0.993
NPI total	0.775	0.496
NPI hallucinations	0.575	0.948
NPI delusions	0.136	0.327
MMSE	0.371	0.252
Motor performance		
UPDRS total	0.007	0.024
UPDRS motor	0.023	0.039
UPDRS tremor item	0.486	>0.99
UPDRS ADL	0.004	0.009
UPDRS complications	0.513	0.466
CGI-S motor	<0.001	0.261

- Motor performance: patients on olanzapine in both studies worsened significantly relative to the improvement in placebo group on UPDRS total, motor and ADL scales
- No significant difference between scores in the UPDRS tremor item and complications scale for olanzapine and placebo-treated in either study
- Patients in both studies who were treated with olanzapine showed significant improvement from baseline in BPRS total, positive cluster, and hallucinations item scores in NPI total and Hallucinations item scores, and in GCI-S psychosis scores.
- There was no significant treatment-group differences in any psychopathologic rating in either study
- MMSE scores were not significantly changed in either treatment group or either study

Withdrawal rates

	➢ US study: significantly fewer patients receiving olanzapine completed the entire 4-week study (p=0.029) ➢ Significantly more olanzapine patients discontinued due to an adverse event (p=0.003) ➢ European study: no treatment differences were found in ether completion rates or discontinuations due to adverse events Adverse events ➢ US study: olanzapine group showed a higher reported incidence in: extrapyramidal syndrome (p=0.003), hallucinations (p=0.013) and increased salivation (p=0.026) ➢ European study: olanzapine was not associated with a significantly higher incidence of any adverse event relative to placebo ➢ No clinically meaningful or consistent findings seen between the two studies with respect to laboratory analyses
Source of funding	Private sector
Additional comments	➢ Methods of randomisation and allocation concealment not stated ➢ Not intention-to-treat analysis ➢ No power calculations provided ➢ Studies were powered independently ➢ Treatment centre-interaction was analysed
Citation	
NCC CC ID (Ref Man)	19776

Evidence Table **PSCH 2** What is the effectiveness of atypical antipsychotic therapies vs placebo or active comparator in the treatment of psychosis in Parkinson's disease?	
Bibliographic reference	Ondo WG, Levy JK, Vuong KD, Hunter C, Jankovic J. Olanzapine treatment for dopaminergic-induced hallucinations. *Movement Disorders* 2002;**17**:1031-5.
Study type	Double-blind, placebo-controlled, parallel design study
Evidence level	1+
Study objective	To determine the effect of low dose olanzapine on hallucinations, motor performance, cognition, and mood in PD patients experiencing hallucinations.
Number of patients	N=30 PD patients N=18 olanzapine

	N=12 placebo Location: USA sites: single
Patient characteristics	All patients were diagnosed with PD based on having 2/3 cardinal criteria. Patients had a Hoehn and Yahr score of II or greater. Both fluctuating and non-fluctuating patients were included. Patients must have had drug-induced hallucinations, which were clinically problematic enough to justify intervention. Mini-mental state examination scores needed to be at least 20/30. The mean age was 71.0 ± 7.1 years, 19 men and 11 women. 18 were fluctuators, only 9 had drug-induced dyskinesia at the time of the study. The mean off Hoehn and Yahr scores was 3.2 ± 0.5, and duration of PD was 9.6 ± 5.1 years. MMSE scores 26.8 ± 3.3. No significant differences between groups for baseline characteristics.
Intervention	Olanzapine starting at 2.5 mg as a single nighttime dose (final mean dose was 4.6 ± 2.2 mg)
Comparison	Placebo (drug equivalent dose of 6.6 ± 2.0 mg, $p<0.05$)
Length of follow-up	Trial duration of 9 weeks
Outcome measures	UPDRS part III (motor), timed tapping scores, UPDRS II (ADL), time on and off, duration of single levodopa dose and time with dyskinesia, UPDRS item 2 (thought disorder), structured interview for hallucinations, neuropsychological test battery (including mini-mental status examination (MMSE), Wechsler Memory Scale, Buschke-Fuld Selective Reminding Test, Timed Verbal Series Attention Test, TRAILS, Benton Controlled Oral Word Association Test, Animal Category Fluency, Hamilton Depression Rating Scale, and Behaviour Alzheimer Disease Test (Global))
Effect size	UPDRS part III ➢ Worsened on olanzapine compared with placebo ($p<0.05$) ➢ Olanzapine patients increased by a mean 4.6 ± 6.9 (range –4 to +17) ➢ Motor decline was driven by worsening in the gait ($p<0.001$) and bradykinesia ($p<0.05$) motor subscales ➢ Timed tapping scores worsened ($p<0.05$) ➢ Total Activity of Daily Living scores (UPDRS II) did not change ➢ In fluctuating patients- subjective time on and off, duration of a single levodopa dose, and time with dyskinesia did not change ➢ UPDRS item 2 (thought disorder) tended to improve on olanzapine- but non-significant ➢ Structured interview for hallucinations in PD tended to improve on drug but non-significantly ➢ The neuropsychological battery showed no significant differences or trends towards differences, between drug and placebo in measures of cognition (executive function, language, memory) or

	mood on any test Follow-up ➢ After study completion eight of the original olanzapine group (50%) continued at a mean daily dose of 2.7 ± 1.6 mg ➢ 6 of the placebo subsequently attempted olanzapine ➢ At the most recent visit (mean 11.0 ± 7.4 months after final visit) only 5/24 (20.8%) who tried olanzapine remained on the drug ➢ 7 (23%) were taking clozapine, 4 (13%) were taking quetiapine, one was taking risperidone and 13 (43.3%) were on no current treatment for psychosis Adverse events ➢ Subjective events reported by 18 patients included: worsening movement (n=6), worse posture (n=3), dysarthria (n=2), oedema (n=2), drooling (n=2), weight gain, dry mouth, nausea, insomnia, sedation, perspiration, and agitation ➢ Subjective events reported by 12 patient son placebo included: insomnia, sedation, leg cramps, lightheadedness, weakness, and tremor in one each Withdrawal ➢ 3 patients discontinued before completion of study ➢ One patient assigned to the drug dropped out before taking any medication ➢ One patient in the drug group and one in the placebo group dropped-out after 3 and 6 weeks respectively due to lack of improvement ➢ These patients were not included in the statistical analyses
Source of funding	Private and non-profit
Additional comments	➢ Methods of randomisation stated (random number generator) 2:1 ratio ➢ Methods of allocation concealment not stated ➢ Not intention-to-treat analysis
Citation	
NCC CC ID (Ref Man)	19778

Evidence Table
PSCH 2
What is the effectiveness of atypical antipsychotic therapies vs placebo or active comparator in the treatment of psychosis in Parkinson's disease?

Bibliographic reference	Ondo, W., Tintner, R., Dat, Vuong K., Lai, D., and Ringholz, G. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. Movement Disorders . 2005.
Study type	Double-blind, placebo-controlled, parallel
Evidence level	1+
Study objective	To test the effectiveness of quetiapine in PD-associated hallucinations.
Number of patients	N=31 Parkinson's disease patients N=21 quetiapine N=10 placebo Location: USA sites: single
Patient characteristics	Patients recruited from Parkinson's Disease Centre and Movement Disorders Clinic. Only patients between 30 and 80 years of age with subjectively problematic visual hallucinations while taking dopaminergic medications. Exclusion criteria included a mini-mental state examination score <21, previous treatment for hallucinations within the past 30 days, the current use of any dopaminergic antagonist for any reason, and presence of a psychiatric diagnosis not believed to be directly related to their PD.

Characteristics	Drug (n=21)	Placebo (n=10)
Age (yr)	74 ± 7	71 ± 5
Gender (m:f)	11:10	6:4
Duration of PD (yr)	12 ± 7	9 ± 4
Fluctuating	12/19	9/12
UPDRS part II	34.2 ± 7.9	30.7 ± 11.9
UPDRS motor	34 ± 8	31 ± 12
Goetz Dyskinesia **	2.0 ± 3.3	5.6 ± 5.2
MMSE	26.1 ± 2.5	27.0 ± 2.9
Initial Brief Psychiatry Rating Scale	11 ± 5	11 ± 5

** p <0.05

	There were no demographic or baseline differences between groups except that drug group had a higher initial score on the Goetz Dyskinesia Rating Scale ($p<0.05$).
Intervention	Drug or placebo was titrated up to 50 mg twice daily. After 3 weeks participants returned for a safety visit and UPDRS testing. They were then further titrated to 100 mg twice daily of quetiapine over 3 weeks, but were allowed to reduce to the dose if adverse events were problematic.
Comparison	Placebo- same procedure as above.
Length of follow-up	Trial duration 12 weeks. No follow-up stated.
Outcome measures	UPDRS, Goetz Dyskinesia Rating Scale, Baylor PD Hallucinations Questionnaire and a battery of neuropsychological tests
Effect size	Dosage ➢ The final daily dose of active drug for completers was 200mg (n=11), 150 mg (n=2), 100 mg (n=3) and 75 mg (n=1) ➢ All placebo participants were on the daily equivalent of 200 mg Efficacy ➢ UPDRS activities of daily living (part II), on motor scores, and Goetz Dyskinesia rating Scale did not change significantly compared to placebo ➢ Both groups showed a similar modest trend towards improvement ➢ Baylor PD Hallucination Questionnaire showed a modest trend towards improvement compared to placebo but did not reach statistical significance (p=0.19) ➢ Change in Brief Psychiatric Rating Scale and hallucination question (12) were not significantly different compared to placebo ➢ Neither the changes of the total neuropsychological battery nor any specific test showed an significant difference changes compared to placebo ➢ Patients on quetiapine globally rated themselves as markedly improved (n=4), moderately improved (n=4), unchanged (n=4), or mildly worse (n=2, p=0.19) ➢ The proportions of those who believed they were meaningfully improved (8 of 17 (47.1%) vs. 2 of 8 (25%) excluding dropouts was not statistically different between the treatment and placebo groups Adverse events ➢ No patient on drug dropped-out secondary to a related adverse event, which included sedation (n=9, 43%), and subjective worsening in PD (n=4, 19%) ➢ One other adverse event was reported by 4 (40%) of placebo participants, and a single different adverse event was reported all 10 subjects Withdrawal rates

	➢ 26 participants completed the study ➢ 17/21 completed drug arm (81%) ➢ 2 dropped out due to serious unrelated illness and 2 dropped out due to lack of effect and poor compliance ➢ 8/10 completed placebo arm (80%) ➢ 2 patients dropped out due to unrelated serious illness, both resulting in death ➢ Drop-outs were not included in statistical analysis where data was not available
Source of funding	pharmaceutical
Additional comments	➢ Not intention to treat ➢ Methods of randomisation and allocation concealment not stated ➢ Power calculations not provided ➢ Small sample size
Citation	
NCC CC ID (Ref Man)	19933

Psych 3 – section 9.2.3

Evidence Table **PSYC 3** Are cholinesterase inhibitors effective cognitive enhancement therapies in Parkinson's disease and Lewy body dementia?	
Bibliographic reference	Wild R, Pettit T, Burns A. Cholinesterase inhibitors for dementia with Lewy bodies. 2003.
Study type	Cochrane Review of randomised, double-blind trials
Evidence level	1++ (applied to Cochrane methodology not included studies)
Study objective	To assess the use of cholinesterase inhibitors in dementia with Lewy bodies (DLB)
Number of patients	N=120 patients (McKeith) N= 59 rivastigmine N=61 placebo Location: Spain, UK, Italy Sites: not stated

Patient characteristics	Patients diagnosed with lewy-body dementia and MMSE > 9. Exclusion criteria: severe extrapyramidal symptoms, asthma, taking neuroleptics, anticholinergics, selegiline, or similar drugs. The baseline demographic characteristics were similar in treatment and placebo groups. The mean age was 74 years, 52% male in rivastigmine and 61% in placebo. The mean MMSE scores were 17.9 and 17.8 in the rivastigmine and placebo groups respectively. Most patients had one or more co-existing medical conditions, musculoskeletal (28%), cardiovascular (28%), gastrointestinal (21%), and psychiatric (18%). The most common concomitant drugs were neurotropic agents, including dopaminergic drugs (30%), hypnotics and sedatives (25% in rivastigmine and 15% in placebo), and antidepressants (19% and 23%)
Intervention	Rivastigmine 1.5 mg/tid (titrated to a maximum of 6mg tid- titrated lasted up to 8 weeks). Mean daily stable dose was at 9.4 mg.
Comparison	Placebo
Length of follow-up	Trial duration was 23 weeks (20 weeks treatment followed by 3 week 'rest')
Outcome measures	Neuropsychiatric inventory (NPI) (scores ranged from 1 (normal) to 144 (severely disturbed), NPI-4 (4 item version), MMSE, clinical global change-plus (CCC-plus) (7 point scale), UPDRS
Effect size	➢ Only one trial was included (McKeith, 2000) Neuropsychiatric inventory: (10 item test) ➢ No significant difference between groups in change of scores from baseline at 20 weeks intention-to-treat analysis (ITT):: (weighted mean difference (WMD) –3.30, 95%CI –8.14 to 1.54, p=0.18) ➢ The treatment was statistically significant in favour of rivastigmine if only observed cases were analysed (WMD –6.94, 95%CI –11.59 to –2.29, p=0.003) ➢ There were similar results for NPI-4, with only the observed cases analysis showing an effect in favour of rivastigmine vs. placebo at 20 weeks (WMD, -3.75,95%CI –6.62 to –0.88, p=0.01) MMSE ➢ No statistically significant difference between the two groups at 20 weeks ITT: (WMD+1.24, 95%CI –0.28 to 2.76, p=0.11) ➢ The last observed analysis carried forward (LOCF) and observed cases (OC) only analysis were both non-significant CCG-plus ➢ Analysis of the proportion of patients who had no change or became worse found no statistically significant difference between rivastigmine vs. placebo at 20 weeks

	➢ ITT analysis: Odds ratio (OR) 0.56, 95%CI 0.24 to 1.28, p=0.07) ➢ LOCF and OC analysis were also non-significant Adverse events ➢ The placebo group experienced fewer adverse events (OR 2.24, 95%CI 1.19 to 10.43, p=0.02) ➢ Using ITT analysis of 20-week data there was no significant difference between the two groups when serious adverse events were considered (OR 1.35, 95%CI0.49 to 3.70, p=0.56) ➢ No significant difference in death rates between 2 groups at 20 weeks (OR 0.20, 95%CI 0.01 to 4.26, p=0.30) Withdrawals ➢ No difference between the two groups at 20 weeks using ITT analysis (OR 2.24, 95%CI 0.93 to 5.37, p=0.07) ➢ Author's conclusions:" patients with dementia with Lewy bodies who suffer from behavioural disturbance or psychiatric problems may benefit from rivastigmine if they tolerate it, but the evidence is weak. Further trials using rivastigmine are needed as are trials of other cholinesterase inhibitors in dementia with Lewy bodies".
Source of funding	None stated
Additional comments	➢ Search date cut-off October 2001 ➢ Method of randomisation stated ➢ Allocation concealment stated ➢ 23% drop-out rate with main cause being adverse events ➢ Intention-to-treat analysis ➢ Number of neuropsychiatric tests were excluded because a large number of patients were unable to complete the tests
Citation	
NCC CC ID (Ref Man)	19787

Evidence Table
PSYC 3
Are cholinesterase inhibitors effective cognitive enhancement therapies in Parkinson's disease and Lewy body dementia?

Bibliographic reference	Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De D *et al*. Rivastigmine for Dementia Associated with Parkinson's Disease. *New England Journal of Medicine, Dec 2004* 2004;**351**:2509-18.
Study type	Randomised, double-blind, placebo-controlled trial
Evidence level	1++
Study objective	To investigate the effects of the dual cholinesterase inhibitor rivastigmine in Parkinson's disease patients.
Number of patients	N=541 Parkinson's disease (PD) patients N=362 rivastigmine N=179 placebo Location: International Sites: multi-centre (number not stated)
Patient characteristics	Patients were men or women who were at least 50 years of age and who received a diagnosis of PD according to UK PDS brain bank criteria and a diagnosis of dementia due to PD according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders. Patients had to have mild-to-moderately severe dementia as defined by a mini-mental state examination (MMSE) scores of 20 to 24,with the onset of symptoms occurring at least two years after the diagnosis of PD. For exclusion criteria see paper. No significant differences in baseline characteristics if two groups (see table below).

Characteristics	Rivastigmine	Placebo
Age (yr)	72.8 ± 6.7	72.4 ± 6.4
Sex (male %: female %)	64.6 : 35.4	65.4 : 34.6
Race (white %: other %)	99.4 : 0.6	100 : 0
Time since diagnosis of PD (yr)	8.7 ± 5.7	9.5 ± 5.9
Time since diagnosis of dementia	1.1 ± 1.4	1.3 ± 1.9
MMSE score	19.4 ± 3.8	19.2 ± 4.1

Most patients 91.1% had a coexisting medical condition at baseline.

Intervention	Rivastigmine 3 to 12 mg (started with 1.5 mg tid, doses were increased by 3 mg per day at intervals of at least 4 weeks during a 16-week dose escalation phase)
Comparison	Placebo
Length of follow-up	Trial duration of 24 weeks

<table>
<tr><td>Outcome measures</td><td>Alzheimer’s Disease Assessment Scale (ASAS-cog), Alzheimer’s Disease Cooperative Study-Clinicians Global Impression of Change (ADCS-CGIC), ADCS- activities of daily living (ADL), Neuropsychiatric Inventory (NPI), mini-mental state examination (MMSE), Cognitive Drug Research (CDR), Delis-Kaplan Executive Function System (D-KEFS), ten-point clock-drawing test</td></tr>
<tr><td>Effect size</td><td>

A total of 501 patients were included in the efficacy analysis- 27 were excluded from the rivastigmine group and 13 from the placebo group because of no post-baseline efficacy data on either primary outcome measure
To investigate possible bias owing to exclusion of 40 patients from efficacy analysis- sensitivity analysis was performed assuming no change from baseline in their primary outcome variables- results were consistent with findings in primary population

Results from efficacy analysis:
<table>
<tr><th rowspan="2">Variable</th><th colspan="2">No of patients</th><th rowspan="2">Between group difference at week 24</th><th rowspan="2">P value</th></tr>
<tr><th>rivastigmine</th><th>placebo</th></tr>
<tr><td>ADAS-cog score</td><td>329</td><td>161</td><td>2.90 *</td><td><0.001</td></tr>
<tr><td>ADCS-CGIC score</td><td>329</td><td>165</td><td>0.5</td><td>0.007</td></tr>
<tr><td>Secondary variables</td><td></td><td></td><td></td><td></td></tr>
<tr><td>ADCS-ADL score</td><td>333</td><td>165</td><td>2.50</td><td>0.02</td></tr>
<tr><td>NPI-10 score</td><td>334</td><td>166</td><td>2.15 *</td><td>0.02</td></tr>
<tr><td>MMSE score</td><td>335</td><td>166</td><td>1.00</td><td>0.03</td></tr>
<tr><td>CDR power of attention tests</td><td>328</td><td>158</td><td>294.84 *</td><td>0.009</td></tr>
<tr><td>D-KEFS Verbal Fluency Test</td><td>258</td><td>144</td><td>2.80</td><td><0.001 **</td></tr>
<tr><td>Ten point clock-drawing score</td><td>49</td><td>50</td><td>1.10</td><td>0.02 **</td></tr>
</table>
* The value is the modelled treatment difference (difference of least-square means)
** Because executive function tests were not performed at all sites, these tests included only patients who actually took these tests

The mean dose of rivastigmine was 8.6 mg/d at the end of the dose escalation period and remained stable throughout the maintenance phase
At the end of the study 55% were receiving 9 to 12 mg of rivastigmine per day, 23% were receiving at least 3mg but less than 6 mg per day

Adverse events

Most adverse events were mild or moderate

</td></tr>
</table>

<table>
<tr><td></td><td>

Occurrence of adverse events rated as serious was similar in both groups
There were 11 deaths (4 in rivastigmine and 7 in placebo)
Parkinsonian symptoms were reported as adverse events more frequently in rivastigmine than placebo (27.3% vs. 15.6%, p=0.002)
These were most commonly manifested as tremor (10.2% vs. 3.9%, p=0.01)

<table>
<tr><th>Most frequently reported adverse events*</th><th>Rivastigmine vs. placebo
P value</th></tr>
<tr><td>Any</td><td><0.001</td></tr>
<tr><td>Nausea</td><td><0.001</td></tr>
<tr><td>Vomiting</td><td><0.001</td></tr>
<tr><td>Tremor</td><td>0.01</td></tr>
</table>
* all of the above occurred more frequently in rivastigmine group

Withdrawal rates
<table>
<tr><th>Reasons</th><th>Rivastigmine</th><th>Placebo</th></tr>
<tr><td>Number of withdrawals (%)</td><td>99 (27%)</td><td>32 (18%)</td></tr>
<tr><td>Adverse events</td><td>62 (17.1%)</td><td>14 (7.8%)</td></tr>
<tr><td>Withdrew consent</td><td>21 (5.8%)</td><td>2 (1.1%)</td></tr>
<tr><td>Lost to follow-up</td><td>4 (1.1%)</td><td>1 (0.6%)</td></tr>
<tr><td>Protocol violation</td><td>5 (1.4%)</td><td>2 (1.1%)</td></tr>
<tr><td>Died</td><td>4 (1.1%)</td><td>7 (3.9%)</td></tr>
<tr><td>Unsatisfactory therapeutic results</td><td>2 (0.6%)</td><td>4 (2.2%)</td></tr>
<tr><td>Abnormal test results</td><td>1 (0.3%)</td><td>-</td></tr>
<tr><td>‘Administrative problem’</td><td>-</td><td>2 (1.1%)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Source of funding</td><td colspan="2">Pharmaceutical</td></tr>
<tr><td>Additional comments</td><td colspan="2">

72.7% rivastigmine and 82.1% of placebo-treated patient s completed study
2:1 randomisation of rivastigmine to placebo
Methods of randomisation and allocation concealment stated
Intention-to-treat analysis
Analyses of centre variance stated
First patient was randomised in October 2002 and recruitment was completed in July 2003

</td></tr>
<tr><td>Citation</td><td colspan="2"></td></tr>
</table>

NCC CC ID (Ref Man)	231

Evidence Table
PSYC 3
Are cholinesterase inhibitors effective cognitive enhancement therapies in Parkinson's disease and Lewy body dementia?

Bibliographic reference	Leroi I, Brandt J, Reich S, Lyketsos C, Grill S, Thompson R *et al*. Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. *International Journal of Geriatric Psychiatry* 2004;**19**:1-8.
Study type	Randomised, double-blind, placebo-controlled trial (pilot study)
Evidence level	
Study objective	To evaluate the efficacy and safety of donepezil as a treatment for cognitive impairment and dementia in patients with Parkinson's disease.
Number of patients	N=16 patients with Parkinson's disease (PD) N=7 donepezil N=9 placebo Location: UK sites: single
Patient characteristics	Study patients were recruited from the outpatient neurology clinic, were men and women with idiopathic PD (defined by UK PDS brain bank criteria) and a clinical diagnosis of either dementia or cognitive impairment secondary to PD (defined by Diagnostic and Statistical Manual- IV). All patients were on stable regimes of antiparkinsonian medications. Exclusion criteria included if patients were no-ambulatory, had a Mini-Mental State Examination (MMSE) score of <10, a DSM-IV diagnosis of substance abuse or dependence, severe cardiac, vascular or renal disease or known intolerability of donepezil. No significant differences between baseline demographic and clinical characteristics between treatment groups.

	Placebo (n=9)	Donepezil (n=7)	P value
Age (yr)	70.80 ± 11.80	66.20 ± 9.30	0.42
Gender (%male)	4 (44.4)	6 (85.7)	0.15
Duration of PD motor symptoms	6.4 ± 2.80	11 ± 5.90	0.06
MMSE	25.44 ± 3.32	26 ± 2.38	0.68
Hoehn and Yahr Stage	2.40 ± 0.5	2.50 ± 0.8	0.86

Intervention	Donepezil 2.5-10 mg/d
Comparison	Placebo
Length of follow-up	Mean trial duration of 15.2 ± 3.4 weeks
Outcome measures	Dementia Rating Scale (DRS), MMSE, Trail Making Test- Part A, Neuropsychiatric Inventory, and a battery of neuropsychological tests (non-significant results- see paper for full list)
Effect size	➢ Drug and placebo were administered for 18 weeks with a titration starting at 2.5 mg/d for 5 days followed by 5mg/d until week 6, when dose was increased to 7.5 mg/d for 5 days followed by 10mg/d until the end of trial (week 18) ➢ The mean highest dose tolerated in the donepezil group was 6.4 ± 2.0 mg/d, as compared to the placebo groups in which the mean highest dose was 8.9 ± 2.2 mg/d (p=0.03) Clinical efficacy ➢ There were no significant differences between groups for the delta values (delta value= (final donepezil- baseline donepezil)- (final placebo- baseline placebo)) on measures of global cognition (MMSE and DRS total scores) ➢ There was a significant difference in the delta value for the DRS Memory subscore (p<0.05)- with an improved (higher) score in the donepezil-treated group and a decline in the placebo group ➢ DRS memory subscores improved in 60% of the donepezil group compared to 12.5% in placebo and worse in 20% donepezil and 63% placebo ➢ Using regression analysis the effect of donepezil persisted after accounting for the relatively greater baseline psychiatric symptoms severity (based on NPI total score) and premorbid IQ estimate in donepezil group ➢ There were no significant group differences for any other cognitive measure ➢ Donepezil group displayed a trend towards improvement in psychomotor processing speed and attention in the Trail Making Test- Part A (TMT-A) whereas placebo group was worse at follow-up (p=0.08) ➢ There were no significant group differences in the delta values for psychiatric symptoms rating Adverse events ➢ Events leading to study withdrawal in the donepezil group included: acute diplopia, lightheadedness, constipation, nausea and vomiting, hypersalivation, rhinorrhea, urinary frequency and worsening of motor symptoms (gait impairment, increased number of falls, increased tremor) ➢ 5 donepezil patients (71.4%) compared to 4 (44.4%) placebo-treated patients reported adverse

	events (non-significant) ➢ adverse events reported in the placebo group included: nausea, fatigue, and lightheadedness Withdrawal rates ➢ Study was completed by 10/16 (62.5%) of patients randomised ➢ Donepezil patients remained in the trial for a mean duration of 13.1 weeks and placebo group for 17.3 weeks ($p<0.05$) ➢ 4/7 donepezil patients withdrew early because of adverse events ➢ a 5th patient requested early withdrawal and refused final assessment in context of a re-lapse of pre-existing mood disorder ➢ 1/9 (11%) of the placebo-treated patients withdrew because of adverse events (diarrhea, disorientation, and visual hallucinations)
Source of funding	Pharmaceutical, non-profit and University funding
Additional comments	➢ Allocation concealment method stated ➢ Randomisation methods not stated ➢ Intention-to-treat analysis ➢ No power calculations ➢ Small sample size
Citation	
NCC CC ID (Ref Man)	243

Evidence Table **PSYC 3** Are cholinesterase inhibitors effective cognitive enhancement therapies in Parkinson's disease and Lewy body dementia?	
Bibliographic reference	Ravina B, Putt M, Siderowf A, Farrar JT, Gillespie M, Crawley A *et al*. Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study. *Journal of Neurology, Neurosurgery & Psychiatry* 2005;**76**:934-9.
Study type	RCT, crossover design
Evidence level	1+
Study objective	To study the safety and efficacy of a cholinesterase inhibitor, donepezil hydrochloride, for the

<table>
<tr><td></td><td>treatment of dementia in Parkinson’s disease (PD).</td></tr>
<tr><td>Number of patients</td><td>N= 22

Location: USA sites: single</td></tr>
<tr><td>Patient characteristics</td><td>Recruitment of patients was performed at the NINDS, Brown University, The University of Pennsylvania, and Northwestern University.

Inclusion criteria: patient over 40 years of age, clinical diagnosis of PD defined as at least two of three cardinal features of parkinsonism with at least one being tremor or rigidity, and a significant and sustained response to dopaminergic medications. Movement disorder specialists made all diagnoses. Dementia patients fulfilled 4th edition DSM criteria for dementia and MMSE between 17 and 26 inclusive. The dementia had to have been developed at least 12 months after the motor manifestations of PD to exclude patients with clinically diagnosed DLB.

Exclusion criteria: alternative sources of dementia such as stroke or metabolic disturbances, pregnancy or lactation, the use of cholinergic or anticholinergic agents except amantadine or tolterodine within 2 weeks prior to screening or medical conditions or uncontrolled psychosis.

<table>
<tr><th>Characteristic</th><th>Donepezil/placebo (n=9)</th><th>Placebo/donepezil (n=10)</th></tr>
<tr><td>Age</td><td>75.0 ± 9.8</td><td>72.1 ± 8.1</td></tr>
<tr><td>M/F</td><td>9/0</td><td>6/4</td></tr>
<tr><td>ADAS-cog total</td><td>29.5 ± 13.5</td><td>32.3 ± 9.5</td></tr>
<tr><td>MMSE</td><td>23.1 ± 2.5</td><td>21.4 ± 3.4</td></tr>
<tr><td>Total UPDRS</td><td>64.9 ± 25.9</td><td>65.8 ± 21.7</td></tr>
<tr><td>Motor UPDRS</td><td>41.2 ± 17.4</td><td>41.2 ± 17.6</td></tr>
<tr><td>Duration of PD</td><td>7.1 ± 2.6</td><td>14.4 ± 13.1</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Study drug was dispensed as 5 mg capsules or matching placebo to be taken orally. Drug was taken once per day for 5 mg dose and 2x per day for 10 mg dose.
In the first period (baseline to week 10) investigator contacted participant by phone at week 4 to ask about side effects and tolerability. At that time study drug was increased from 5mg/day to 10 mg/day or matching placebo. If the higher dose was not tolerated than the lower dose was continued. Safety and efficacy evaluations were performed at weeks 7 and 10. An open-label washout occurred from weeks 10 – 16 during which participants did not take any study drug. Study procedures were identical</td></tr>
</table>

<table>
<tr><td></td><td>in the second period (weeks 16-26) with a baseline evaluation at week 16 followed by phone contact and titration as tolerated at week 20 and study visits at weeks 23 and 26.</td></tr>
<tr><td>Comparison</td><td>Matching placebo</td></tr>
<tr><td>Length of follow-up</td><td>10 week treatment periods with 6 week washout period inbetween.</td></tr>
<tr><td>Outcome measures</td><td>Alzheimer’s disease assessment scale cognitive subscale (ADAS-cog), MMSE, Mattis Dementia Rating Scale (MDRS), clinical global impression of change (CGI), brief psychiatric rating scale (BPRS), and UPDRS</td></tr>
<tr><td>Effect size</td><td>

28 patients screened of which 22 were randomised
Three subjects withdrew during the first period
Included in safety analysis but not efficacy analysis (n=19)
3 subjects withdrew during the second period- these people were included in efficacy analysis

<table>
<tr><th>Test</th><th>Mean scores on drug (± SD)</th><th>Mean scores on placebo (SD)</th><th>Treatment effect (SE)</th><th>P value</th><th>Adjusted p value*</th></tr>
<tr><td>ADAS-cog</td><td>22.5 ± 6.9</td><td>24.4 ± 9.4</td><td>-1.9 ± 1.4</td><td>0.18</td><td>0.54</td></tr>
<tr><td>MMSE</td><td>24.5 ± 3.2</td><td>22.5 ± 4.7</td><td>2.0 ± 0.61</td><td>0.0044</td><td>0.018</td></tr>
<tr><td>MDRS</td><td>108.3 ± 17.13</td><td>108.5 ± 18.2</td><td>-0.2 ± 1.9</td><td>0.98</td><td>0.98</td></tr>
<tr><td>MDRS attention</td><td>31.0 ± 5.1</td><td>31.1 ± 5.2</td><td></td><td></td><td></td></tr>
<tr><td>MDRS initiative</td><td>25.9 ± 6.3</td><td>25.5 ± 7.0</td><td></td><td></td><td></td></tr>
<tr><td>CGI</td><td>3.58 ± 0.77</td><td>3.95 ± 0.85</td><td>-0.37 (NA)</td><td>0.0056</td><td>0.022</td></tr>
</table>

* Adjusted for multiple comparisons using Hommel method

MMSE scores were significantly improved on donepezil 0.0044
The CGI test also showed significant improvement in favour of drug 0.0056
No difference between treatments for BPRS (treatment effect –0.26 ±1.8, p=0.68
A repeated measures model that considered each point individually instead of averaging across weeks, and that adjusted for both period and sequence effects on the ADAS-cog approach significance with a 1.9 ± 0.97 point improvement in favour of drug p=0.055

Adverse events

The drug was well tolerated and did not exacerbate the PD symptoms

</td></tr>
</table>

	➢ In the first period 3 subjects withdrew from the study- 2 on donepezil (worsening psychosis and worsening arrhythmia) and one on placebo (worsening psychosis) ➢ In the second period there were no withdrawals but 2 discontinued use of donepezil and one placebo ➢ Adverse events were experienced by 11/21 (52%) subjects on drug and 9/20 (45%) placebo ➢ Worsening psychosis and agitation were the most common effects and occurred in near equal frequency in both groups ➢ No evidence impact of treatment on UPDRS or motor section of UPDRS
Source of funding	Non-profit
Additional comments	➢ Randomisation performed by University of Pennsylvania Investigational Drug Services unit ➢ Allocation concealment not stated ➢ Subjects were randomised in blocks of 4 ➢ Power calculations specified ➢ Small sample size ➢ Not intention to treat in second period
Citation	
NCC CC ID (Ref Man)	19948

Evidence Table **PSYC 3** Are cholinesterase inhibitors effective cognitive enhancement therapies in Parkinson's disease and Lewy body dementia?	
Bibliographic reference	Aarsland D, Laake K, Larsen JP, Janvin C. Donepezil for cognitive impairment in Parkinson's disease: A randomised controlled study. *Journal of Neurology, Neurosurgery & Psychiatry* 2002;**72**:708-12.
Study type	Double blind, placebo-controlled, randomised controlled crossover trial
Evidence level	1+
Study objective	To study the safety and efficacy of the cholinesterase inhibitor donepezil in patients with Parkinson's disease (PD) and cognitive impairment.
Number of patients	N= 14 PD patients with cognitive impairment Location: Norway sites: single

<table>
<tr><td>Patient characteristics</td><td>Consecutive patients with PD and cognitive impairment diagnosed at an outpatient clinic were invited to participate. Dementia diagnosis was based on DSM-IV criteria. PD diagnostic criteria stated. Inclusion and exclusion criteria stated.
13 men and one woman.
7 subjects were diagnosed as clinically definite PD and 5 as clinically probable PD.
The two groups did not differ with regards to baseline MMSE score, age or duration of disease.
11 patients had impairment of at least 2 cognitive domains other than memory. 8 patients fulfilled all DSM-IV criteria for dementia due to PD, while significant functional impairment due to cognitive deficits could not be definitely verified in 4.</td></tr>
<tr><td>Intervention</td><td>Donepezil (5 or 10 mg/day) for 10 weeks. Dose was initiated at 5mg but increased to 10mg per day at 6 weeks if well tolerated.</td></tr>
<tr><td>Comparison</td><td>Matching placebo for 10 weeks</td></tr>
<tr><td>Length of follow-up</td><td>Assessments took place at baseline and after 6 and 10 weeks of each treatment period. Washout period was deemed not necessary based on previous literature.</td></tr>
<tr><td>Outcome measures</td><td>MMSE score, clinician’s interview based impression of change plus caregiver input (CIBIC+) score, and motor subscore of UPDRS scale</td></tr>
<tr><td>Effect size</td><td>

33 patients were screened and 14 were randomised
2 patients both male withdrew due to side effects before evaluation at week 6 in the first study period- both were on donepezil
The remaining 12 all completed the study

<table>
<tr><th>Test</th><th>Baseline</th><th colspan="2">After 6 weeks</th><th colspan="2">After 10 weeks</th></tr>
<tr><th></th><th></th><th>Donepezil</th><th>Placebo</th><th>Donepezil</th><th>Placebo</th></tr>
<tr><td>MMSE score</td><td>20.8 ± 3.4</td><td>22.7 ± 3.6 *</td><td>19.9 ± 4.0</td><td>22.8 ± 3.7 *</td><td>21.0 ± 5.0</td></tr>
<tr><td>CIBIC+ score</td><td>-</td><td>3.1 ± 0.9 *</td><td>3.7± 0.5</td><td>3.3 ± 0.9 *</td><td>4.1 ± 0.8</td></tr>
<tr><td>UPDRS motor</td><td>32.1 ± 15.2</td><td>-</td><td>-</td><td>31.8 ± 15.4</td><td>35.1 ± 8.1</td></tr>
<tr><td>Subjective impression of parkinsonism</td><td>-</td><td>3.6 ± 1.2</td><td>3.8 ± 1.4</td><td>3.7 ± 1.1</td><td>4.2 ± 1.5</td></tr>
</table>

*p <0.05; values are mean ± SD
Higher MMSE scores and lower CIBIC scores indicate and improvement on donepezil
A significant treatment effect of donepezil on MMSE score compared with placebo was found (p=0.013)

</td></tr>
</table>

	➢ A significant treatment effect of donepezil on CIBIC scores compared to placebo was also found (p=0.034) ➢ The scores of UPDRS motor detected no deterioration due to treatment ➢ Few of the 12 patients had positive NPI scores on delusions (n=3), hallucinations (n=2), agitiation (n=1), depression (n=6), or apathy (n=5) a baseline, and mean NPI scores were low at baseline ➢ No significant treatment effects were observed with regard to any of the NPI items Adverse events ➢ Patients reported adverse events on donepezil was 10/14 (71%) and placebo was 9/12 (75%) ➢ Most specific examples of adverse events were more common on donepezil but not significantly ➢ Most common: nausea, headache, tiredness, increased dreaming, dizziness, increased sweating, increased salivation, dry mouth and constipation
Source of funding	pharmaceutical
Additional comments	➢ Methods of randomisation and allocation concealment stated ➢ Tests for carryover effect and period effect performed ➢ Power calculations were not performed ➢ Small sample size
Citation	
NCC CC ID (Ref Man)	19965

Evidence Table **PSYC 3** Are cholinesterase inhibitors effective cognitive enhancement therapies in Parkinson's disease and Lewy body dementia?	
Bibliographic reference	Giladi N, Shabtai H, Gurevich T, Benbunan B, Anca M, Korczyn AD. Rivastigmine (Exelon) for dementia in patients with Parkinson's disease. *Acta Neurologica Scandinavica* 2003;**108**:368-73.
Study type	Before and after study
Evidence level	3
Study objective	To study the efficacy of cholinesterase inhibitors in the treatment of dementia in patients with PD
Number of patients	N=28 patients with PD and dementia

	Location: Israel sites: single
Patient characteristics	28 consecutive patients with PD and dementia (17 males) who attended a movement disorders unit were enrolled. PD diagnosed according to UK PDS brain bank criteria and recently published clinical criteria. Patients were considered mildly or moderately demented if they fulfilled DSM-IV criteria for dementia and scored 13-25 points (inclusive) on MMSE (18). Exclusion criteria stated (see paper for details). Mean age 75.0 ± 4.6 years and mean symptoms duration of 7.0 ± 5.3 years and levodopa total daily dose was 670 ± 340 mg/day. Hoehn and Yahr stage at 'off' 3.1 ± 0.7, UPDRS total score during 'on' 67.5 ± 12, MMSE total score 19.5 ± 4.7, mean ADAS-cog total score 28.3 ± 10.5. 4 patients had chronic visual hallucinations when they entered the study.
Intervention	Rivastigmine was given openly at an initial dose of 1.5 mg twice daily and was increased after 4 weeks to 3 mg twice daily, after 8 weeks to 4.5 mg twice daily and after 12 weeks to a maximum dose of 6 mg twice daily. Between weeks 12 and 26 the dose was kept constant at the maximum tolerated dose. At week 26 the dose was tapered down over a period of 2 weeks and final assessment was at week 34. During the study no alteration in antiparkinsonian medication was allowed during the baseline period (2 weeks) and for the first 12 weeks and afterwards only 6 patients needed change in their antiparkinsonian medications because of worsening of symptoms.
Comparison	Baseline evaluation
Length of follow-up	34 week trial duration
Outcome measures	UPDRS, ADAS-cog, adverse events
Effect size	➢ Mean dose of rivastigmine at week 12 was 7.3 ± 3.3 mg/day (n=26) and 7.5 ± 3.5 mg/day at week 26 (n=20) ➢ The clinical impression of change (CIC) was significant at weeks 12 and 26 (p<0.0001) ➢ This improvement disappeared at the end of the washout period (week 34) ➢ Improvement in total UPDRS score from baseline to week 26 (p<0.06- mixed model analysis) ➢ And slight deterioration from week 26 to washout ➢ The only UPDRS subscore to show significant improvement was part I Mental (P<0.001) while activities of daily living and motor showed non-significant improvements ➢ The MMSE total score showed slight but non-significant improvements at week 26 ➢ ADAS-cog total score improved significantly over the study period p=0.002

	Adverse events ➢ Increased salivation (in 46% of patients) and tremor (39%) were the most frequent ➢ Overall 17 patients experienced side effects and usually more than one ➢ 11 patients had to decrease rivastigmine daily dose because of side effects ➢ 8 patients discontinued because of different reasons: n=3 motor worsening, n= 1 confusional state, n=1 palpitations, n=1 fell and had minor brain concussion and shortly afterwards developed acute psychosis, n=1 died (autopsy refused), n=1 acute myocardial infarction
Source of funding	Pharmaceutical
Additional comments	➢ Non randomised, non controlled, non blinded ➢ Small sample size ➢ No power calculations
Citation	
NCC CC ID (Ref Man)	19967

Evidence Table **PSYC 3** Are cholinesterase inhibitors effective cognitive enhancement therapies in Parkinson's disease and Lewy body dementia?	
Bibliographic reference	Aarsland D, Hutchinson M, Larsen JP. Cognitive, psychiatric and motor response to galantamine in Parkinson's disease with dementia. *International Journal of Geriatric Psychiatry* 2003;**18**:937-41.
Study type	Open-label before and after study
Evidence level	3
Study objective	To evaluate the effects of galantamine on cognition, psychiatric symptoms and parkinsonism in PDD patients.
Number of patients	N=16 Parkinson's disease dementia (PDD) patients Location: Norway and US sites: two
Patient characteristics	Consecutive patients referred to the outpatient clinics in Norway and US were included. PD diagnosis based on UK brain bank criteria. Patients were included in they fulfilled the DSM-IV criteria for dementia due to PD. Duration from onset of PD until development of cognitive impairment or

	hallucinations had to be at least one year. Exclusion criteria stated (see paper for details). 16 subjects (six female), 11 from Norway and 5 from US. Mean age (±SD) was 75.6 ± 5.2 years, duration of PD 13.4 ± 5.9 years, and of dementia 2.1 ± 1.7 years, MMSE score was 17.7 ± 6.8, Hoehn and Yahr score 3.8 ± 0.8.
Intervention	Galantamine initial dose was 4mg bid and after 4 weeks this was increased to 8mg bid. Other antiparkinsonian medication remained stable during treatment period.
Comparison	Patients evaluated before treatment and after 8 weeks of treatment
Length of follow-up	8 week trial duration
Outcome measures	MMSE scores, Neuropsychiatric Inventory (NPI), adverse events
Effect size	➢ 3 patients withdrew prematurely due to adverse events: 1 developed vomiting after 3 days which recurred when he re-started, 1 because of worsening tremor and 1 because of anorexia, nausea and vomiting. ➢ Of the completers: 3 had mild gastrointestinal side effects, one had sedation, and one had headache ➢ Only the 13 who completed the 8 weeks of treatment were included in the analysis ➢ Cognition improved in 8 (62%) patients ➢ In four (31%) patients a declined was noted ➢ Hallucinations improved in 7/9 (78%) with hallucinations at baseline ➢ In 3 of these patients who had marked symptoms before treatment the hallucinations disappeared completely ➢ One patient without hallucinations at baseline developed marked symptoms during treatment ➢ Parkinsonism improved in 6 patients (46%) ➢ In 3 patients (23%) worsening of parkinsonism occurred ➢ Mean MMSE score improved from 18.5 ± 7.1 to 20.8 ± 5.4 (p=0.09) ➢ 6 (46%) patients improved 3 points or more (four of these improved 4-points or more) ➢ One patient worsened 3 points and one worsened 4 points ➢ No association between baseline score and improvement on MMSE improved performance was found on clock-drawing test (p=0.016) ➢ Non-significant trend on verbal fluency (p=0.15)
Source of funding	Not stated
Additional comments	➢ Non randomised non controlled ➢ Not intention to treat

	➢ No power calculations
Citation	
NCC CC ID (Ref Man)	19958

Evidence Table **PSYC 3** Are cholinesterase inhibitors effective cognitive enhancement therapies in Parkinson's disease and Lewy body dementia?	
Bibliographic reference	Pakrasi S, Mukaetova-Ladinska EB, McKeith IG, O'Brien JT. Clinical predictors of response to Acetyl Cholinesterase Inhibitors: experience from routine clinical use in Newcastle. *Int J Geriatr Psychiatry* 2003;**18**:879-86.
Study type	Retrospective before and after study
Evidence level	3
Study objective	To investigate the clinical variables that may distinguish between acetyl cholinesterase inhibitors (AChEI) responders and non-responders
Number of patients	160 consecutive patients with dementia Location: UK sites:
Patient characteristics	Male to female ratio was 1:2 and the age range was 55-93, mean 75.9 ± 7.1. The mean duration of illness was 18.7 months ± 11.0
Intervention	AChEI: donepezil prescribed in 78%, rivastigmine 16% and galantamine 6%.
Comparison	Baseline evaluations
Length of follow-up	Varied
Outcome measures	MMSE scores all other outcomes not specific to PDD
Effect size	➢ 169 case notes were screened ➢ 9 were excluded as they were not on AChEI (4) or started after January 2002 (5) ➢ 150 patients tolerated treatment for more than 4 weeks and paired MMSE data from baseline to efficacy was available for 137 ➢ No difference in the proportions of responders between drugs was observed ➢ Patients diagnosed with PDD there was an association with increased probability of an MMSE response (p=0.02)

	➢ Patients with hallucinations had significantly higher increase in their MMSE scores compared to those without hallucinations (mean difference =2, p=0.03) ➢ PDD patients improved by a mean of 2.3 MMSE points
Source of funding	None stated
Additional comments	➢ Limited evidence specific to PDD patients ➢ All other outcomes included all dementia disease types ➢ Non randomised non controlled
Citation	
NCC CC ID (Ref Man)	19981

TxNS1 – sections 9.3.1 and 2

Evidence Table **TxNS1** What sleep disorders are seen in Parkinson's disease and how are they best treated?	
Bibliographic reference	Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Movement Disorders* 2003;**18**:287-93.
Study type	Randomised, double-blind, placebo controlled cross over study (1 week washout period)
Evidence level	1++
Study objective	To assess the safety and efficacy of modafinil for the treatment of excessive daytime sleepiness in patients with Parkinson's disease
Number of patients	N=21 Parkinson's disease (PD) patients N=11 started on modafinil N=10 started on placebo Location: USA Site: single
Patient characteristics	27 consecutive patients with PD who admitted having excessive daytime sleepiness were questioned using the Epworth Sleepiness Scale (ESS).

	Patients were included if they scored ≥ 10. 21 of the 27 patients questioned met these criteria and were included in the study. Patients were not allowed to start new PD medications during the study. Inclusion criteria: ≥ 30 years of age, a Folstein Mini-Mental Status Exam score >24, and ability to complete diary forms. Mean baseline characteristics: mean age 65 years, F:M was 6:14, duration of PD 7.4 years, ESS 16.9 Of the 20 patients who completed the trial 19 had motor fluctuations
Intervention	Modafinil 200mg/d for 3 weeks
Comparison	Matching placebo for 3 weeks
Length of follow-up	Baseline, week 3, week 4 (baseline visit 2), week 7 and week 8 (1 week after discontinuation)
Outcome measures	ESS, Excessive Daytime Sleepiness Rating Scale (EDSRS), modified Fatigue Assessment Inventory (FAI), Excessive Daytime Fatigue Rating Scale (EDFRS), Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr stage (H&Y), Schwab and England Activities of Daily Living Scale, Timed Tapping Test, and a Clinical Global Impression of Change (CGI-C) scale
Effect size	➢ Drug compliance was 93% ± 28% while on modafinil and 113% ± 36% on placebo ESS ➢ Demonstrated a carry-over effect (p=0.013) from period to 1 to period 2 ➢ At visit 3, before the second treatment period the modafinil group/placebo group had decreased 2.3 ± 4.2 from a baseline of 17.8 ± 4.2 ➢ The placebo/modafinil group increased 2.0 ± 2.5 from a baseline of 16.0 ± 4.2 ➢ The carry-over effect was replicated after period 2 (p=0.006) ➢ At visit 5 (end of second washout period) modafinil/placebo group had increased 0.9 ± 2.1 from 15.5 ± 4.1 at visit 3 ➢ Placebo/modafinil group decreased 3.3 ± 3.8 from 18.0 ± 5.1 at visit 3 ➢ Comparing changes from baseline- the ESS for patients treated with 200 mg/d modafinil was better (p=0.039) than placebo treated patients ➢ ESS for patients treated with modafinil was 4.4 points better than placebo (95%CI –8.6 to –0.2) ➢ Two patients had an ESS <10 while receiving modafinil CGI-C ➢ Patient-rated CGI-C improved +0.75 on modafinil compared with +0.15 for placebo (p=0.07) ➢ Physician-rated CGI-C improved +0.75 on modafinil compared to +0.25 placebo (p=0.12)

	➢ Improvements were reported by 7 (35%) of patients on modafinil only, 1 (5%) patient on placebo-only, 2 patients (10%) receiving both modafinil and placebo, and 10 patients (50%) reported no change on either treatment (p=0.070) ➢ No significant differences were found in any of the other secondary outcome measures of sleepiness or fatigue ➢ Modafinil did not have an effect on sleep time based on diary analysis Parkinson's disease scores ➢ Modafinil did not cause any worsening or improvement of PD signs ➢ No significant differences between modafinil and placebo treatment periods on UPDRS, H&Y, timed tapping test, or diaries ➢ Modafinil had no effect on the percentage 'on' time Adverse effects ➢ There were no clinically or statistically significant effects of modafinil compared with placebo ➢ The following treatment-emergent effects were reported by one patient each: atrial fibrillation (patient with known paroxysmal atrial fibrillation), bruise, elevated blood pressure, flu, insomnia, rectal prolapse, and skin redness ➢ One patient reported: hot flashes, gas, increased 'off' time ➢ Another patient reported: pruritic rash and sore tongue ➢ On placebo one patient reported: allergy symptoms, anxiety, back spasm, headache, and heart burn ➢ No patients described any episodes of 'sleep attacks'
Source of funding	Pharmaceutical company
Additional comments	➢ Exams were performed when patients were in their 'on' states ➢ Modafinil and placebo tablets were identical in size, colour, and taste ➢ Methods of randomisation and allocation concealment stated ➢ Pills were counted at each visit to monitor compliance ➢ Elimination half-life of modafinil after multiple doses in 15 hours in healthy controls- no data regarding the duration of benefit that might occur after discontinuation of drug in patients with PD ➢ The sample size (n=16) was based on 80% power to detect differences of 0.75 standard deviations used the paired T-test ➢ Sample size was increased to n=21 in case of premature withdrawals ➢ 1 patient dropped out of modafinil group a few days after starting trial

NCC CC ID (Ref Man)	2780

Evidence Table **TxNS1** What sleep disorders are seen in Parkinson's disease and how are they best treated?	
Bibliographic reference	Hogl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K *et al*. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: A double-blind, randomized, crossover, placebo-controlled polygraphic trial. *Sleep* 2002; **25**:905-9.
Study type	Double-blind, randomised, placebo-controlled, cross-over study (2-week washout phase)
Evidence level	1++
Study objective	To assess the therapeutic efficacy of modafinil in the treatment of increased daytime sleepiness in patients with Parkinson's disease
Number of patients	N=15 patients with Parkinson's disease Location: Austria Sites: single
Patient characteristics	Recruited from outpatient clinic at University Hospital Department of Neurology All patients had a score of 10 or more on Epworth Sleepiness Scale (ESS) Exclusion criteria: see paper 12 patients completed study- 9 men, 3 women; mean age 65.0, mean symptomatic PD duration 6.8 years, all patients were on levodopa therapy
Intervention	Modafinil dose was 100mg in first week and 200mg in second week
Comparison	Placebo
Length of follow-up	2 week treatment phase, 2 week washout and 2 week treatment phase
Outcome measures	ESS, maintenance of wakefulness test (MWT) sleep log and depression scale, Unified Parkinson's disease Rating Scale (UPDRS) and Hoehn and Yahr (H&Y) staging, adverse effects
Effect size	ESS ➢ Modafinil improved perceived sleepiness ➢ ESS scores at baseline did not differ between treatment and placebo ➢ Subjective sleepiness improved by 0.83 $\pm$ 1.99 points with placebo and by 3.42 $\pm$ 3.90 with modafinil

	➢ Analysis of variance revealed a significant interaction (p=0.011) between medication condition and ESS changes from baseline to end MWT ➢ Latency to stage 1 sleep was calculated using (MWT) ➢ No significant difference was found between the treatment groups at baseline (p=0.26) and at the end of the treatment phase (p=0.114) ➢ The mean changes of sleep latencies at the end versus beginning of each block were also not significantly different (p=0.139) Sleep logs ➢ Similar amounts of sleep were obtained in both treatment groups ➢ Estimated time of sleep 390 ± 80 min at baseline of placebo treatment, 360 ± 94 min at end of placebo treatment, 375 ± 86 min at baseline of modafinil treatment, and 360 ± 50min at the end of modafinil treatment (median standard deviation, p=0.3) Depression scores ➢ Beck depression scores were not statistically different between baseline and end of treatment for placebo and modafinil Side effects ➢ Modafinil: insomnia (n=1), constipation (n=1), diarrhea (n=2), dizziness (n=1) ➢ Placebo: constipation (n=1), flatulence (n=1), diarrhea (n=1), insomnia (n=1) ➢ In no case did side effects lead to study withdrawal
Source of funding	Pharmaceutical
Additional comments	➢ Method of randomisation and allocation concealment stated ➢ Modafinil and placebo were prepared in identical-looking capsules ➢ 3 patients did not complete study ➢ Not intention-to-treat analysis
NCC CC ID (Ref Man)	2781

Evidence Table **TxNS1** What sleep disorders are seen in Parkinson's disease and how are they best treated?	
Bibliographic reference	Ondo WG, Faye R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. *J Neurol Neurogurg Psychiatry* 2005;**76**:1636-1639.
Study type	Randomised, double-blind, placebo controlled trial
Evidence level	1++
Study objective	To determine whether modafinil is effective in reversing daytime sleepiness in people with PD.
Number of patients	N=40 Parkinson's disease (PD) patients (37 completed the study). N=20 started on modafinil N=20 started on placebo Location: USA Site: single
Patient characteristics	40 patients satisfying diagnostic criteria for PD between 35 and 80 years of age and who reported daytime somnolence as measured by an ES score of greater than 10. Exclusion criteria: Serious medical conditions, known narcolepsy, known sleep apnoea and pregnancy. Patients were not allowed to take prescription stimulant medications. Mean baseline characteristics: 29 men/ 11 women, mean age 64.8, mean duration of PD 6.8 years, mean dopaminergic dose 8.5mg/day, 12/40 fluctuating response, UPDRS activities of daily living mean score 13.7, UPDRS mean motor score 26.7 and mean Epworth score (ES) 15.8.
Intervention	Modafinil one 100mg upon waking and at lunch (200mg/day). After one week the dose was increased to two pills twice a day (400mg/day).
Comparison	Matching placebo administered as for intervention.
Length of follow-up	Visit 1 at baseline and visit 2 at 4 weeks.
Outcome measures	ES, UPDRS activities of daily living and motor scores, Multiple sleep latency test (MSLT), SF-36, Fatigue Severity Scale (FSS), Hamilton Depression scale, change in sleepiness "much or very much improved", adverse events.
Effect size	➢ Three patients dropped out: 2 men on placebo and 1 woman on modafinil (the latter was instructed to stop taking study medication by her local physician due to back pain). All drop-outs were prior to post drug evaluation.

	ES and MSLT ➢ There was no significant change in the primary endpoint, the ES score. Patients on modafinil showed an improvement of 2.7 points compared with the placebo group who improved by 1.5 points (p=0.28). ➢ MSLT results were not significantly different although the scores worsened less with modafinil (-0.16 (3.59) minutes) than with placebo (-0.70 (3.28) minutes), p=0.14. Other outcomes ➢ The UPDRS, Fatigue Severity Scale, Hamilton Depression Scale, SF-36 and global impression scores did not significantly change compared to placebo. In fluctuating subjects, there was no change in on/off time. Adverse effects ➢ Only one patient taking modafinil elected to return to the lower dose, secondary to nausea and anxiety. Other advere events thought to be at least possibly drug related included dry mouth (N=1), dizziness (N=1), and back pain (N=1).
Source of funding	Cephalon Pharmaceuticals, the makers of Provigil.
Additional comments	➢ The authors performed a power analysis and found that they required a total of 28 participants (14 per group) to achieve a power of 0.81. ➢ Modafinil and placebo tablets were identical in size and appearance. ➢ Methods of randomisation and allocation concealment stated. ➢ The authors concluded that "Modafinil failed to significantly improve EDS in PD compared with placebo. The drug did not alter motor symptoms and was well tolerated".
NCC CC ID (Ref Man)	2780

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	The U.K.Madopar CR Study Group. A comparison of Madopar CR and standard Madopar in the

	treatment of nocturnal and early-morning disability in Parkinson's disease. *Clin Neuropharmacol* 1989;**12**:498-505.
Study type	Double-blind crossover study
Evidence level	1+
Study objective	To compare the effects of Madopar CR with that of conventional Levodopa/benserazide (Madopar) on nocturnal and early morning disability in patients with Parkinson's disease.
Number of patients	N=103 patients with Parkinson's disease (PD) Location: UK Sites: 11 centres
Patient characteristics	Majority of patients had difficulty turning in bed or getting out of bed and suffered from cramps and pain at night; foot spasms and spontaneous jerks were also common. The mean age was 67.7 years and 67% of the population was male. Disease duration ranged from 1 to 29 years, with a mean of 8 years. Mean duration of levodopa therapy was 6.4 years. The majority of patients (52%) were rated as Hoehn and Yahr stage III, 26% were stage II, 19% were stage IV and 2% were stage I. Daytime fluctuations in response to levodopa and/or abnormal involuntary movements were reported by 42 of 103 patients (41%).
Intervention	Controlled-release Madopar 125 mg (CR) immediately before going to bed. If insufficient effect on symptoms was observed, the dose was increased by 125mg weekly to a maximum of 4 capsules at night. Once optimum night time dose was determined, patients remained at this dosage for 2 weeks. They then transferred to alternative treatment, starting at one capsule, the procedure was repeated.
Comparison	Standard Madopar 125 mg (STD) immediately before going to bed
Length of follow-up	Trial duration: 6 weeks (3 weeks per arm). No follow-up stated.
Outcome measures	Patient diaries and opinion of investigator
Effect size	➢ 82/103 patients completed the study Dosage ➢ Mean optimum dosages for the treatments was similar (2.4 capsules for CR, 2.2 for STD) Sleep ➢ On entry to study mean time taken to fall asleep (recoded by investigator) was 47 min ➢ During optimum treatment periods this time was reduced to 38 min (CR) and 39 min (STD) ➢ Mean time taken to fall asleep (patient diaries) was little different between treatments ➢ Both CR and STD reduced total nocturnal and early-morning disability scores recorded by investigator compared with baseline to a statistically significant degree ➢ Little difference between total scores for two optimum treatment periods for either nocturnal or

	early-morning disability ➢ Nocturnal and early-morning disability scores taken from patient diaries and averaged over the periods of optimum treatment were also very similar for STD and CR ➢ Patient ratings of early morning condition also improved from baseline but not between treatments ➢ The majority of patients considered their overall nocturnal condition was better after optimum treatment with either STD or CR than on entry to study ➢ 62% of patients felt better after CR and 59% felt better after STD ➢ The number of patients who felt their nocturnal condition was worse from baseline was 4% CR and 10% STD ➢ Overall early-morning condition was rated as better than on entry to the study was 46% after CR and 45 after STD ➢ Percentage of patients who felt overall condition was worse was 2% cr and 6% STD ➢ 2/3 of patients gave the same response for both treatments with respect to their effect on overall condition compared to baseline ➢ Only 27% felt the two treatments were the same in relation to their effect on nocturnal condition ➢ 41% felt CR was better 33% felt it was worse ➢ Corresponding percentages for early-morning condition are 41% the same, 33% felt CR was better and 26% felt CR was worse ➢ CR was considered to be advantageous by 61% of patients and STD by 60% ➢ Patients who found treatments to be disadvantageous: 23% CR and 28% STD ➢ After the optimum treatment period the investigator (patient) felt it was justified to continue treatment with CR 55% (63%) of cases and with STD in 50% (55%) of cases ➢ Good agreement between patient and investigatory opinions ➢ Despite many little differences between treatments investigator thought that there was a difference between the two treatments in 60% of cases ➢ Of these CR was felt to be preferable in 65% and STD in 35% Adverse effects ➢ 63 adverse events were reported by 37 patients (32 CR and 31 STD) ➢ Majority were consistent with levodopa profile ➢ Dyskinesia was the most commonly reported adverse event (8 CR, 7 STD) ➢ Other adverse events: disorders of movement, gastrointestinal, central effects such as confusion, expression, hallucinations etc was evenly distributed between the 2 treatments Withdrawal rates ➢ 21 patients withdrew

	➢ Lack of effect was the reason given in 3 cases (one on STD and 2 on CR) ➢ Adverse side effects in 11 cases (4 on STD and 7 on CR) ➢ 7 due to other reasons
Source of Funding	Not stated
Additional comments	➢ There was no washout period between arms and no first arm results were reported ➢ Period and carry-over effects were analysed ➢ Differences from baseline to the end of the first treatment period were assessed within each treatment group separately, also using analysis of variance techniques ➢ Methods of randomisation or allocation concealment not stated ➢ No sample size calculations ➢ Intention-to-treat not stated ➢ Centre comparisons were performed ➢ No details of blinding procedure ➢ No details of clinical diagnosis criteria
Citation	
NCC CC ID (Ref Man)	19641

Evidence Table **Q TxCM8** What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	Sage JI,.Mark MH. Comparison of controlled-release Sinemet (CR4) and standard Sinemet (25 mg/100 mg) in advanced Parkinson's disease: A double-blind, crossover study. *Clinical Neuropharmacology* 1988;**11**:174-9.
Study type	Randomised, double-blind, crossover trial
Evidence level	1+
Study objective	To compare controlled-release sinemet with standard sinemet in patients with Parkinson's disease who had motor fluctuations.
Number of patients	N=25 Parkinson's disease (PD) patients Location: USA Sites: single

Patient characteristics	10 women, 15 men who were experiencing motor fluctuations while receiving standard sinemet therapy. Their mean age was 64 years (range 50-77 years) onset of PD was 53 years (range 39-74 years), duration of PD was 11 years (range 3-20 years) and duration of fluctuations was 5 years (range 0.5-16 years). All patients were taking sinemet at least 4x per day and exhibited end-of-dose wearing off phenomenon.
Intervention	Controlled-release sinemet (CR) 50/200 mg
Comparison	Standard sinemet (STD) 25/100 mg
Length of follow-up	Study duration was 24 weeks, initial 8-week open phase, followed by 16-week double blind phase.
Outcome measures	UPDRS, Hoehn and Yahr, Schwab and England activities of daily living, patient diaries
Effect size	➢ During the first 4-weeks of open phase patients were titrated to optimal dose of STD, then followed by 4 weeks of CR titration ➢ Patients then assigned randomly to SRD or CR in two 8-week double blind phases Significant increases in the number of patients doing better on CR: ➢ Hours 'on' without dyskinesias were better in 58% during CR phase and 29% during STD phase ($p<0.05$) ➢ Walking when 'off' was better in 29% of patients during CR phase and in no patients on STD phase ($p<0.05$) ➢ Sensory complaints when 'on' were improved in 17% of patients during CR phase and in no patients in during STD phase ➢ Duration of dyskinesias improved in 25% of patients during STD phase an in no patients in CR phase ($p<0.05$) ➢ More patients were better at cutting food when 'on' with STD (25%) than CR (4%) ($p<0.05$) Sleep ➢ During STD phase more patients slept more hours during recorded 24h period (58%) than CR (29%) ($p<0.05$) ➢ Total hours of sleep during the 24h period was no different on CR (8.2 ± 2.2 h) than STD (8.6 ± 2.1h) ($p<0.05$) Dosage ➢ 19 patients took fewer doses per day on CR (79%) whereas only one patient (4%) took fewer doses on STD ($p<0.05$) ➢ During CR phase patients took a mean of 5.3 doses per day (range 3-10) whereas the mean

	number of doses per day on STD was 7.8 (range 4-15) ➢ Total LD use (mg/d) was increased on CR 67% of patients whereas only 29% used more on STD ($p<0.05$) ➢ During CR phase, mean daily LD was 1544 mg (range 600-2800 mg) while mean daily LD use on STD was 1303 mg (range 250-2400 mg) ➢ Results of hourly examinations during the 6h visit did not show any significant differences for: ➢ Parkinson's disability score (12 improved on CR vs. 10 improved on STD) ➢ Dyskinesias (9 improved on CR vs. 7 improved on STD) ➢ Total disability score (12 improved on CR and 10 on STD) ➢ All $p>0.05$ Withdrawal rates ➢ One patient dropped-out – not due to study medication- death of family member
Source of Funding	Not stated
Additional comments	➢ Not intention-to-treat ➢ Methods of randomisation or allocation concealment not stated ➢ No sample size calculations ➢ 1/25 (4%) dropped-out of study
Citation	
NCC CC ID (Ref Man)	348

AHP1 – section 10.3

Evidence Table **AHP 1** What is the effectiveness of physiotherapy vs. standard therapy or placebo in the treatment of Parkinson's disease?	
Bibliographic reference	Deane KHO, Jones D, Playford ED, Ben Shlomo Y, Clarke CE. Physiotherapy versus placebo or no intervention in Parkinson's disease. (Cochrane Review). *The Cochrane Library* 2003.

Study type	Cochrane review (RCTs) 2/11 cross-over designs- 9/11 were parallel group design
Evidence level	1++
Study Objective	To compare the efficacy and effectiveness of physiotherapy with placebo or no interventions in patients with Parkinson's disease.
Number of patients	N=280 Parkinson's disease patients N=6 (Cerri) N=67 (Chandler) N=18 (Comella- cross-over design) N=11 (Forkink) N=24 (Gibberd- cross-over study) N=15 (Homann) N=30 (Hurwitz) N=16 (Katsikitis) N= 20 (Patti) N=51 (Schenkman) N=22 (Thaut) Location: not stated Sites all were single centre (7 out-patient clinics; 3 home-based; 1 hospital inpatients)
Patient characteristics	The similarity between physiotherapy and control groups at baseline could not be determined in 5 trials because the baseline characteristics were not given separately for the two groups. The trials, which did give baseline characteristics, showed a high degree of similarity between groups. Only one trial used strict criteria for the diagnosis of idiopathic PD. Only 32% of 236 patients who gender was specified were female.
Intervention	The 264 patients that received physiotherapy directed to trunk and limb functions were treated for 8-30 hours over 3-52 weeks. The 16 patients who received orofacial physiotherapy were treated for 8 hours over four weeks. The method of physiotherapy was usually described in a very broad manner-even the time spent by therapist with the patient was not specified in 5/11 trials.
Comparison	9/11 trials the control group did not receive a placebo form of therapy, they were observed In one trial (Gibberd) inactive physiotherapy was 20min per session of infrared radiation to the thoracic

	region In another trial (Hurwitz) nurses visited the placebo group as often as the physio group but carried out no exercises
Length of follow-up	Only one of the parallel designs (Patti) followed their patient's progress after treatment (two and 5 months) to determine duration of effect. The remaining parallel studies assessed patients at baseline and immediately after therapy. The two cross-over trials (Gibberd and Comella) assessed their patients at baseline and immediately after the first arm of the trial and then immediately before the second arm (wash out period in these trials was 3 and 6 months respectively) and immediately afters second arm.
Outcome measures	UPDRS, Webster Rating scale, Parkinson's Home Visiting Assessment Tool, Walking velocity, stride length, cadence, time and number of steps taken to turn 360 degrees, Functional Axial Rotation (FAR)-visual, FAR-physical,
Effect size	➢ Cerri and Homann were reported as abstracts only so no numerical data was available ➢ Comella and Gibberd were cross-over trials- neither trial reported data from the end of the first arms so the cross-over design could have been influenced by carry-over effects- this data was not analysed by review ➢ Hurwitz did not provide raw data only results of statistical analysis- thus size of any change due to physiotherapy could not be assessed ➢ **Chandler and Forkink provided mean and SD at baseline and after treatment for each therapy group- the Cochrane review group is waiting advice from the Cochrane collaboration and other statistical departments on a valid method of calculating the SD of the change from this given data- when this advice is received the review will be updated** ➢ Katsikitis and Patti provided similar data but did carry out statistical analysis comparing change in the therapy group with the change in the control group ➢ Schenkman and Thaut provided data on the mean change and SD for each group and carried out analysis comparing statistical significance of these changes between the groups ***Motor impairment and disability*** ➢ Total UPDRS: Patti, significantly improved in physiotherapy by 22.5 points ($p<0.001$) when

	assessed immediately after course of therapy and this was maintained for up to 5 months after therapy (26.5 points, p<0.001) ➢ However baseline UPDRS scores of the control group and treatment group differed by a mean of 22.88 points casting doubts on comparability of two groups ➢ Webster Rating scale: Patti, no significant improvement immediately after physiotherapy ➢ 5 months later control group increased impairments while physiotherapy group maintained their improvement (mean difference 4.58 points, p=0.011) ➢ Parkinson's Home Visiting Assessment Tool: Hurwitz, reported significant changes (p<0.05) in 5/53 items after 8 months of therapy ➢ ***Motor impairment: global*** ➢ The UPDRS motor section was measured by Chandler and Comella but data was only amenable to analysis in Chandler ➢ Chandler reported there was an improvement immediately after physiotherapy of 4 points ***Motor impairments: Gait*** ➢ Patti- increased walking velocity by 0.48 m/sec (p=0.002) and this improvement was mostly maintained over 5 months 0.38 m/sec (p=0.006) ➢ Thaut- increased walking velocity immediately after physiotherapy by 0.22 m/sec (p=0.0001) ➢ Schenkman- increased velocity by 0.06 m/sec (not significant) ➢ Chandler- increased by 0.03 m/sec immediately after course of physiotherapy ➢ Thaut- stride length increased significantly immediately after therapy by 20 cm (p=0.0045) ➢ Patti- stride length increased immediately after therapy 19cm (p=0.016)- improvement was maintained over 5 months (18 cm, p=0.044) ➢ Thaut-Cadence (steps/sec) did not improve significantly post-therapy ➢ Schenkman measured both time and number of steps taken to turn 360 degrees and neither improved significantly after therapy

	Motor impairments flexibility ➢ Schenkman: Spinal rotation (FAR) was measured two ways: visual (patient asked to turn as far as possible and read the furthest symbol that could be seen) and physical (patients were wearing a head-piece with a pointer on it and the symbol with which the pointer aligned was recorded as FAR-physical) ➢ FAR-visual improved by 9.7 degrees (3.6%) not significant ➢ FAR-physical improved by 12.4 degrees, 6.8% (p=0.019) ***Motor impairments: balance*** ➢ Schenkman- functional reach- improved significantly by 1.85cm after therapy ➢ Forkink- equilibrium score- only changed 1 point after physiotherapy ***Motor improvements: dexterity*** ➢ Patti demonstrated this was reduced by 15 sec (improvement) in physiotherapy group but difference was not statistically significant ➢ Gibberd also measured this outcome but did not provide data at end of first arm of cross-over ***Motor impairments: orofacial*** ➢ Katsikitis 12 facial measurements- not clear which should have increased and which should have decreased with an improvement in facial expressions- therefore the review did not present data in as cannot the review authors could not assess its significance ***Activities of Daily living*** ➢ No ADL score was used by more than one study ➢ Patti- used two different ADL scores:

	➢ Barthel index increased significantly (improvement) after physiotherapy by 12 points (p=0.05)- this improvement was maintained for 5 months (14 points, p=0.045) ➢ Northwestern University Disability Scale (NUDS) decreased (improvement) after physiotherapy- immediately after therapy was not significant- but this improvement was mostly maintained for 5 months afterwards and controls were worse resulting in significance of 6.8 points (p=0.018) ➢ Chandler and Patti used functional index measure (FIM) but only Patti provided 'usable' FIM improved significantly after physiotherapy by 13.9 points (p=0.048) and this was maintained over 5 months (17.4 points, p= 0.016) <u>Quality of Life</u> ➢ Chandler- used generic SF-36 and disease-specific PDQ-39- both showed no significance <u>Depression</u> ➢ Comella- UPDRS mental subsection and Geriatric Depression scale- data not available at end of first stage in this cross-over study so no analysis performed by review ➢ Katsikitis also measured depression but no numerical data was available
Source of Funding	None stated
Additional comments	➢ 8 trials did not have adequate placebo treatments ➢ All used small numbers of patients ➢ Method of randomisation and allocation concealment was good in only 4 trials ➢ Ten trials examined the effect of physiotherapy on trunk and limb function (264 patients) ➢ 5/10 trials did not specify the number of hours treatment was given and none specified the intensity of therapy provided ➢ One trial examined orofacial physiotherapy (16 patients) ➢ Four trials had additional intervention from other therapists or component of their protocol could be described as occupational therapy (Chandler, Comella, Gibberd, Patti)- these trials can be said to examine physiotherapy generally rather than specifically- however most of the aims were physiotherapeutic in nature ➢ The therapy was conducted by a physiotherapist in 6 trials (Cerri, Chandler, Forkink, Katsikitis, Schenkman, Thaut) by a physiotherapist and an occupational therapist in two trials (Comella and Gibberd) and senior nursing students in one trial (Hurwitz) ➢ Unclear what the qualifications were of those conducting the therapy in the remaining two trials (Homann and Patti) ➢ Assessors were blinded in only 4 trials- but blinding is difficult for this type of intervention- still liable for many forms of bias

	➢ Authors included in review: Chandler (1999), Comella (1994), Gibberd (1981), Patti (1996), Cerri (1994), Homann (1998), Hurwitz (1989), Forkink (1996), Katsikitis (1996), Schenkman (1998), Thaut (1996)
Citation	
NCC CC ID (Ref Man)	90

Evidence Table **AHP 1** What is the effectiveness of physiotherapy vs. standard therapy or placebo in the treatment of Parkinson's disease?	
Bibliographic reference	Bergen JL, Toole T, Elliott RG, III, Wallace B, Robinson K, Maitland CG. Aerobic exercise intervention improves aerobic capacity and movement initiation in Parkinson's disease patients. *NeuroRehabilitation* 2002;**17**:161-8.
Study type	Randomised controlled trial- open design
Evidence level	1+
Study Objective	To investigate the effect of a 16 week aerobic exercise program on aerobic capacity and movement initiation (MI) time for Parkinson's disease (PD)
Number of patients	N= 8 Parkinson's disease (PD) patients N=4 intervention group N=4 control group N=6 healthy volunteers Location: USA Sites: single
Patient characteristics	Patients were recruited from patient list of the Tallahassee Neuroscience Centre Intervention group: Mean age 56.8 years, all subjects within Hoehn and Yahr stage II, and were an average of 8 years post-diagnosis, moderate active not regular exercisers Control group: Mean age 63.5 years, within stage II of Hoehn and Yahr scale, moderately active not regular exercisers

	Healthy volunteers: Mean age 61.4 years, low to moderately active but not regular exercisers
Intervention	16 week exercise intervention program: 3 min warm-up period on a cycle, 5 min of pre-determined stretching exercises, followed by equal time cycling and walking on the treadmill at target heart rate intensity. Speed and/or resistance were adjusted on the cycle along with adjustments in speed and incline on the treadmill. The duration during the first 4 weeks was 10 min of cycling and 10 min on the treadmill. This was increased for weeks 5 to 8, with exercise set at 15 min both on cycle and treadmill. Weeks 9 through 16 the exercise times were increased to 20 min for both cycle and treadmill.
Comparison	No exercise program
Length of follow-up	16 week duration 1 week follow-up
Outcome measures	Pre-test and post-test for aerobic capacity and movement initiation (MI) time
Effect size	Aerobic capacity ➢ Significant group by time interaction between PD intervention group and controls, and pre- and post-tests using aerobic capacity p=0.013 ➢ The treatment group significantly improved their peak VO2 scores from 19.5 ml/kg/min to 24.5 ml/kg/min while the control group declined slightly from 15.9 ml/kg/min to 14.1 ml/kg/min ➢ There was also a significant interaction between groups pre and post test power output p=0.037 ➢ The treatment group had a significant increase from pre-to-post test with 32% improvement from 123 watts to 163 watts ➢ While the control group lost 10% from pre to post test (109 watts to 98 watts) MI time ➢ Exercise intervention improved MI time for both simple and choice conditions ➢ Significant improvement in choice MI mean time p=0.003 (532 ms to 415 ms) ➢ Simple MI mean time improved non-significantly (285 ms to 261 ms) ➢ Significant interaction effect p=0.016 between pre and post test scores for simple and choice conditions ➢ Pre-test scores were comparable between PD exercise group and PD controls ➢ Post-test scores were similar between PD exercise group and healthy controls (p=0.38)
Source of Funding	None stated
Additional comments	➢ No methods of randomisation or allocation concealment ➢ Not practical to be blinded therefore open trial ➢ Small sample size
Citation	
NCC CC ID (Ref Man)	2778

Evidence Table **AHP 1** What is the effectiveness of physiotherapy vs. standard therapy or placebo in the treatment of Parkinson's disease?	
Bibliographic reference	Stallibrass C, Sissons P, Chalmers C. Randomized controlled trial of the Alexander technique for idiopathic Parkinson's disease. *Clin Rehabil* 2002;**16**:695-708.
Study type	Randomised controlled trial
Evidence level	1++
Study Objective	To determine whether the Alexander Technique, alongside normal treatment is of benefit to people disabled by idiopathic Parkinson's disease (PD)
Number of patients	N=88 PD patients N=29 Alexander technique N=29 Massage N=30 control group Location: UK Sites: Single
Patient characteristics	Volunteers were recruited through advertisement in national and London press, at Parkinson's disease clinics in several London hospitals and through Parkinson's disease Society. Inclusion criteria: diagnosed by a consultant neurologist, committed to keeping PD medication unchanged during course of trial and follow-up, able to climb 20 stairs, able to lie on floor and get up alone (with help of furniture), reasonable short-term memory Exclusion criteria: taking medication for another serious neurological illness, been hospitalised for depression in the last 10 years, receiving non-pharmacological therapy on last 6 months, individual Alexander technique lessons in the last 10 years. Alexander technique group: mean age 64.1 yrs, duration of illness 4.8 yrs, female: male 10:19 Massage group: mean age 66.1, duration of illness 4.7 yrs, female: male 8:21 Control group: mean age 64.8 yrs, duration of illness 4.9 yrs, female: male 9:21

Intervention	Interventions started 3-10 days after randomisation and were completed within 3 months Alexander Technique group: 2 lessons per week for 12 weeks- 40 min each- 5 weeks after completion the participants received a short-audio tape that lead them through a 20min lying down exercise Massage group: 2 massage sessions per week for 12 weeks (the massage group as to control for touch and attention)
Comparison	No treatment
Length of follow-up	6 months
Outcome measures	Self-assessment Parkinson's disease Disability Scale (SPDDS) at best and worst time of the day. Secondary measures include the Beck Depression Inventory (BDI) and an Attitudes to Self Scale
Effect size	➢ SPDDS: participants rated how easy or difficult it was to perform 25 separate actions at their best (SPDDS at best) and at their worst times (SPDDS at worst) in the last week, on a 5-point scale (range of total scores 25- 125) 1: 'able to do alone or without difficulty' to 5:' unable to do at all' ➢ Questionnaires were administered on 3 occasions: pre-intervention, post-intervention, and at 6 months follow-up ➢ BDI: participants 'feelings in the last week'- asked how they felt about 21 items by selecting one of the four statements which best described their feelings. The most positive score was 0 and the most negative was 3 (range of total scores 0-63) ➢ Attitudes to Self Scale: 'feelings and attitudes towards our bodies/selves'. Consists of 15 semantic paired opposite (e.g. tense/relaxed). Positive score was 0 and negative score was 6 (range of total scores 0-90) ➢ BDI and attitudes to self scale were administered the same as the SPDDS scale Alexander Technique vs. no additional intervention ➢ Attendance and compliance was high for both groups ➢ Pre-to post intervention the Alexander Technique group improved compared to no additional intervention group on both the SPDDS at best (95%CI –6.4 to 0.0, p=0.04) and at worst (95%CI –11.5 to –1.8, p=0.01) ➢ The comparative improvements were maintained at the end of the 6-month follow-up, SPDDS at best (95%CI –7.7 to 0.0, p=0.04) and at worst (95%CI –1.8 to –0.9, p=0.01) ➢ The mean scores of both groups has decline at 6 months follow-up ➢ The Alexander technique group did not fall below pre-intervention levels while the no intervention group did ➢ The sample size criterion of a mean change of 3 points in the Alexander technique group on the SPDDS at best was not achieved, while the SPDDS at worst it was exceeded ➢ Post-intervention: in response to an open-ended question about changes arising from the interventions: the Alexander technique group made 59 mentions of improvement in specific actions ➢ Post-intervention the Alexander technique group compared to the no additional intervention group felt significantly better on the BDI (p=0.03) and the 6-month follow-up on the Attitudes to Self Scale (p=0.04) ➢ The results were positive but not statistically significant for the attitudes to self post-intervention (p=0.07) and the BDI

	at 6-month follow-up (p=0.17) ➢ Post-intervention the Alexander technique group had a mean improvement of –5.1 points on the Attitudes to Self Scale compared with only -1.6 for the no additional intervention group ➢ At 6-month follow-up the mean improvement for the Alexander technique was –2.6 compared to a deterioration of +2.9 for the no intervention group (p=0.04) ➢ BDI changes pre- to post-intervention were –1.9 for the Alexander technique group and –0.2 for the no intervention group ➢ Pre-intervention to 6 months follow-up they were +0.9 to –0.1 respectively Massage vs. no additional intervention ➢ Measured on the SPDDS at best and SPDDS at worst showed no statistical significant in differences either immediately or post-intervention or at 6 month follow-up ➢ There were no significant differences for the BDI or Attitudes of Self Scale ➢ The BDI changes for the massage group were positive pre- to post intervention (-1.7) and pre-intervention to 6-month follow-up (-1.3) and were close to the changes on the Alexander group (-1.9 and –0.9 respectively) ➢ The mean scores of the no intervention group barely changed pre-to post-intervention (-0.2) and pre-intervention to 6-month follow-up (-0.1) ➢ The attitudes of self scale showed little change post-intervention (-0.1) and worsening at 6-months follow-up (+3.7) and were relatively close to the no intervention group mean changes –1.6 and +2.9, especially in contrast to the Alexander Technique group (-5.1 and –2.6 respectively) ➢ The massage group made only 10 mentions of improvement from massage in specific physical actions compared with 59 from the Alexander Technique group ➢ Pre- to post medication change in the massage group was lower than no intervention group (4 sc. 7) but higher than Alexander technique group (4 vs. 1) ➢ During the 6 month follow-up there were 12 participants who changes their medication in the massage or no intervention groups and only 4 in the Alexander technique group ➢ The rate of medication change was statistically lower in the Alexander technique group than the other two groups (p=0.001) ➢ Fewer participants in the Alexander technique group changed their medication and yet were not experiencing worsening symptoms (p=0.047)
Source of Funding	
Additional comments	➢ Patients were recruited in 3 successive cohorts during 1998 to 1999 ➢ Sample size calculations were performed- test size set at 5% and power set at 85% ➢ Target sample size was 30 per group and 90 in total ➢ Methods of randomisation and allocation concealment stated

	➢ Both of the Alexander Technique teachers were members of the Society of Teachers of the Alexander technique ➢ Practitioners were trained in therapeutic massage ➢ The massage group was intended to control only for touch and personal attention of Alexander Technique lessons ➢ Independent and blinded assessment
Citation	
NCC CC ID (Ref Man)	2779

AHP4 – section 10.2

Evidence Table **AHP4** What is the effectiveness of the Parkinson's disease nursing specialist care vs. standard care or placebo in the treatment of Parkinson's disease?	
Bibliographic reference	Jarman, B., Hurwitz, B., & Cook, A. 2002, "Effects of community based nurses specialising in Parkinson's disease on health outcome and costs: randomised controlled trial. (Research to evaluate the value of nurse specialists working with GPs with Parkinson Disease patients on outcomes, cost, and wellbeing)", *BMJ*, vol. 324, no. 7345, pp. 1072-1075.
Study type	RCT (with 2 year follow-up) **nursing specialists vs. GP standard care**
Evidence level	1+
Number of patients	N=1859 patients with Parkinson's disease (PD) ➢ N=1041 (56%) nurse specialist group ➢ N=818 (44%) control group Location: England Sites: 438 general practices in 9 randomly selected health authority areas
Patient characteristics	➢ All general practices in 9 health authorities selected were asked to identify eligible patients based on patients taking one or more anti-parkinsonian drugs ➢ Patients aged 17 years or less were excluded and those with severe mental illness or cognitive

<table>
<tr><td></td><td>impairment sufficient to preclude valid informed consent
➢ No noticeable differences were observed between treatment groups at baseline for age, sex, accommodation, social class, disease duration, disease severity, or drugs
➢ Study sample was representative of population of the England and Wales with Parkinson's disease in terms of disease duration and age (except with slight under-representation of >85 yrs)</td></tr>
<tr><td>Intervention</td><td>Community based care from nurse specialist: 9 nurses were employed by the university and trained at the Nursing and Midwifery School, University of Sheffield. They completed a course on meeting the special needs of people with Parkinson's disease and their carers.</td></tr>
<tr><td>Comparison</td><td>Standard care from general practitioner</td></tr>
<tr><td>Length of follow-up</td><td>2 years</td></tr>
<tr><td>Outcome measures</td><td>Clinical outcomes (inc. Survival) and quality of life outcomes (inc. global health question, PDQ-39, Euroqol) and health care costs</td></tr>
<tr><td>Effect size</td><td>End of study data comparing the effectiveness of nursing specialists vs. standard care
<table>
<tr><td>Clinical outcomes
% (SD)</td><td>Nurse group
(n= 696)</td><td>Control
(n=558)</td><td>Hazard ratio (95% CI)
(nurse vs. control)</td><td>P
value</td></tr>
<tr><td>Stand-up group:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>1. No problems</td><td>248 (35.6)</td><td>221 (39.6)</td><td></td><td></td></tr>
<tr><td>2. Without holding on</td><td>114 (16.4)</td><td>82 (14.7)</td><td>1.15 (0.93 to 1.42)</td><td>0.19</td></tr>
<tr><td>3. Unable or had to hold on</td><td>329 (47.3)</td><td>247 (44.3)</td><td></td><td></td></tr>
<tr><td>Bone fracture during study</td><td>92 (13.2)</td><td>62 (11.1)</td><td>1.20 (0.85 to 1.69)</td><td>0.31</td></tr>
<tr><td>Mean best hand score</td><td>45.3 (21.2)</td><td>46.0 (21.1)</td><td>-0.70 (-3.25 to 1.84)</td><td>0.59</td></tr>
<tr><td>Mortality (after 2 years)</td><td>169 (16.6)</td><td>146 (18.2)</td><td>0.91 (0.73 to 1.13)</td><td>0.38</td></tr>
<tr><td>Mortality (after 4 years)</td><td>353 (34.7)</td><td>307 (38.2)</td><td>0.89 (0.76 to 1.03)</td><td>0.12</td></tr>
<tr><td>Quality of life measures</td><td>Nurse group</td><td>Control
group</td><td>Difference (95% CI)
(nurse vs. control)</td><td>P
value</td></tr>
<tr><td>Global health</td><td>4.79 (1.50)</td><td>5.02 (1.38)</td><td>-0.23 (-0.40 to –0.06</td><td>0.008</td></tr>
<tr><td>Euroqol tariff (high score good)</td><td>0.37 (0.35)</td><td>0.39 (0.35)</td><td>-0.02 (-0.06 to 0.02</td><td>0.30</td></tr>
<tr><td>PDQ (high score bad)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mobility</td><td>61.1 (31.9)</td><td>59.8 (32.9)</td><td>1.38 (-2.57 to 5.34)</td><td>0.49</td></tr>
<tr><td>Activities of daily living</td><td>52.4 (28.6)</td><td>51.7 (29.9)</td><td>0.71 (-2.73 to 4.14)</td><td>0.69</td></tr>
</table></td></tr>
</table>

	Emotional well-being	34.7 (24.7)	34.5 (25.8)	0.21 (-2.79 to 3.20)	0.89
	Stigma	30.6 (27.5)	30.8 (28.7)	-0.14 (-3.44 to 3.16)	0.93
	Social support	51.9 (22.1)	13.7 (20.8)	2.21 (-0.66 to 5.08)	0.13
	Cognition	39.3 (23.2)	38.0 (24.4)	1.30 (-1.52 to 4.11)	0.37
	Communication	28.6 (24.4)	28.7 (25.1)	-0.10 (-3.02 to 2.82)	0.95
	Bodily discomfort	45.4 (24.8)	43.7 (25.3)	1.68 (-1.26 to 4.62)	0.26
	PDQ-39 summary index	39.7 (21.2)	39.2 (22.1)	0.47 (-2.72 to 3.66)	0.77
	NHS and local health authority costs (in £000s. Values are mean (max)	Nurse group (n=1028)	Control group (n=808)	Difference (95% CI) (nurse vs. control)	P Value
	Year preceding study	4.05 (55.4)	3.48 (35.0)		
	Year 2 (patients at end of study)	5.86 (39.1)	5.63 (33.1)		
	Individual mean increase	2.54 (34.6)	2.80 (31.6)	-0.26 (–0.98 to 0.45)	0.47
	➢ The patient's responses to the **global health question** (a measure of patient's perception of change in well-being) was statistically significant for the patients receiving the nursing intervention vs. standard care (**p=0.008**) (thus the intervention group benefited in subjective well-being) ➢ The study showed that nurse specialists assessed an average of 13.7 patients per week ➢ 75% of patients assessed at home, 14% at general practices, 11% in hospital clinics ➢ Patients in the nurse group received an average of 8 assessments by the nurse per year ➢ The health care costs to NHS and local health authorities did not increase significantly for providing this service				
Source of Funding	Paul Hamlyn Foundation, the Parkinson's disease Society, and Britannia Pharmaceuticals				
Additional comments	➢ **Aim**: to determine the effects of the community based nurses specialising in Parkinson's disease on health outcomes and healthcare costs Recruitment: ➢ Sampling frame included all English health authorities in 1995 that did not already have well-developed community-based services of nurse specialists in Parkinson's disease ➢ Randomly chose nine health authorities out of an eligible 57 ➢ Randomisation of patients to control/intervention groups was performed by an independent social survey organization				

	➢ Trained lay workers employed by an independent survey organization were sent to interview participants in their place of residence and collect information on health outcomes and costs at one and two years ➢ Before each interview the patients were sent questionnaires eliciting information about self-perceived health status ➢ Self-completed questionnaire including: the validated PDQ-39 instrument used for measuring the functioning and well-being of patients with PD (score range 0-100: higher score represents worse functioning), and the Euroqol a health-related quality of life measure (score range –0.59 to +1: higher value represents better quality) ➢ Based in primary care setting ➢ Author's conclude: ''the provision of community based nurses specialising in the care of patients with Parkinson's disease has little effect on clinical progression of the disease when compared with patient's receiving standard care from their general practitioner''.
Citation	
NCC CC ID (Ref Man)	223

Evidence Table **AHP4** What is the effectiveness of the Parkinson's disease nursing specialist care vs. standard care or placebo in the treatment of Parkinson's disease?	
Bibliographic reference	Jahanshahi, M., Brown, R. G., Whitehouse, C., Quinn, N., & Marsden, C. D. 1994, "Contact with a nurse practitioner: A short-term evaluation study in Parkinson's disease and dystonia", *Behavioural Neurology*, vol. 7, no. 3-4, pp. 189-196.
Study type	RCT: questionnaire format **nurse practitioner vs. standard care**
Evidence level	1+
Number of patients	N=40 PD patients ➢ N= 20 intervention group (received contact with nurse practitioner) ➢ N=20 control group (standard care no extra nurse contact) Location: London, UK sites: 1

Patient characteristics	Characteristics ➢ 25 male, 15 female ➢ Mean age 63.7 years ➢ Average age of onset 53.6 years ➢ Average duration of illness 10.1 years (range 1-25 years) Selection criteria: ➢ Diagnosis of idiopathic disease ➢ Current treatment with dopaminergic medication ➢ Hoehn and Yahr stage of illness II or above ➢ Age less than 70 years ➢ No clinical evidence of dementia ➢ All patients lived within 50 mile radius of hospital ➢ Half the patients were randomly allocated to 'intervention' or 'control' groups ➢ There were no differences in age, sex, age at onset, or duration of illness
Intervention	Consisted of two home visits and five telephone contacts form the nurse practitioner, over 6 months. Each home visit lasted three or more hours depending on the needs of the patient. In the intervening period the nurse practitioner made 5 telephone contacts. In addition to the scheduled contacts, the patients in the intervention group were free to telephone the nurse practitioner at any time during the trial. All patients completed a set of questionnaires relating to psychological and social functioning on two occasions, separated by an interval of 6 months. For those allocated to the 'intervention' group the first set of questionnaires were completed before the first contact and the second immediately after the end of this contact with the nurse practitioner.
Comparison	Standard care without nurse practitioner intervention
Length of follow-up	6 month follow-up
Outcome measures	Psychosocial variables, practical outcomes, and results of independent assessment
Effect size	➢ There was a slight improvement in patients allocated to the intervention group for 7/9 psychosocial measures- these changes did not reach statistical significance ($p>0.05$) ➢ Greatest change in reduction of anxiety and depression ➢ Patients in the control group showed an improvement in only 3/9 measures and none were significant

	<u>The results below were not separated for PD and dystonia groups</u> ➢ *The most common information given by the nurse practitioner was practical; regarding income support and mobility allowance* ➢ *Other common needs concerned the way to obtain a disability sticker for their car, dietary advice, and information regarding holidays for the disabled* ➢ *Other interventions concerned referrals to other health professionals through the patient's own GP (in total 22 referrals were arranged in 6 months (18.9% to an OT and 15.6% to a neurologist)* *Results of independent assessment questions:* ➢ *Mean rating of contact was 8.5, half rated 10, ''10= very useful''* ➢ *Aspects of contact rank ordered in terms of usefulness were: 'opportunity to talk to someone about the illness and the problems caused by it'', ''knowing that someone could be contacted if problems arose'', referrals to other health professionals'', ''sorting out practical problems'', ''information given about the illness and its treatment''* ➢ *88.5% considered the home visits the most useful aspect of the intervention* ➢ *80.8% thought the duration of contact needed to be prolonged* ➢ *58% thought the intervention would be useful to other sufferers of PD (mean 9.0)* ➢ *96.2% of patients agreed this intervention should be an important priority of the Health Service*
Source of Funding	Parkinson's Disease Society (UK), the Dystonia Society (UK), the Wellcome Trust, Du Pont Pharma and Roche Products Ltd.
Additional comments	➢ **Aim**: to assess the value of access to and contact with a nurse practitioner ➢ Patients recruited from National Hospital for Neurology and Neurosurgery, London ➢ At the end of the trial, the patients allocated to the intervention group were contacted by investigators not involved in the intervention program – asked them 7 questions concerning intervention ➢ Author's conclusions: ''the service was highly valued by the patient, and led to a high rate of new referral to other health-care agencies and take-up of state-provided benefits. However, there was no evidence that these inputs had any significant impact on adjustment and psychological well being on the measures used''. ➢ Longer follow-up period required to see more effects
Citation	
NCC CC ID (Ref Man)	200

Evidence Table **AHP4** What is the effectiveness of the Parkinson's disease nursing specialist care vs. standard care or placebo in the treatment of Parkinson's disease?	
Bibliographic reference	Reynolds, H., Wilson-Barnett, J., & Richardson, G. 2000, "Evaluation of the role of the Parkinson's disease nurse specialist", *International Journal of Nursing Studies*, vol. 37, no. 4, pp. 337-349.
Study type	RCT: questionnaire to measure the effectiveness of **PDNS vs. consultant neurologist care**
Evidence level	1+
Number of patients	N=185 Parkinson's disease (PD) patients ➢ N=85 consultant care only (control) (group A) ➢ N=35 Parkinson's disease nursing specialist (PDNS) care only (group B) ➢ N=65 mainly PDNS, with consultant follow-up (group C) Location: London Location: sites: 3
Patient characteristics	Mean age in the groups were similar 64-68 Mean time since diagnosis ranged from 4 to 8 years Sample of 62 males and 46 females Entry criteria: seen by a consultant at least once for medical assessment and confirmation of a diagnosis of idiopathic PD, not previously seen by PDNS, able to understand requirements of study and give informed consent, no clinical evidence of dementia, new referral to clinic
Intervention	Parkinson's disease nursing specialists (PDNS) (specific details of intervention not provided)
Comparison	Consultant neurologist care
Length of follow-up	One year
Outcome measures	Parkinson's disease questionnaire (PDQ), SF-36, Hospital anxiety and depression scale, costs
Effect size	***Health Outcomes*** ➢ Baseline scores were analysed for statistically significant differences between groups ➢ Out of 22 dimensions **only communication scores on the PDQ were significantly different**

	between groups at baseline (**p=0.05**) favouring the PDNS group (B) ➢ At the end of study analysis of score differences were performed where baseline scores were deducted from the end of study scores to look at individual change scores ➢ Only 2 out of 22 dimensions reached statistical significance (p=0.05): physical functioning (p=0.02) and general health (p=0.02) both measured by the SF-36 and both favoured the consultant group only ***Hospital anxiety*** ➢ At the end of the study group B maintained median-normal anxiety level and groups A and C maintained median-mild anxiety levels ➢ All median depression scores at baseline and at the end of study were in the normal range Economic study: ➢ Economic analysis of 47 patients (30 randomised to PDNS and 17 to consultant group) ➢ Cost per month significantly higher in PDNS group (p=0.001) ➢ Mean costs of care were: £53.96 in PDNS and £4.76 in consultant group for first follow-up period ➢ And £66.77 and £5.41 at the second follow-up (p=0.001) ➢ Not known what resources each group consumed before the intervention
Source of Funding	Nuffield Trust, London
Additional comments	➢ **Aim**: to demonstrate whether there are any differences in outcome from treatment when this is given, primarily by PDNS or specialist neurologist ➢ Patients randomised according to established pattern of care at that centre ➢ Small pilot study was performed to test methods for data collection ➢ Bias potential for sites selected not at random but which promoted PDNS services ➢ **185 patients began the study, however only 108 completed (58%)** ➢ Study did not use a control centre (centre without PDNS services) ➢ All patients were seen at least twice during the study (but this varied depending on need) ➢ Author's conclude: ''Medical and nursing specialists valued their complementary expertise, and patient and carers responses to consultations also reflect that PDNS's have particular contributions''. ➢ Author's conclude: '' given that there were few differences in patient outcomes, it is difficult to recommend the provision of specialist nurses for patients with Parkinson's disease solely on cost-

	effectiveness grounds''.
Citation	
NCC CC ID (Ref Man)	744

Evidence Table **AHP4** What is the effectiveness of the Parkinson's disease nursing specialist care vs. standard care or placebo in the treatment of Parkinson's disease?	
Bibliographic reference	Bell, L. 2004, *Changing Roles: The Impact of Parkinson's Disease Nurse Specialists*, Parkinson's Disease Society of the United Kingdom.
Study type	Report
Evidence level	4
Number of patients	N/A
Patient characteristics	N/A
Intervention	Parkinson's disease Nurse Specialists
Comparison	N/A
Length of follow-up	N/A
Outcome measures	descriptive
Effect size	➢ **Essential Skills of the PDNS:** • Clinical leadership • Research awareness • Developing nursing knowledge • Providing consultancy • Educating patients, carers and colleague • Initiating and managing change • Evaluating care ➢ The role of the PDNS will depend on local need and the experience and qualifications of the individual nurse ➢ Making and receiving referrals direct creating integrated and responsive Parkinson's services

	➢ Admitting and discharging patients for specified conditions and within agreed protocols- this has highlighted the need for a care pathway ➢ Managing patient caseloads- providing both information and support to patients in their homes, in clinics and in hospitals- under-resourcing is an issue ➢ Prescribing medicines and treatment-to monitor the effectiveness of changes in medication and treatment, and to provide information and education-PDNS will soon be able to prescribe according to the new guidelines for 'supplementary' prescribing for non-medical health professionals like nurses and pharmacists to prescribe medication once a doctor has made diagnosis ➢ To use the latest IT to triage patients to the most appropriate health professional-using IT to identify patients at risk and speed up responses to crises ➢ Taking the lead in the way local health services are organized and run ➢ The exact role of the PDNS should be tailored to the needs of the local community and patients ➢ Primary Care Trusts need to ensure nurses' knowledge and skills match their intended role
Source of Funding	Parkinson's Disease Society UK
Additional comments	
Citation	
NCC CC ID (Ref Man)	787

AHP2 – section 10.5

Evidence Table ***AHP 2*** What is the effectiveness of speech and language therapy versus standard medical therapy or control in the treatment of speech disturbance in Parkinson's disease?	
Bibliographic reference	Deane KHO, Whurr R, Playford ED, Ben Shlomo Y, Clarke CE. Speech and language therapy versus placebo or no intervention for dysarthria in Parkinson's disease. (Cochrane Review). *The Cochrane Library* 2003.

Study type	Systematic review of parallel group, single centre studies
Evidence level	1++ (applied to Cochrane methodology)
Study objective	To compare the efficacy of speech and language therapy versus placebo or no interventions in patients with Parkinson's disease
Number of patients	N=63 Parkinson's disease patients N=12 (Johnson) N=29 (Ramig) N=22 (Robertson) Location = Not stated Sites =3
Patient characteristics	Patients with a diagnosis of PD; any duration of PD; all ages; any drug therapy; any duration of treatment. Johnson: Mean age: 63.5 yrs treatment, 64.8 placebo; Male/female: 5 males, 1 female per group Ramig: Mean age: 67.9 treatment, 71.2 placebo; Male/Female: 7/7 treatment, 7/8 placebo Robertson: Mean age: 58.4 treatment, 68.1 placebo; Male/female: 12/0
Intervention	Speech and language therapy ➢ Johnson- individual therapy with the emphasis placed on prosodic features of pitch and volume, reinforced by a number of visual feedback systems; ➢ Robertson- group therapy aimed at improving loudness and pitch variation, respiration, voice production and intelligibility. Included visual feedback to reinforce therapy ➢ Ramig- aimed solely at maximizing phonatory effort and increasing volume on an individual basis.
Comparison	Placebo or no intervention (no description of control intervention)
Length of follow-up	No follow-up stated for Johnson and Ramig both had trial duration of 4 weeks. Robertson had a trial duration of 2 weeks and follow-up at 3 months.
Outcome measures	Speech and voice production parameters; activities of daily living; handicap and quality of life measures; depression rating scales; adverse effects; carer outcomes; economic analyses
Effect size	Summary assessments of speech impairment ➢ Johnson measured total impairment with the Frenchay Dysarthria Assessment, which improved with therapy by 29 points compared to the placebo group. Statistical analysis of this result was not possible with the data provided. ➢ Robertson stated that the scores of the Dysarthria profile were comparable in the two groups at baseline. Immediately after therapy the scores were significantly higher in the treatment group compared to the placebo group (ANOVA: $F(1,16) = 3.85$, $p<0.05$).

	Speech impairments: <u>loudness</u> ➢ Ramig measured loudness objectively (sound pressure level, dB) with four different speaking modes, whilst Johnson measured it objectively in two different speaking modes (volume, dB). Ramig statistically compared loudness values at the end of therapy between the two groups, rather than the difference between the mean change due to each therapy. ➢ Objective loudness improved by 11 dB in Johnson and by 5.4 dB ($p<0.005$) in Ramig immediately after therapy. ➢ Ramig – objective mean loudness of a monologue reduced to 3.5 dB after 6 months but this was still significant ($p<0.05$). ➢ Ramig – measured the mean objective loudness of speech when the patients were asked to describe a picture. Again the loudness improved by 5.2 dB ($p<0.025$) and this improvement was maintained over 6 months (4.2 dB, $p<0.02$). ➢ Ramig & Johnson found improvements in mean objective loudness of reading a standard passage immediately after therapy (6.3 dB and dB respectively). Ramig found of patients receiving LSVT was more than the placebo group immediately after therapy and showed that this improvement was mostly maintained (4.5 dB, $p<0.005$). Ramig found improved mean objective loudness when patients were asked to give a prolonged 'a'. This improved after therapy (12.1 dB, $p<0.001$) and improvement was maintained for 6 months (9.4 dB, $p<0.001$). Speech impairments: <u>Monotonicity</u> ➢ Johnson- Maximum pitch range improved by 66Hz after therapy. Maximum volume range improved by 23.7 dB after therapy. Speech impairments: <u>Pitch</u> ➢ Johnson- mean pitch reduced in the therapy group and increased in the placebo group by approximately 30 Hz in both groups. Overall this lead to a difference of 65.4 Hz between the two groups.
Source of funding	Not stated
Additional comments	➢ *Numerical data was only available in two of the trials and these trials varied significantly in their methodology* ➢ *Small sample sizes and lack of power calculations* ➢ *Method of randomization not stated in Johnson 1990* ➢ *Alternate allocation was used in the Ramig 2000 & Robertson 1984 trials* ➢ *Eligibility criteria not well defined* ➢ *Unclear what sort of PD population was treated or severity of PD* ➢ *No placebo interventions.*

	➢ *No description of control intervention in all studies* ➢ *Outcome measures varied greatly between trials* ➢ *There were significant differences in the duration and intensity of the therapy given to the patients* ➢ *Methods of speech and language therapy differed in all of the trials.* ➢ *Robertson 1984 data was analysed per protocol- the other studies were analysed as per intention-to-treat* ➢ Included trials: Johnson, 1990; Ramig, 2000; Robertson, 1984
Citation	
NCC CC ID (Ref Man)	77

AHP3 – section 10.4

Evidence Table ***AHP3*** What is the effectiveness of occupational therapy vs. standard medical therapy or placebo in the treatment of Parkinson's disease?	
Bibliographic reference	Deane, K. H. O., Ellis-Hill, C., Playford, E. D., Ben-Shlomo, Y., Clarke, C. E. Occupational therapy for Parkinson's disease (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.
Study type	Systematic review of two parallel group, open label, single centre trials
Evidence level	1++ (applied to Cochrane methodology only and not trials contained therein)
Study objective	To compare the efficacy and effectiveness of occupational therapy (OT) with placebo or no interventions (control group) in patients with Parkinson's disease.
Number of patients	Total participants N=84 N=64 (Gauthier 1987) N=20 (Fiorani 1997). Location: not stated Sites: single centre trials

Patient characteristics	Parkinson's disease patients (any duration of illness, all ages, any drug therapy, any duration of treatment) Fioriani: N=10 per study arm, mean age= 70.6 yrs, male/female=13/7 Gauthier**:** N=32 per study arm, mean age=60.9 yrs, Gender not given
Intervention	Method of OT: Fiorani: handicrafts, picture drawing, basketry, folk singing, dancing, and games. Gauthier: mobility activities, dexterity activities, functional activities, educational talks.
Comparison	Placebo control intervention or no intervention Fiorani: Individual physiotherapy sessions Guthier: No treatment described
Length of follow-up	Trial duration: (Fiorani) 12 hours of treatment over one month and (Gauthier) 20 hours of treatment over 5 weeks and follow-up for 1 year.
Outcome measures	Motor impairment, Activities of daily living, Handicap and quality of life measures
Effect size	➢ Studies could not be combined due to methodological limitations. ➢ Gauthier: Barthel Index score (designed to assess geriatric patients in nursing homes to see if they were capable of returning home or still required nursing) was maintained over one year in those treated with occupational therapy, whilst the untreated group lost an average of 4.6 points ➢ Statistical significance of this was not available. ➢ Extrapyramidal symptoms rating scale (ESRS) items were measured post treatment, six months and one year later ➢ The review reported the items measured did not seem relevant to the aims of occupational therapy for PD and the scoring system was crude (e.g. ESRS was designed for the measurement of tardive dyskinesia in schizophrenia and was validated in that group) • Fioriani: differences in mean changes between groups on all outcome measures were all small and statistical significance was not available.
Source of funding	None stated
Additional comments	➢ Occupational therapy and physiotherapy methods were poorly described. ➢ Components of physiotherapy in both trials. **Gauthier 1987:** ➢ No details about the method of randomization or concealment of allocation ➢ Discrepancy in the reporting of the number of patients who completed the trials

	➢ No description of the control intervention ➢ Method of occupational therapy used was described in a very broad manner ➢ Data-analysis per protocol ➢ Not clear whether patients were in 'on' or off' status when assessed **Fiorani 1997:** ➢ Randomisation was adequate but blinding of assessors was not stated ➢ Number of drop-outs not stated ➢ The control group were treated with physiotherapy individually, whereas the therapy group received physiotherapy and occupational therapy as a group
Citation	
NCC CC ID (Ref Man)	72

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