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Atypical Antipsychotics for Schizophrenia: Combination Therapy and High Doses — Project Protocol

Supporting Informed Decisions

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services.

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ABBREVIATIONS

AAP	atypical antipsychotic
ACP	Advisory Committee on Pharmaceuticals
APD	antipsychotic drug
BPRS	Brief Psychiatric Rating Scale
CAC	COMPUS Advisory Committee
CADTH	Canadian Agency for Drugs and Technologies in Health
CERC	COMPUS Expert Review Committee
CGI-S	Clinical Global Impressions — Severity scale
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DPAC	Drug Policy Advisory Committee
DSM-IV TR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EMBASE	Excerpta Medica Database
EPS	extrapyramidal symptoms
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD-10	World Health Organization International Statistical Classification of Diseases and Related Health Problems, 10th revision
NICE	National Institute for Health and Clinical Excellence
OUWG	Optimal Use Working Group
PANSS	Positive and Negative Syndrome Scale
PICOS	population, intervention, comparators, outcome, and study design
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SAS	Simpson-Angus Scale
SIGN	Scottish Intercollegiate Guidelines Network
TAP	typical antipsychotic
WDAE	withdrawals due to adverse events

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1 INTRODUCTION

Optimizing drug-related health outcomes and the cost-effective use of drugs is a goal of the Canadian Agency for Drugs and Technologies in Health (CADTH). Where possible, CADTH builds on existing applicable Canadian and international initiatives and research.

CADTH goals are achieved through three main approaches:

- identifying evidence-based optimal use in the prescribing and use of specific drugs
- identifying gaps between clinical practice, then proposing evidence-based interventions to address these gaps
- supporting the implementation of these interventions.

Direction and advice are provided to CADTH through various channels, including the following:

- the former COMPUS Advisory Committee (CAC) and the former Advisory Committee on Pharmaceuticals (ACP), which include representatives from the federal, provincial, and territorial Health Ministries and related health organizations.
- the Drug Policy Advisory Committee (DPAC)
- the DPAC Optimal Use Working Group (OUWG))
- DPAC and its OUWG were formed following the selection of this report's topic.
- the COMPUS Expert Review Committee (CERC) stakeholder feedback.

1.1 The COMPUS Expert Review Committee

CERC consists of eight Core Members appointed to serve for all topics under consideration during their term of office, and three or more Specialist Experts appointed to provide their expertise in recommending optimal use for one or more specific topics. For topics in the area of mental health, four specialists were appointed as Specialist Experts. Two of the Core Members are Public Members who bring a lay perspective to the committee. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists, or have other relevant qualifications, with expertise in one or more areas such as but not limited to: family practice, internal medicine, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization expertise, methodology, affecting behaviour change (through health professional and/or patient and/or policy interventions), and critical appraisal. The Core Members, including Public Members, are appointed by the CADTH Board of Directors.

The mandate of CERC is advisory in nature, and consists of providing recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada. The overall perspective used by CERC members in producing recommendations is that of public health care policy-makers in pursuit of optimizing the health of Canadians within available health care system resources.

2 ISSUE

CAC and ACP have identified atypical antipsychotics (AAPs) for schizophrenia — specifically high-dose and combination therapy — as being a priority topic for optimal practice initiatives, based on the following criteria:

- large deviations from optimal utilization (overuse or underuse)
- size of patient populations
- impact on health outcomes and cost-effectiveness
- benefit to multiple jurisdictions
- measurable outcomes
- potential to effect change in prescribing and use.

2.1 Schizophrenia

Schizophrenia is a mental illness that requires lifelong treatment.[1] It is associated with symptoms that include hallucinations, delusions, cognitive impairment, disorganized thoughts, social withdrawal, and amotivation.[2] Its worldwide prevalence is 0.5% to 1.5%;[3] in Canada, it affects about 1% of the population[2] or 234,000 people (2004 data).[4] Schizophrenia is a chronic or recurrent illness and patients are at an increased risk for numerous other medical illnesses, suicide, substance abuse, homelessness, and unemployment.[5] Diagnostic criteria for schizophrenia are currently based on the latest revisions of either the World Health Organization International Statistical Classification of Diseases and Related Health Problems (ICD-10) or the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[3]

The total financial burden of schizophrenia in Canada was estimated to be C$6.85 billion in 2004.[6] The annual direct health care and non-health costs were estimated at C$2.02 billion (2004 dollars); acute (23%) and non-acute (38%) hospital care accounted for the majority of these costs.[6]

2.1.1 Management of schizophrenia

Antipsychotic medications form the cornerstone of treatment for schizophrenia,[2] as they target the characteristic symptoms of the disease.[3] These symptoms can be positive or negative in nature[3] whereby positive symptoms reflect a distortion or an excess of normal functions and negative symptoms reflect a loss or restriction of normal function.[7] The underlying principles in place for the administration of pharmacotherapy include the individualization of medication (including patient preferences), simple medication regimens, appropriate dosing, attention to side-effect profiles, regular evaluation of responses in general (including adverse events),[5] and short- and long-term clinical efficacy, safety, and tolerability.[1]

Although there have been important developments in this area over the last 40 years, about one-third of persons with schizophrenia have a poor response to antipsychotic medications.[8] Surveys of prescribing practices in the United Kingdom showed that the use of doses higher than the ones usually recommended is commonly encountered, either when antipsychotic agents are used alone or in combination with another antipsychotic medication.[8] Also, although combination therapy with two antipsychotic agents is not recommended in current clinical management guidelines,[5] with the exception of combination therapy with clozapine,[8] it appears this practice is not

uncommon.[8,9] Overall prevalence rates of antipsychotic polypharmacy range from 4% to 58%,[9] and rates of up to 69%[10] have been reported depending on treatment setting and patient population. Data from British Columbia indicate that the rate of antipsychotic polypharmacy increased between 1996 when an estimated 28% of patients discharged from hospital were on polypharmacy, compared with 45% in 2000. For patients using clozapine, the rate of polypharmacy increased from 22% in 1996 to 53% in 2000.[10] Two longitudinal studies from the United States reported that 9.5% to 22.0% of patients with schizophrenia received two antipsychotic agents concurrently.[11,12] The proportion of patients treated with more than one AAP increased from 3.3% in 1999 to 13.7% in 2004.[11] Reasons identified for this increasing prevalence include the use of *pro re nata* or take-as-needed medication, the gradual switch (bridging) from one antipsychotic drug (APD) to another one, as well as the combination of two antipsychotic medications to achieve greater therapeutic response when there has been an unsatisfactory response to a single APD.[8]

2.1.2 Technology description — Atypical antipsychotics

Most existing antipsychotic therapies fall into one of two classes. The typical antipsychotics (TAPs), also known as conventional antipsychotics or neuroleptics, are of the first-generation antipsychotic class. The atypical antipsychotics (AAPs) are of the second-generation antipsychotic class. Both classes are accepted by clinicians to be equally effective in the treatment of positive symptoms. AAPs appear to be more effective in the treatment of negative symptoms.[1]

There are currently seven AAPs available in Canada: aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Also, two other AAPs (asenapine, Iloperidone) were recently approved in the United States. Since these new AAPs may eventually be available in Canada, asenapine and Iloperidone were included in the list of interventions considered for this project (Table 1).

Table 1: List of Atypical Antipsychotics Available in Canada and the United States

Generic Name	Trade Name	Dose Range	Manufacturer
Aripiprazole	Abilify	10 mg/day to 15 mg/day	Bristol-Myers Squibb
Asenapine*	Saphris	10 mg/day (5 mg b.i.d.)	Schering-Plough
Clozapine	Clozaril	300 mg/day to 600 mg/day	Novartis
Olanzapine	Zyprexa, Zyprexa Zydis	5 mg/day to10 mg/day	Eli Lilly
Olanzapine†	Zyprexa Relprevv		Eli Lilly
Iloperidone	Fanapt	12 mg/day to 24 mg/day (administered 6 mg to12 mg, b.i.d.)	Titan Pharmaceuticals
Paliperidone	INVEGA	6 mg/day to12 mg/day	Janssen-Ortho
Paliperidone injection†	INVEGA SUSTENNA	39 mg/month to 234 mg/month	Janssen-Ortho
Quetiapine	Seroquel	600 mg/day to 800 mg/day	AstraZeneca

Generic Name	Trade Name	Dose Range	Manufacturer
Quetiapine	Seroquel XR	400 mg/day to 800 mg/day	AstraZeneca
Risperidone	Risperdal, Risperdal M-Tab	4 mg/day to 6 mg/day	Janssen-Ortho
Risperidone injection†	RISPERDAL CONSTA	25 mg every 2 weeks to 50 mg every 2 weeks	Janssen-Ortho
Ziprasidone	ZELDOX	120 mg/day to160 mg/day	Pfizer

b.i.d. = twice daily.

* Approved by the FDA but not Health Canada.

†Long-acting injectable agent.

3 OBJECTIVE

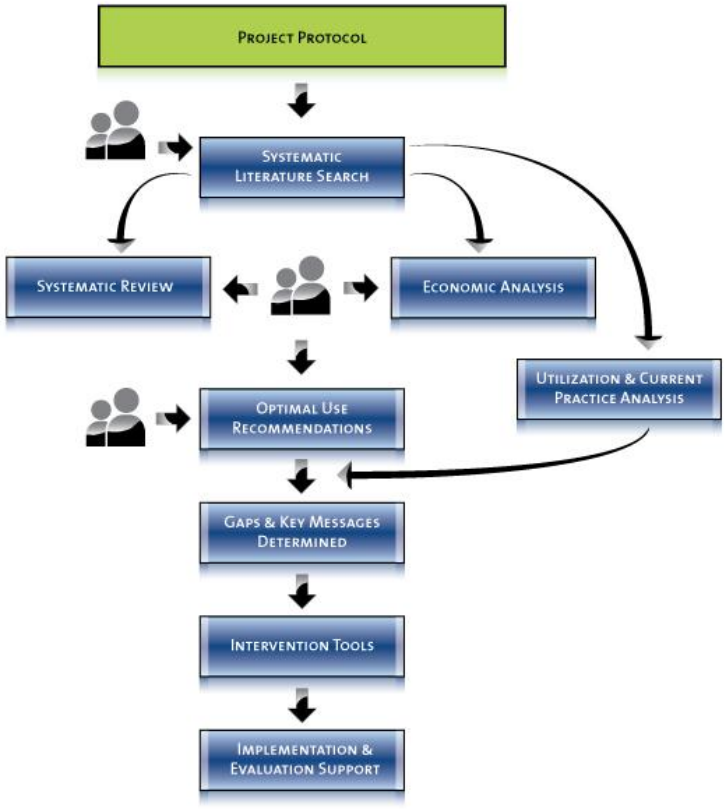
For the purpose of each project objective, the patient population includes adolescents and adults with schizophrenia or schizoaffective disorder. The term schizophrenia will be implied to include schizoaffective disorder for the purposes of this document.

The objectives of this project are to:

- Identify and appraise the clinical and cost-effectiveness evidence pertaining to use of AAP combination and high-dose treatment strategies in the defined population and to develop evidence-based optimal use recommendations for these strategies.
- Identify current utilization of AAP combination and high-dose treatment strategies in Canada.
- Identify current practices of physicians and patients regarding the use of AAP combination and high-dose treatment strategies in Canada.
- Identify differences (i.e., the gaps) between optimal prescribing and use of AAP combination and high-dose treatment strategies, as well as actual current utilization and practice.
- Identify potential barriers to optimal use of AAP combination and high-dose treatment strategies.
- Identify key messages to encourage optimal prescribing and use of AAP combination and high-dose treatment strategies.
- Identify effective activities and strategies (interventions), which could be directed toward a variety of audiences such as health and allied health professionals, patients, or government decision-makers, to encourage optimal prescribing and use of AAP combination therapy and high-dose treatment strategies.
- Develop intervention tools to support optimal prescribing and use of AAP combination therapy and high-dose treatment strategies.
- Support implementation of tools and evaluation.
- Develop evaluation mechanisms to measure the impact of intervention tools.

4 PROJECT OVERVIEW

Once a topic is selected, CADTH undertakes activities related to key areas in the procedure. The CAC and ACP provide advice and guidance around topic identification. The OUWG, formed after topic identification, will provide advice and guidance throughout the process, through to supporting intervention and evaluation tools. CERC provides expert advice and recommendations on the topic area relating to the identification, evaluation, and promotion of optimal prescribing and use of drugs. A broad range of stakeholders are invited to provide feedback at key stages in the CADTH process.



This report represents the initial step toward the development of optimal use recommendations for the prescribing and use of combination and high-dose treatment strategies involving AAPs for schizophrenia.

5 RESEARCH QUESTIONS

The following research questions were developed for the project objectives relating to appraisal of the clinical and cost-effectiveness evidence, and assessment of current utilization and current practice.

5.1 Clinical

1. What is the comparative clinical effectiveness (including clinical benefits and harms) of using combination therapy with AAPs (including the use of an AAP or a TAP as the other agent) compared with AAP monotherapy for the treatment of adolescents and adults with schizophrenia or schizoaffective disorder inadequately controlled on AAP or TAP monotherapy?
2. What is the clinical effectiveness (including clinical benefits and harms) of using AAP high-dosing regimens compared with standard-dose AAP monotherapy for the treatment of adolescents and adults with schizophrenia or schizoaffective disorder inadequately controlled on standard-dose AAP or TAP monotherapy?

5.1.1 Populations of interest

For each research question in this section, the following patient groups with schizophrenia (as defined by the Diagnostic and Statistical Manual of Mental Disorders-IV [DSM-IV]) or the International Statistical Classification of Diseases and Related Health Problems 10th Revision [ICD-10]) — including first episode, acute relapse, and chronic schizophrenia and schizoaffective disorder — inadequately controlled with one or more AAPs will be examined:

- Adolescents (age 13 to 17 years)
- Adults (age 18 years and older).

5.1.2 Interventions of interest

Therapeutic agents to be considered include the AAPs aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, injectable paliperidone palmitate, quetiapine, risperidone, and ziprasidone. See methods section (6.1.2a) for specific high-dose and combination interventions and comparators.

5.1.3 Comparators

For the analysis of combination therapy, the comparator of interest was AAP or TAP monotherapy at any dose. For the analysis of high-dose AAP therapy, the comparator was AAP or TAP monotherapy at any dose.

5.1.4 Outcomes of interest

CERC members identified possible outcomes of interest in considering evidence related to the use of AAP combination and high-dose treatment strategies in adolescents and adults with schizophrenia and/or schizoaffective disorder. Data on the following outcomes will be extracted and analyzed in the clinical review.

Efficacy

- Positive and Negative Syndrome Scale (PANSS) (total, positive, negative score)
- Brief Psychiatric Rating Scale (BPRS)
- Clinical Global Impression — Improvement scale
- Clinical Global Impression — Severity scale (CGI-S)
- Barns Akathisia Rating Scale
- Abnormal Involuntary Movement Scale
- Simpson Angus Scale
- Response Rate
- Relapse Rate
- Clinical remission
- Functional capacity (e.g., employment)
- Quality of life
- Cognition
- Withdrawals (e.g., persistence with therapy, due to lack of efficacy)

Harms

- Mortality (including suicide)
- Suicidality
- Serious adverse events (including hospitalization)
- Adverse events (including endocrine [prolactin], metabolic [A1C (glycated hemoglobin), weight gain], extrapyramidal symptoms, agranulocytosis)
- Withdrawals due to adverse events (WDAE)

5.1.5 Study design of interest

- Randomized controlled trials (RCTs), including parallel, crossover, placebo-controlled, and active comparator

5.1.6 Populations of interest

- Adults and adolescents with schizophrenia or schizoaffective disorder

5.2 Economic Evaluation and Current Utilization

1. What is the cost-effectiveness of using combination therapy with AAPs (including the use of an AAP or a TAP as the other agent) compared with AAP monotherapy for the treatment of adolescents and adults with schizophrenia or schizoaffective disorder inadequately controlled on AAP or TAP monotherapy?
2. What is the cost-effectiveness of using AAP high-dosing regimens compared with standard-dose AAP monotherapy for the treatment of adolescents and adults with schizophrenia or schizoaffective disorder inadequately controlled on standard-dose AAP or TAP monotherapy?
3. What is the current utilization and expenditure on high-dose or combination atypical antipsychotics therapy in public and private drug plans in Canada?
4. What are the incremental costs or savings that may be realized by public drug plans between 2011 and 2014 under conditions where there is more restricted use of high-dose or combination atypical antipsychotic therapy?

5.3 Current Practice

What are the experiences and preferences of health care professionals in Canada who provide care for patients with schizophrenia regarding the use of antipsychotic agents for patients inadequately controlled on AAP monotherapy and in high-dosing or AAP combination treatment strategies?

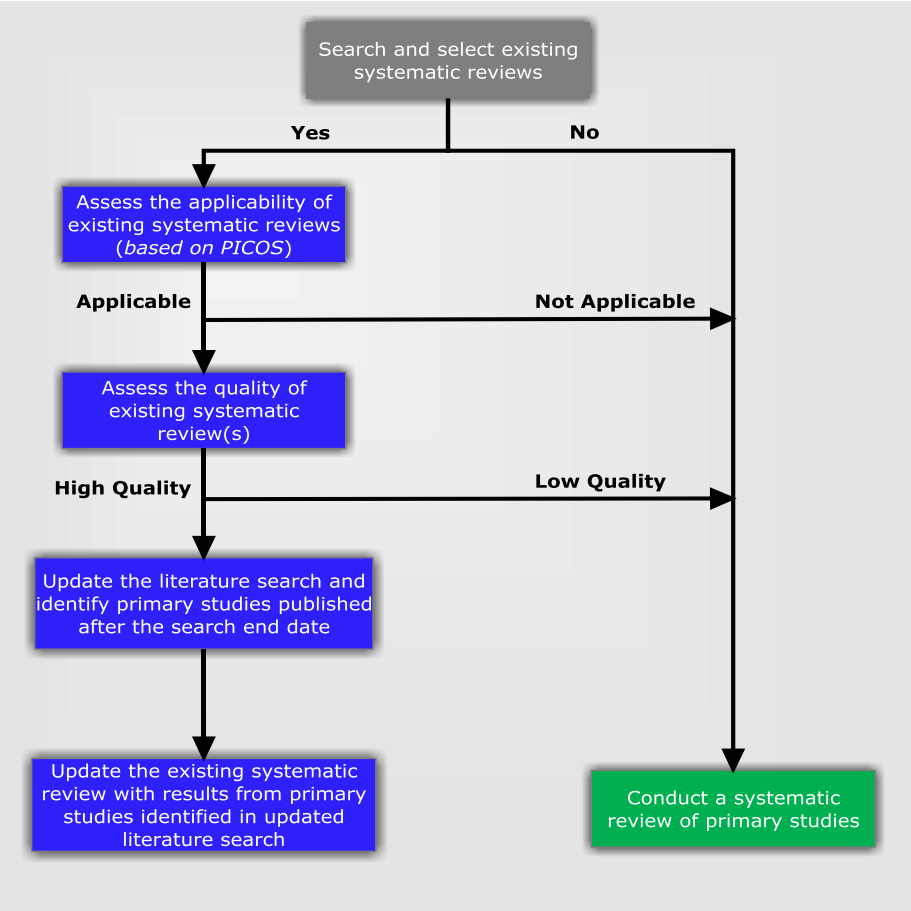
6 METHODS

6.1 Clinical

Where possible, CADTH builds on existing applicable Canadian and international initiatives and research. Therefore, the first stage in the research process will be to conduct a literature review to identify existing systematic reviews that have examined the efficacy of AAP combination and high-dose treatment strategies in adolescents and adults with schizophrenia and schizoaffective disorder. Should relevant, recently published, high-quality systematic review(s) be identified, they will be used (as described in section 6.3) as a basis for development of recommendations by CERC. If necessary, the literature search used in existing systematic review(s) will be updated, and results from eligible studies published after the review's search end date will be incorporated with results from the systematic review(s). If no suitable systematic reviews are identified, CADTH will conduct its own systematic review of primary studies. Where appropriate, study results will be pooled. Otherwise, results will be summarized and presented in narrative and tabular form.

The overall methodology for the clinical review is presented in the figure below:

Figure 1: Clinical Review Methodology



PICOS = population, intervention, comparators, outcome, and study design.

6.1.1 Identification of existing systematic reviews

a) Selection criteria

A systematic review will be considered as the basis for development of optimal use recommendations if it meets all of the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

- Study design — Systematic review or health technology assessment
- Populations, interventions, comparators, and outcomes included as described in section 5.1

Exclusion criteria

- Reviews in which research methods were inadequately described[1]
- Publications other than those presented in English or French

b) Literature search

The literature search will be developed and performed by the information specialist using a peer-reviewed search strategy. MEDLINE will be searched through the Ovid interface for existing systematic reviews, meta-analyses, and health technology assessments. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be each AAP drug name plus more general terms (e.g., AAPs, SGAs), schizophrenia, schizoaffective disorder, drug combinations, and drug dosage. The search will be used to capture studies published between 2004 and May 2010. An additional MEDLINE search will be conducted for clinical practice guidelines for schizophrenia or schizoaffective disorder covering the same time period. A general search for review articles dealing with AAP, schizophrenia and dosing combination therapy will also be performed in MEDLINE to capture articles published between 2009 and May 2010. Regular alerts will be established to update all of the aforementioned searches until the publication of the final report. The Internet will be searched to identify unpublished (grey) literature from websites and databases of health care associations and related agencies. See Appendix 1 for all search strategies and for more information on the grey literature search.

c) Systematic review selection

Two reviewers will independently select systematic reviews for consideration based on the predefined inclusion and exclusion criteria previously listed. Each reviewer will independently perform an initial screening of 10% of the citations (or 20 citations, whichever is less) identified through the literature search by examining titles and abstracts for relevance to the review topic, reach agreement with the other reviewer, then independently screen the remaining citations. Abstracts of articles will be assessed and categorized as "included" or "excluded." If the relevance of an article is uncertain, it will be retained in the included list. Citations with discrepant selection results will be reselected by a third reviewer. The judgment of the third reviewer will be considered final.

[1]Factors such as search strategy, selection criteria, quality assessment of included studies, and data analysis were not clearly or comprehensively defined.

Full-text articles of the citations included by both reviewers or by the third reviewer will be ordered, then independently selected by two reviewers. Exclusion reasons will be recorded and compared. Discrepancies between reviewers will be discussed until consensus is reached; the judgment of a third reviewer will be considered final if consensus cannot be reached by the first two reviewers. In the event that a systematic review is reported in more than one publication, the most recent or informative systematic review will be selected for inclusion.

If existing systematic reviews are selected, reviewers will complete these subsequent steps. Otherwise, reviewers will proceed to section 6.1.2.

d) Assessment of systematic review quality

The methodological quality of included systematic reviews will be assessed by two reviewers independently. The systematic reviews must also fulfill the following criteria:

- An "a priori" design must be provided where the research question and inclusion criteria are established before the review was conducted
- The literature search performed in the systematic review must be conducted on at least two databases
- The review process must include two reviewers.

Reviewers will compare their individual ratings, discuss discrepancies, and reach agreement before assigning a final quality rating to each systematic review. Unresolved discrepancies will be resolved by a third reviewer.

If the selected systematic reviews are of acceptable quality, reviewers will complete these subsequent steps. Otherwise, reviewers will proceed to section 6.1.2.

e) Data extraction of included systematic reviews

General information regarding included systematic reviews of high quality — such as the year of publication, source, organization, funding sources, and type and number of included primary studies — will be extracted from all included systematic reviews. The literature search strategy, research questions, population, interventions, comparators, outcomes assessed, and key findings will also be extracted, where necessary. For systematic reviews found to be applicable based on the assessment described under section (f) that follows, all primary studies included in each review will be listed in a separate table. One reviewer will extract data and a second reviewer will verify their accuracy. Discrepancies will be resolved by consensus. The decision of a third reviewer will be considered final for unresolved discrepancies.

f) Applicability assessment of systematic reviews

The overall process of applicability assessment of included systematic review(s) is outlined in Appendix 2. Existing high-quality systematic reviews will be selected as a basis for generating optimal use recommendations based on four main considerations:

- Relevance regarding population, interventions, comparators, outcomes, and study designs considered
- Degree to which the selection criteria used by the authors correspond with the selection criteria listed in section 6.1.2 (a)

- Currency of the search dates
- Degree of effort required to update the systematic review.

Systematic reviews of AAP pharmacotherapy that are broader in scope than the research questions listed in section 5.1 will be considered as a basis for generating optimal use recommendations if they report appropriate subgroup analyses or provide enough study-level data to conduct a subgroup analysis.

Members of CERC will be consulted regarding the decision on whether existing systematic reviews will be used as the basis of optimal use recommendations for use of AAPs in combination and high-dose treatment strategies. The results of this assessment and the proposed approach to use existing systematic reviews will be summarized and presented in a table (see Appendix 2). If one or more reviews are chosen, reviewers will complete the following steps (g) and (h) to update the selected reviews with new evidence published after the literature search end date of the corresponding systematic reviews. If none of the systematic reviews considered is deemed appropriate as a basis for CERC to develop optimal use recommendations, a systematic review of primary studies will be conducted as described in section 6.1.2.

g) Updating of systematic review literature search

A literature search will be conducted to identify relevant primary studies published after the search end date of selected systematic review(s) identified through applicability assessment. The search strategy will be based on the strategy used by the authors of the systematic review, although it may be modified to reflect the research questions of interest or to ensure it conforms to CADTH standards. Similarly, the inclusion and exclusion criteria applied by the authors of the included systematic reviews may be modified if necessary. Identified studies will be evaluated for quality and data extracted as described in section 6.1.2.

h) Incorporation of updating data

If no new primary studies are identified, the selected systematic reviews will be used as the basis of optimal use recommendations. If new primary studies are identified, these results will be summarized in narrative form to augment the results of the selected systematic reviews. If deemed necessary by members of CERC, and where appropriate based on clinical and methodological considerations, data from studies selected from the update search may be pooled with studies included in the systematic reviews. Pooling will be conducted according to the methods described in section 6.1.2.

6.1.2 Systematic review and meta-analysis of primary studies

As noted in Section 6.1, if no suitable systematic reviews are identified, CADTH will conduct its own systematic review of primary studies (i.e., RCTs).

a) Selection criteria

A study will be included if it meets all of the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

- Population — Adolescents (13- to17-years-old) and adults (≥ 18 years) with schizophrenia and/or schizoaffective disorder (including the first episode of schizophrenia, acute phase, or chronic phase) inadequately controlled with one or more antipsychotic (atypical or typical) standard dose monotherapy regimens
- Intervention —
    - Combinations consisting of one of the AAPs listed in Table 2 at doses lower than or equal to the definition of (high dose) together with one or more other AAP or APD, or
    - AAP monotherapy at high doses (as defined in Table 2)

Table 2: Atypical Antipsychotics Considered as High Dose in the Current Systematic Review

Generic Name	Trade Name	Definition of High Dose in CADTH Evaluation*
Aripiprazole	Abilify	> 30 mg/day
Asenapine†	Saphris	> 10 mg/day
Clozapine	Clozaril	> 600 mg/day‡
Olanzapine	Zyprexa, Zypexa Zydis	> 20 mg/day
Olanzapine§	Zyprexa Relprevv	> 300 mg/2 weeks (405 mg/4 weeks)
Iloperidone	Fanapt	> 24 mg/day
Paliperidone	INVEGA	> 12 mg/day
Paliperidone injection§	INVEGA SUSTENNA	> 234 mg/month
Quetiapine	Seroquel	> 800 mg/day
Quetiapine	Seroquel XR	> 800 mg/day
Risperidone	Risperdal, Risperdal M-Tab	> 6 mg/day¶
Risperidone injection§	RISPERDAL CONSTA	> 50 mg/2 weeks
Ziprasidone	ZELDOX	> 160 mg/day

* Based on product monograph unless otherwise indicated.

† Approved by the FDA but not Health Canada.

‡ Based on expert opinion. Maximum according to product monograph is 900 mg/day.

§ Long-acting injectable agent.

¶ Based on expert opinion. Maximum according to product monograph is 16 mg/day.

- **Comparators:**
    - AAP or TAP monotherapy at any dose
    - Combinations of APDs at any dose
- Outcomes — As shown in Section 5.1.4.
- Study design — RCTs (including parallel, crossover, active- or placebo-controlled)

Exclusion criteria

- A study with a mixed population (i.e., more than 15% of participants) were not diagnosed with schizophrenia or schizoaffective disorder and no subgroup analysis was reported for patients with schizophrenia or schizoaffective disorder
- Studies on first episode of psychosis, which is not specified as first episode of schizophrenia
- Study on schizophreniform disorder
- Studies on monotherapy comparisons between different APDs at standard doses.
- Studies of high-dose TAP therapy or combinations of two or more TAPs.
- Studies on combination therapy with antipsychotic agents (AAP or TAP) and non-antipsychotic agent (e.g., mood stabilizer)
- Non-English or non-French publications

b) Literature search

The literature search will be developed and performed by the information specialist using a peer-reviewed search strategy. Published literature will be identified by searching the following databases via the OVID interface: MEDLINE (1950–), MEDLINE In-Process & Other Non-Indexed Citations, Embase (1980–), PsycINFO (1967–) and The Cochrane Central Register of Controlled Trials. A parallel search will be run in the CINAHL database via EBSCO. PubMed will also be searched to capture additional citations not found in MEDLINE. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concepts will be each AAP drug name plus more general terms (e.g., atypical AAPs, SGAs), schizophrenia, schizoaffective disorder, drug combinations, and drug dosage. Methodological filters will be applied to limit retrieval to RCTs or controlled clinical trials. Retrieval will not be limited by publication year, but will be limited to the English or French language. Where possible, retrieval will be limited to the human population. These searches will be supplemented by reviewing bibliographies of selected articles (i.e., included primary studies and existing systematic reviews), and conference proceedings. The Internet will be searched to identify unpublished (grey) literature from websites and databases of health professional associations, health technology assessment agencies, and related entities. Regular alerts will be established to update the literature search until the publication of the final report. See Appendix 2 for all search strategies and for more information on the grey literature search.

c) Study selection

Two reviewers will independently select articles for inclusion in the review based on the aforementioned selection criteria. The process of study selection will be as described in Section 6.1.1. A flow chart (based on the Quality of Reporting of Meta-analyses or QUOROM statement) will be generated to illustrate the study selection process. The list of included studies will be posted on the CADTH website to elicit stakeholder feedback. Studies provided by stakeholders will be considered for inclusion based on previously stated selection criteria.

d) Assessment of study quality

The methodological quality of included RCTs will be assessed using a modified version of the Scottish Intercollegiate Guidelines Network (SIGN) 50 checklist[13] (see Appendix 3). Two

reviewers will independently assess methodological quality for each study and assign a rating of "very good," "good," or "poor." Reviewers will compare ratings and come to a consensus for each attribute of the SIGN 50 checklist and for the overall rating. The judgment of a third reviewer will be considered final if consensus cannot be achieved. Before proceeding with the quality assessment of all included studies, a pilot test will be conducted on one or more studies to improve consistency between reviewers in how the checklist is applied. To determine the impact of study quality on pooled estimates of effect, a sensitivity analysis will be performed by excluding low-quality studies (see "Sensitivity and subgroup analyses" later in this section).

e) Data extraction

Data extraction forms designed a priori in Microsoft Excel will be used to document and tabulate all relevant information contained in studies selected for inclusion in the systematic review. One reviewer will extract data on outcomes of interest from included studies using these forms, and the second reviewer will verify accuracy and completeness. Discrepancies between reviewers will be identified and resolved by consensus; the judgment of a third reviewer will be considered final if consensus cannot be reached. Authors of included studies will be contacted for any missing or incomplete data, where necessary. Before proceeding with data extraction of all included studies, a pilot test will be conducted using a small number of studies to assess the usability of the data extraction form and improve the consistency of data extraction between reviewers.

Caution will be exercised to ensure that duplicate or companion publications of the same study are identified. Where duplicate or companion publications exist, data from the most recent or informative article will be used. As well, subgroup or single-centre results will be excluded if the corresponding main analyses are included in the review, unless they provide data on additional outcomes.

f) Handling of crossover randomized controlled trials

Data from crossover RCTs will be included in the same meta-analyses as parallel trials, using the results of paired analyses. If paired analyses are not reported, study authors will be contacted for the necessary data. If the necessary information is not provided, a correlation coefficient between comparator arms will be calculated from similar studies reporting complete summary data (i.e., means and standard deviations for each treatment arm, as well as the mean and standard deviation of the paired difference between arms), as described by Elbourne et al.[14] For crossover trials reporting a significant carry-over effect, only the data from the pre-crossover phase will be included in meta-analyses. In the absence of reported carry-over effects, data from the pre-crossover phase will be preferred; if unavailable, mixed data from pre- and post-crossover phases will be combined with those from parallel trials in a single meta-analysis (sample sizes will be doubled accordingly).

g) Data synthesis and analysis

The meta-analytic methods most commonly used to investigate the effectiveness of health care interventions are those presented by Cochran[15] and DerSimonian and Laird.[16] Those methods involve combining results of individual RCTs to provide a comparison of success rates between two comparators and an estimation of the effect size.[17,18] Data from head-to-head, direct treatment comparisons will be combined using random-effects meta-analyses. Results of individual studies will be pooled only if populations, interventions, comparators, and outcome measures across studies are sufficiently similar to produce a clinically meaningful result. Otherwise, results will be summarized qualitatively. Forest plots will be generated wherever

appropriate to determine if heterogeneity exists between the results of individual studies included in the review. Heterogeneity will be ascertained using the I^2 statistic.[19] The I^2 statistic describes the proportion of unexplained variability in effect estimates across studies in a meta-analysis. Where heterogeneity is greater than 75%, pooled estimates will not be presented.

Data will be analyzed by a single reviewer. A second reviewer will verify the results. All analyses will be performed using Review Manager 5.0 software.

Continuous outcomes

For continuous outcomes such as PANSS or body weight, the difference between treatment groups in mean change from baseline will be meta-analyzed. If estimates of variability (such as standard error) for mean change from baseline are not reported, they will be imputed based on standard errors from similar studies. In instances when imputation is not possible, or when a study reports only mean values at end point, study authors will be contacted for the required data. Mean values at end point will be meta-analyzed only when efforts to obtain adequate change from baseline data have failed.

Quality-of-life and patient satisfaction will be recorded based on the measures reported in primary studies. It is expected that most studies will report mean change from baseline, allowing for meta-analysis as a continuous outcome. If studies employ various instruments to measure quality-of-life or patient satisfaction, results will be summarized qualitatively.

Dichotomous outcomes

Dichotomous outcomes, such as serious adverse events or suicidality, will be analyzed using relative risk as an effect measure. Dichotomous categories will be defined as "no event" or "one or more events."

h) Sensitivity and subgroup analyses

To determine robustness of the results, the following sensitivity analyses will be performed to explore methodological or reporting differences across individual studies:

- Removal of crossover studies
- Removal of studies assessed as being of low quality (i.e., a SIGN 50[13,20,21] rating of "–")
- For analyses of duration, removal of studies of less than three months, and 12 months in duration
- Removal of studies that did not report intention-to-treat analyses
- Removal of studies testing agents not approved in Canada
- Removal of studies where clozapine dose is < 350 mg/day.

Subgroup analyses will be conducted based on patient and treatment characteristics that are based on the evaluation structure.

If data are available, the following subgroup analyses will be performed:

- For high-dose comparisons:
    - Individual AAP agent
    - Number of APDs failed prior to the trial (i.e., ≥ 1, ≥ 2)

- Specific APDs failed prior to the trial (when applicable)
- Severity of disease at baseline (based on PANSS, CGI-S)
- Ethnicity/geographic origin of study

- For combination-use data:
  - Combinations or agents studied
  - Number of APDs failed prior to the trial (i.e. ≥1, ≥2)
  - Specific APDs failed prior to the trial (when applicable)
  - Severity of disease at baseline (PANSS, CGI-S)
  - Ethnicity/geographic origin of study

i) Stakeholder feedback

The results of the analysis will be presented in the form of a draft systematic review report that will be posted on the CADTH website to elicit stakeholder feedback. Relevant stakeholder feedback will be incorporated into the final version of the systematic review based on input from CERC.

6.2 Economic

If the clinical review finds sufficient clinical evidence of meaningful differences between treatment strategies, a model will be developed to forecast differences in health outcomes and cost consequences between competing treatment strategies. Otherwise, a cost analysis will be performed based on the utilization analysis and unit costs of individual agents. The decision as to whether the available clinical evidence warrants economic modelling will be made in consultation with CERC.

6.2.1 Type of evaluation

An incremental cost-utility analysis of standard-dose AAP therapy relative to AAP combination therapy and high-dosing treatment strategies in adolescents and adults with schizophrenia will be conducted.

6.2.2 Interventions assessed

The choice of interventions assessed in the economic analysis will be primarily determined based upon the availability of data identified in the systematic review of the clinical evidence. Ideally, clinical information will be available for the following interventions:

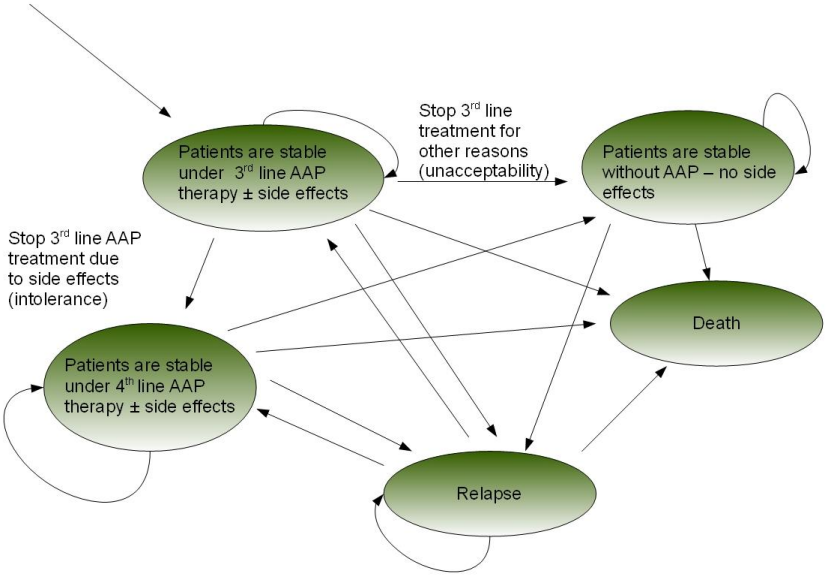
- Patients switched to a third standard-dose AAP monotherapy after being inadequately controlled on two sequential trials of AAP standard dose monotherapy
- Patients increasing the dose of their second AAP therapy beyond the high dose threshold defined in Table 2, after being inadequately controlled on two sequential trials of AAP standard-dose monotherapy
- Patients adding a TAP to standard-dose AAP therapy (combination TAP therapy) after being inadequately controlled on two sequential trials of AAP standard-dose monotherapy
- Patients adding an AAP to standard-dose AAP therapy (combination AAP therapy) after being inadequately controlled on two sequential trials of AAP standard-dose monotherapy.

For the primary analysis, combination and high-dose treatment strategies will be compared with standard-dose AAP based on studies that have the highest quality clinical data and where treatments included in the studies are among the most widely used in Canadian clinical practice. Current utilization patterns in Canada will be identified by obtaining data from public and private drug plans from IMS Brogan Inc. — the largest source of drug payment information (i.e., administrative claims data) in Canada.

6.2.3 Model structure and evaluation

A cohort level Markov model will be developed to forecast health outcomes and cost consequences of schizophrenia-related complications for each cohort of patients (see Figure 2). The model will be flexible and enable the user to specify various time horizons (e.g., one year, five years); however, the primary analysis will be based on a five-year time horizon and the model will run in three-month cycles. Data used to populate the model will be derived from the systematic review, as well as RCTs and epidemiological studies. Validation analyses will be performed to compare model predictions with those observed in published clinical and epidemiological studies.

Figure 2: Schematic Diagram of Economic Model Structure



AAP = atypical antipsychotic

The aim of the model structure is not to assess specific sequences of AAP therapies, but to assess whether AAP combination therapy and high-dosing treatment strategies are cost-effective relative to standard-dose AAP therapy for patients who are inadequately controlled on two separate sequential treatment regimens of AAP monotherapy. The rationale for focusing on patients failing two previous trials of AAP monotherapy was based on a preliminary review of the available clinical data, which suggested that the majority of studies were conducted among those who were inadequately controlled on two separate sequential treatment regimens of AAP monotherapy (i.e., high dose or combinations were used as third-line therapy).

The natural history of schizophrenia among patients using third-line therapies will be captured by five health states:

- Patients are stable using third-line AAP treatment with/without side effects associated with treatment
- Relapse
- Patients are stable using fourth-line AAP treatment with/without side effects associated with treatment
- Patients are stable and not using AAP therapy and have no AAP-associated side effects
- Death.

The relapse state includes patients who are experiencing exacerbation of their symptoms; patients may manage their relapse on either an inpatient or outpatient basis. When patients do not relapse or die, they are in one of the three stable states. Patients who experience side effects (intolerance) on their current AAP treatment and switch to another AAP therapy enter the stable fourth-line AAP treatment state. Patients who discontinue their AAP therapy for other reasons (unacceptability) and discontinue AAP treatment altogether enter the stable "without treatment" state. All patients who do not experience intolerance or discontinue for other reasons (unacceptability) are assumed to remain stable on their respective third-line AAP therapy.

The death state captures all patients who died from any cause, including suicide and death resulting from comorbid conditions. Patients with schizophrenia in the model were assumed have a higher risk of death than the general population. To calculate the number of deaths occurring each year, the model uses age- and gender-specific death rates for Canadians multiplied by the standardized mortality ratio observed in people with schizophrenia. Death is assumed to occur in the middle of each cycle, and the risk of death was independent of AAP use because there is a lack of sufficient data to suggest otherwise.

6.2.4 Population

The patient population will be reflective of adults with schizophrenia who are inadequately controlled after using two separate sequential courses of AAP monotherapy.

6.2.5 Time horizon

The primary analysis will be conducted over a five-year time horizon. Results for time horizons of one and 10 years will also be reported.

6.2.6 Clinical evidence

a) Meta-analysis of randomized controlled trials

Treatment effects (probability of relapse, probability of stabilization, probability of discontinuation because of side effects, probability of discontinuation due to other reasons) for the cohorts of will be derived from the systematic review of high-dose and combination therapies. Sensitivity analyses will be conducted to determine whether the use of other clinical effect estimates (such as, for example, National Institute for Health and Clinical Excellence [NICE] and Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE]) impact cost-effectiveness estimates.

b) Modelling of adverse effects

Patients are assumed to initiate their high-dose or combination AAP treatment because they were inadequately controlled with previous treatment on AAP monotherapy. At the start or during treatment with high-dose or combination treatment, patients are assumed to visit their psychiatrist, where the following may occur:

- AAP was efficacious and side effects were absent or tolerable: Patient remains on current treatment strategy.
- AAP was efficacious, but patient was experiencing one or more intolerable adverse effects (intolerance):
    - Extrapyramidal symptoms (EPS)
    - Prolactinemia
    - Glucose intolerance/insulin resistance or diabetes
    - Weight gain.
- AAP was efficacious, but patient discontinued for other reasons (unacceptability).
- AAP was not efficacious (with or without adverse effects) and the patient relapses: In these instances, patients are assumed to switch to a new AAP regimen.

Other treatment-specific adverse events will also be incorporated where necessary (e.g., neutropenia or agranulocytosis associated with clozapine).

6.2.7 Perspective

The perspective of this analysis will be that of a Canadian ministry of health.[22] Therefore, only direct costs to the Canadian health care system will be considered.

6.2.8 Outcomes of interest

The following outcomes of interest will be tracked over the five-year time period:

- Proportion of patients who relapse on each AAP regimen
- Proportion of patients who discontinue due to side effects on each AAP regimen
- Proportion of patients who discontinue each AAP regimen due to other reasons
- Proportion of patients who remain stable on third-line AAP regimen
- Proportion of patients who die on each AAP regimen
- Proportion of patients who experience side effects (EPS, hyperprolactinemia, weight gain, glucose intolerance/diabetes)
- Mean annual treatment cost for patients on each AAP regimen
- Total discounted costs over five-year time horizon on each AAP regimen
- Total discounted quality-adjusted life-years gained on each AAP regimen
- Cost-effectiveness of each AAP treatment as measured by incremental cost per quality-adjusted life-year gained and net-monetary benefit
- Probability that each AAP treatment is the most cost-effective.

6.2.9 Utility data and quality-adjusted life-years

The primary outcome(s) of interest in our analysis will be the incremental cost per quality-adjusted life-year (QALY) and net monetary benefit of each treatment. Each of these outcomes relies on the use of the QALY, an outcome which captures both morbidity and mortality (i.e., quality and quantity of life). Utility scores for the reference case will be based on published studies. The time spent in each health state will be based upon a review of published literature. Sensitivity analyses will be conducted where utility scores are derived from other public sources and alternative times spent in each health state are used.

6.2.10 Resource use and costs

a) Price and dose of atypical antipsychotic therapies

Unit costs for drugs will be obtained from the Ontario Public Drug Program (when available).[23] Otherwise, prices will be obtained from other public drug programs in Canada.[24-27] For the reference case analysis, the price of the lowest cost alternative for each drug class will be applied, plus a 10% mark-up and $7.00 pharmacy fee per 90-day supply. The average dose of each AAP treatment will be based upon data obtained in our current utilization analysis. Sensitivity analyses will be conducted to explore how the choice of AAP and the assumed dose (e.g., dose from the utilization study versus the World Health Organization's Defined Daily Dose) impacts cost-effectiveness results.

b) Cost of switching atypical antipsychotic therapies

Patients may switch their AAP therapy because of either a lack of efficacy or because of side effects. For the reference case, it will be assumed that patients will switch to the most commonly used fourth-line therapy in Canada. The most widely used fourth-line therapy in Canada will be derived using utilization data (if available) or expert opinion. Unit costs and doses for the fourth-line agent will be assigned.

c) Direct costs of schizophrenia-related adverse events

Resource utilization and costs associated with managing schizophrenia-related complications will be obtained from the Ontario Ministry of Health and Long-Term Care. Inpatient, outpatient, and emergency room visits, prescription drug claims, long-term care, and home care costs for managing schizophrenia-related complications will be included in the model. Costs will be inflated to 2010 Canadian dollars using the health component of the Canadian Consumer Price Index. Resource utilization associated with managing schizophrenia-related complications will be based on published Canadian studies or expert opinion.

6.2.11 Discount rate

Both costs and QALYs will be discounted at a rate of 5%, as recommended by CADTH guidelines.[22] Sensitivity analyses will be conducted where discount rates are varied between 0% and 5%.

6.2.12 Handling of uncertainty

Probabilistic decision modelling will be used to estimate the mean life expectancy, quality-adjusted life-expectancy, and costs for each treatment arm. Net-benefits and cost-effectiveness acceptability curves will be generated based on the proportion of iterations, with the highest net-monetary benefit across a range of willingness-to-pay thresholds.

One, two, and multi-way sensitivity analyses will be performed to examine the robustness of results to changes in parameters and model assumptions. Specifically, variation in how the following parameters impacts cost-effectiveness estimates will be assessed:

- Treatment effects for AAPs (e.g., relapse rates, rates of discontinuation due to side effects, discontinuation for other reasons)
- Rates of adverse events (EPS, hyperprolactinemia, dyslipidemia, weight gain, glucose intolerance/diabetes)
- Disutilities associated with adverse events (EPS, hyperprolactinemia, weight gain, glucose intolerance/diabetes)
- Source of treatment effects (e.g., NICE report, CATIE trial)
- Price of AAPs (e.g., prices from other formularies)
- Dose of AAPs (e.g., World Health Organization's defined daily dose)
- Switching patterns (e.g., variation in fourth-line AAP treatment that patient is switched to when third-line AAP therapy is not efficacious or is associated with side effects)
- Patient characteristics (e.g., age)
- Increase in costs associated with managing schizophrenia-related complications
- Data for costs of schizophrenia-related complications derived from Alberta rather than Ontario
- Time horizon (i.e., one year, 10 years)
- Number of physician visits required when switching medications
- Probability of hospitalization for relapse
- Discount rate (i.e., 0% and 3%).

6.2.13 Utilization and expenditure on high-dose or combination atypical antipsychotic therapy in Canada

Utilization and expenditure on high-dose or combination AAP therapy by patients with schizophrenia in Canada will be examined by conducting a retrospective database analysis of administrative claims data from public and private drug plans between 2005 and 2009.

a) Data sources

Data will be obtained from IMS Brogan Inc. The IMS Brogan Inc. database is the largest source of drug payment information (i.e., administrative claims data) in Canada.28 IMS Brogan Inc. databases comply with federal and provincial privacy legislation.28 Patient-level data provided by IMS Brogan Inc. are protected by means of anonymous identifiers to ensure patient confidentiality.

Aggregate-level data

Aggregate-level data from public drug plans in Canada will be available for nine of the 10 provinces (i.e., British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, and Newfoundland and Labrador) and the Non-Insured Health Benefits Program (NIHB). In addition, data will be available from 67% of privately funded drug plans in Canada.[28] Aggregate-level data will not be available for publicly funded programs in Prince Edward Island, Northwest Territories, Yukon, and Nunavut because data from these programs are not provided to IMS Brogan Inc.

Patient-level data

Patient-level data for antipsychotic use will be available from the Ontario Drug Benefits Program and 67% of Canada's privately funded drug plans.[28] Patient-level data refer to information from individual patients' pharmacy claims; such data permit more analytical flexibility, as summary statistics can be estimated for various subgroups of interest (e.g., schizophrenia patients).

b) Time period of analysis

The analysis will cover a five-year period beginning January 1, 2005 and ending December 31, 2009.

c) Diagnosis of patients with schizophrenia

IMS Brogan Inc. data does not contain the prescription's indication (the physician's prescribing intent). However, IMS Brogan Inc.'s Rx Dynamics team — in collaboration with internal experts (e.g., clinical analysts, MDs) and external users — developed an algorithm to classify patients by indications based on inferred diagnosis, according to their drug claims histories (Table 3).

Table 3: Algorithm for Identifying Patients with Schizophrenia in IMS Brogan Inc. Database

Inferred Diagnosis	Criteria for Inferred Diagnosis
ADHD	Patients with recent claims (within two years) for methylphenidate, dextroamphetamine, and dexmethylphenidate hydrochloride are classified under. New psychostimulants indicated for ADHD will be added to this list as they enter the market.
Bipolar	Claimants must have a previous claim (within two years) for one of the selection drugs: lithium, valproic acid, carbamazepine or divalproex sodium.
Depression	Patients with a history of taking antidepressants prior to ever starting any APD are classed in this group. A minimum of two years of history is searched on every patient, and the antidepressants must pre-date the first antipsychotic by at least 30 days.
Schizophrenia	Claimants under 65 and without previous bipolar, depression, or ADHD inferred diagnosis are classed in this group.
Dementia	Patients over the age of 65 commencing an antipsychotic with no record of bipolar drugs or prior antipsychotic treatment are classed in this group.

ADHD = attention-deficit/hyperactivity disorder; APD = antipsychotic drug.

The IMS Brogan Inc. algorithm has been reviewed by CERC Specialist Experts. The experts expressed concern that the IMS Brogan Inc. algorithm may not capture all patients with schizophrenia, particularly elderly patients who may be classified as having dementia. To address this, two analyses will be conducted to ensure validity of findings from this study:

- Patients who are defined as having schizophrenia according to the IMS Brogan Inc. algorithm (see Table 3)
- Any patient who used APDs.

d) Target drugs

Total utilization and expenditure on either AAPs or typical APDs that are available in Canadian public and private drug plans (as per Table 1) during the analysis period will be captured.

e) Data analysis

Aggregate-level data

Total utilization (i.e., number of units of APDs claimed) and expenditures on AAPs and APDs will be determined for public (i.e., British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, and Newfoundland and Labrador, NIHB) and private drug plans in Canada for each year over the five-year analysis period beginning January 1, 2005 and ending December 31, 2009 (if available). Total utilization and expenditure will be broken down for each agent and drug class, and stratified by drug plan.

Patient-level data

Patient-level data for APDs use will be available for the Ontario Drug Benefits Program and 67% of Canada's privately funded drug plans.[28] Patient-level data refer to information from individual pharmacy claims; such data permit more analytical flexibility, as summary statistics can be estimated for various subgroups of interest. Therefore, CADTH will be able to conduct more detailed analyses for Ontario and for private drugs plans in Canada. Utilization and expenditure on APDs by beneficiaries with schizophrenia (and any patient who uses APDs) in Ontario and in private drug plans will also be classified into treatment groups based upon their pharmacy claims histories each year:

- Patients using standard-dose non-clozapine AAPs
- Patients using standard-dose injectable non-clozapine AAPs
- Patients using standard-dose typical AAPs
- Patients using standard-dose clozapine therapy
- Patients using high-dose non-clozapine AAPs
- Patients using high-dose injectable non-clozapine AAPs
- Patients using high-dose clozapine
- Patients using dual-combination non-clozapine AAPs
- Patients using dual-combination typical APDs
- Patients using dual-combination therapy with a non-clozapine AAP and a typical APDs
- Patients using dual-combination therapy with a non-clozapine atypical AAP and injectable non-clozapine AAP
- Patients using dual-combination therapy with clozapine and a non-clozapine AAP
- Patients using dual-combination therapy with a clozapine and an injectable non-clozapine AAP
- Patients using dual-combination therapy with clozapine and a non-clozapine AAP
- Patients using dual-combination therapy with clozapine and a typical APD
- Patients using ≥ three APDs.

Patients will be classified as using high-dose AAP therapy based on the definitions presented in Table 2. Combination therapies are defined as the use of two or more antipsychotic therapies. To

be classified in any of the high-dose and combination therapy categories, patients must use each of the strategies for ≥ 30 days.

The primary outcome for this analysis will be patient use, defined as "active months" on therapy. Specifically, patient use per therapy type will be quantified based on the number of active months spent on a specific therapy type in each year. Results will be aggregated for all patients in the study and reported as an annual total. For example, in 2009, patient "x" was active on typical monotherapy for four months and triple-combination therapy for three months, patient "y" was active on dual-combination typical therapy for 12 months; therefore, total active months (denominator) equals 19 months (4 months + 3 months + 12 months). The secondary outcome of interest will be to associate costs to the distribution of "active months" based on each of the therapy types.

6.3 Current Practice

To understand how atypical APDs are currently prescribed and used in the treatment of patients with schizophrenia in Canada, a qualitative approach will be employed. Specifically, data derived from focus groups or interviews of health care providers will be used to identify and highlight current practice and perceptions surrounding the use of atypical APDs, particularly high dose and combination treatment strategies.

This portion of the project will be conducted under contract by Vision Research Inc. . Development of interview questions was guided by the results of a literature review, and in consultation with members of CADTH, CERC, and staff at Vision Research Inc.

Vision Research Inc. will use a thematic analysis approach to analyze the findings. Data from the focus groups and/or interviews will be sorted manually based on the overall direction of each response. A team of experienced analysts at Vision Research Inc. will review the notes and audio tapes of all groups and summarize the results, noting any areas of consensus or directionality. Themes will be identified based on prevalence among the responses of all participants and organized around the structure of the moderator's guide. In analyzing the data, the focus will be not only on prevalence but also on range, indicating where participants diverged and noting the variety of responses. Questions of which a large majority of respondents agree, questions that prompt a split response (noting the two or three themes most prevalent), and questions that generate no consensus whatsoever (although these are likely rare, given the professional homogeneity of the group) will be identified and described. Underlying themes that emerge across the various groups studied and across questions will also be identified. Representative responses from the focus group participants will be used to support the findings of the analysis.

6.4 Development of Optimal Use Recommendations

CADTH will use a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to develop optimal use recommendations for high-dose and combination treatment strategies involving AAPs, based on the evidence from the systematic review and cost analysis. The GRADE Working Group, an international collaboration of methodologists and others with an interest in grading quality of evidence and strength of recommendations, developed the GRADE methodology to provide committees charged with

formulating recommendations with a framework for evaluating evidence. GRADE provides a systematic and transparent approach to judge quality of evidence, weigh the balance of benefits versus harms, identify underlying values and preferences, and rate the overall strength of generated recommendations.[29] The GRADE methodology is used by a number of organizations around the world, such as the World Health Organization[30] and the American Thoracic Society, to generate recommendations.[31]

6.4.1 Formulating recommendations

When formulating recommendations, CERC considers both clinical effectiveness regarding benefits, harms, and burdens, as well as cost-effectiveness. Members of the committee bring their individual expertise and experience to bear (as experts, general practitioners, interventionists, and members of the public) and draw upon their own values and preferences to discuss the evidence and reach conclusions.

CERC will take the perspective of health care policy-makers pursuing maximal health outcomes for the Canadian population given finite health care system resources. Where one intervention appears to be more effective and more costly than another, CERC will determine whether the intervention represents reasonable "value for money" over the alternative. There is no empirical basis for assigning a particular value (or values) to the cut-off between clinical-effectiveness and cost-ineffectiveness. In situations where the evidence regarding clinical-effectiveness, cost, and cost-effectiveness fail to demonstrate important differences between treatments, the recommendations will be formulated to reflect that either treatment is appropriate. Where possible, the recommendations developed by CERC will provide guidance regarding specific patient subgroups that may benefit from alternate treatment approaches.

CERC may also develop clinical notes and context statements to accompany the recommendations. Clinical notes provide guidance based on clinical judgment where there is insufficient evidence. Context statements are related, but not limited to, quality and quantity of evidence, cost-effectiveness, directness of evidence, and clinical issues. These are intended to augment knowledge transfer to the intended audiences.

Key elements of the process that CERC will use to develop optimal use recommendations are:

- Individual feedback on the available clinical and cost evidence
- Committee discussion of individual member feedback
- Development of draft recommendations, and voting by secret ballot
- Assessment of the overall quality of evidence available for each recommendation
- Identification of underlying values and preferences for each recommendation.

CERC members will discuss the clinical and cost evidence "in committee," and will provide individual written feedback using a structured feedback form. Members will be asked for feedback on benefits, harms, and costs; quality of evidence; possible draft recommendations; values and preferences; and possible clinical notes and context statements. Feedback from all members will be collated and provided to the Committee for discussion.

Prior to developing recommendations, CERC will meet to discuss the collated individual feedback, and clarify any outstanding issues or questions related to the clinical and cost

evidence. Any new perspectives on the evidence arising from committee discussions will be added to the collated feedback, and the revised feedback document will be provided to members prior to the development of recommendations.

Based on the available evidence and collated feedback, CERC will draft recommendation statements, and vote by secret ballot upon the recommendations and the quality of the available evidence for the recommendation (high, moderate, or low). Members will also be asked to specify up to two of the most important values or preferences upon which their vote is based.

CERC will also identify, as gaps in research or knowledge, instances where there is insufficient information with which to produce optimal use recommendations. These will consist primarily of comparisons and populations for which no peer-reviewed reports of RCTs are identified. Research gaps will be also be identified when there is a paucity of comparative data on outcomes of interest for particular comparisons or populations.

Once recommendations have been voted upon, CADTH staff will develop a draft recommendations report containing the recommendations and vote results, CERC's rating of the quality of evidence, values and preferences expressed by the Committee, clinical notes and context, a summary of the key evidence considered by CERC in developing the recommendation, and research gaps. This document will be circulated to the Committee for feedback. If CERC determines that significant changes to a recommendation are necessary, a re-vote will be required.

6.4.2 Stakeholder feedback

A report containing the draft optimal use recommendations for use of AAP combination and high-dose treatment strategies in adolescents and adults with schizophrenia inadequately controlled on AAP monotherapy, supporting evidence in the form of summary of findings tables, and contextual material identified by CERC will be posted on the CADTH website to elicit stakeholder feedback. Stakeholder feedback will be collated by CADTH staff and considered by CERC in developing the final optimal use recommendations.

6.5 Identification of Gaps and Key Messages

The processes related to identification of gaps, development of key messages to close those gaps through development of intervention tools, and the implementation of the tools are part of the knowledge exchange planning process. A generic knowledge exchange plan guides the process for each individual CADTH project — in this case, Atypical Antipsychotics for Schizophrenia: Combination Therapy and High Doses. The generic plan identifies the types of interventions, related audiences, and potential tools that would be considered and adapted for each topic. The relative effectiveness of the interventions is well documented in the *Rx for Change* interventions database. *Rx for Change* is a publicly accessible database (www.rxforchange.ca) for health care policy-makers and health care professionals. It provides easy access to current research evidence about the effectiveness of strategies and programs to improve drug prescribing and use.

6.5.1 Gaps in practice

This phase of the project will address the following questions:

- What are the differences between recommendations for optimal prescribing and use of atypical antipsychotics for schizophrenia: combination therapy and high doses (based on the available clinical and economic evidence), and current utilization and practice?
- Which of the identified gaps are practice gaps and which are knowledge gaps?

Knowledge and practice gaps related to the use of atypical antipsychotics for schizophrenia will initially be identified by CADTH and validated by CERC members through comparison of the current practice and current utilization analyses with the Optimal Use Recommendations developed by CERC. This analysis will focus on identifying the following:

- Discrepancies between the recommendations and actual practice, as indicated by the utilization data and responses in the current practice analysis. Quantitative patterns from the utilization analysis will be compared with the recommendations to identify evidence of suboptimal use.
- Discrepancies between the recommendations and perceptions regarding the optimal use of AAPs, as indicated by the current practice analysis. Prevalent views regarding the advantages or benefits of high-dose and combination treatment strategies involving AAPs for schizophrenia, and the clinical situations or patient groups for whom they might be useful, will be compared with the recommendations to identify perceptions that are not supported by the available evidence.
- Knowledge deficits regarding the optimal use of atypical antipsychotics for schizophrenia identified in the current practice analysis.

6.5.2 Key messages

a) Addressing gaps

The identified gaps in practice and knowledge related to the use of AAPs for schizophrenia will be scrutinized to determine relevancy to optimal prescribing and use of these agents. Issues to be considered include the following:

- What are the barriers to the implementation of recommendations for the optimal prescribing and use of AAPs for schizophrenia?
- What action is needed to address those barriers?
- Are interventions and tools designed to address the gap likely to have significant impact, or is the gap unlikely to be amenable to change?
- Does the gap lend itself to the development and implementation of interventions, or is it difficult to address in a meaningful way?
- Would addressing the gap make a discernable difference in the prescribing and use of AAPs for schizophrenia?

If multiple gaps are identified, they will be prioritized according to the urgency of the attention they require; that is, those most relevant to the optimal prescribing and use of AAPs for schizophrenia. This will enable a focused approach to addressing gaps in practice and knowledge related to the optimal use of AAPs for schizophrenia.

For gaps identified as being of highest priority, key messages related to the gaps will be developed based on the optimal use recommendations. When developing key messages, consideration will be given to the intended audiences, barriers to change, and how those barriers could potentially be overcome, as well as factors favouring change (i.e., enablers). In addition, key messages are formulated as intended behaviour change statements where possible, rather than solely knowledge acquisition/reinforcement statements, and they are crafted in such a way that, where possible, behaviour change targets are measurable.

b) Feedback

Feedback on the key messages will be sought from key stakeholders (ideally through focus groups or interviews); for example, physicians, psychiatrists, other relevant health care practitioners. CADTH may also solicit input from the Canadian Academic Detailing Collaboration, CADTH Liaison Officers, and advisory committees (CERC and OUWG) as part of this process. All feedback will be collated by CADTH staff and considered by CERC and OUWG as the final key messages are developed.

6.5.3 Intervention tools

In conjunction with CERC and OUWG, CADTH will identify and explore barriers to the implementation of the key messages and develop a collection of evidence-informed intervention tools and materials to address those barriers. CADTH may solicit input from the Canadian Academic Detailing Collaboration, CADTH Liaison Officers, advisory committees (CERC and OUWG), and topic-specific partners as part of this process.

These interventions may include presentations, newsletters, prescribing aids, decision aids, and academic detailing support materials. CADTH does not implement these interventions, because delivery of health care is a jurisdictional responsibility. For this reason, a suite of intervention tools is developed to meet a variety of needs, from simple to complex interventions, and to meet health care professional and policy-maker needs.

The following steps describe the process for development of the intervention tools:

- Target audiences are identified and confirmed.
- Types and variety of tools required for the different audiences are identified and confirmed.
- Input is sought from OUWG, CERC, the Canadian Academic Detailing Collaboration, CADTH Liaison Officers, and topic-specific partners regarding additional intervention tools.
- A combination of external contractors and internal knowledge exchange resources are utilized to develop intervention tools.
- Content of the tools is adapted and presented at levels appropriate for each of the targeted audiences, and to meet the needs of multiple users and interventionists.
- The accuracy of the information contained in all tools is validated by the AAP Project Team.

6.5.4 Evaluation of tools

A Generic Evaluation Framework is available on the CADTH website (www.cadth.ca) to guide CADTH and users of CADTH products in their evaluation activities, from simple survey tools to more complex impact evaluations. The framework considers a variety of parameters that can be evaluated, recognizing that each of the parameters may not be applicable for each of the groups — such as the interventionists, jurisdictions, or CADTH — and thus, not each needs to be evaluated by each group. Some of the parameters that are considered include:

- Scope, usage, and reach: extent of dissemination and uptake of tools
- Awareness
- Perceived value and quality of the tools and interventions
- Enablers and barriers to implementation
- Sustainability: the cost-effectiveness of implementing the interventions
- Changes in attitudes, skills, and knowledge
- Changes in behaviour: prescriber and patient
- Changes in health outcomes (may not be feasible in all jurisdictions; may not be measurable in the short term)
- Changes in economic outcomes
- Changes in jurisdictional drug plan policies.

6.5.5 Implementation of tools

Implementation of these tools by jurisdictions, health care providers, and educators will serve to promote the optimal use of AAP combination therapy and high-dosing treatment strategies in adolescents and adults with schizophrenia.

6.5.6 Tool adaptation

CADTH offers a tool adaptation service. In this way, the core suite of intervention tools may be modified to meet specific jurisdictional and other needs.

All adapted tools are subject to a scientific validation by CADTH to ensure the content is an accurate representation of the evidence.

7 EXECUTION OF THE PROJECT

To promote timely execution of this project, roles and responsibilities for individual project members have been formulated, and the structure of the project has been drafted.

8 DELIVERABLES

On completion of this project, reports and intervention tools will be made available on the CADTH website at http://www.cadth.ca/index.php/en/new-topics/atypical-antipsychotics-for-schizophrenia.

The reports will include:

- Systematic review of the clinical evidence surrounding AAP combination high-dose treatment strategies in adolescents and adults with schizophrenia
- Results of cost-effectiveness analysis
- Current utilization analysis of AAP combination high-dose treatment strategies in adolescents and adults with schizophrenia
- Budget impact analysis which explores the incremental cost or savings that may be realized by public drug plans between 2011 and 2014 under conditions where there is more restricted use of AAP combination and high-dose treatment strategies
- Current practice analysis of AAP combination high-dose treatment strategies in adolescents and adults with schizophrenia
- Project summary reports
- Optimal use recommendations for AAPs: combination and high-dose treatment strategies in adolescents and adults with schizophrenia
- Summary of key clinical messages report on the use of AAPs: combination and high-dose treatment strategies in adolescents and adults with schizophrenia.

The final selection of intervention tools to be developed may include:

- Health care provider education materials
- Patient education materials
- Academic detailing tools
- Others, as directed.

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APPENDIX 1: Literature Search Strategy

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a term, indicates that the marked subject heading is a primary topic; or, immediately after a word, a truncation symbol (wildcard) to retrieve plurals or variant word endings
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
cctr	Cochrane Central Register of Controlled Trials
.po	Population group
.la	Language
.lg	Language
.mp	Mapped word
.jw	Journal word
.md	Methodology
.yr	Year

Search Strategy for Randomized Controlled Trials and Controlled Clinical Trials

OVERVIEW	
Interface:	Ovid
Databases:	Cochrane Central Register of Controlled Trials; EMBASE <1980 to present>; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) <1950 to present>; PsycINFO <1967 to present> **Note**: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Alerts:	Monthly until publication of report
Study Types:	Randomized controlled trials; Controlled clinical trials
Limits:	Publication dates – no limit Human population English or French language

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process, Cochrane Central, PsycINFO	
Line #	**Strategy**
1	exp schizophrenia/ or schizophrenia.hw.
2	(schizophreni* or schizoaffect* or schizo affect* or hebephreni* or schizophreniform or dementia praecox or dementia precox or shared paranoid disorder* or (delusional adj2 disorder*) or (brief psychotic adj2 disorder*) or first psychotic episode* or first episode psychos*).ti,ab.
3	or/1-2
4	risperidone/
5	clozapine/
6	aripiprazole*.rn.
7	olanzapine*.rn.
8	quetiapine*.rn.
9	9-hydroxy-risperidone*.rn.
10	ziprasidone*.rn.
11	asenapine*.rn.
12	(risperidone* or clozapine* or aripiprazole* or olanzapine* or quetiapine* or 9-hydroxy-risperidone* or paliperidone* or ziprasidone* or ziprazidone* or asenapine*).ti,ab,nm,hw.
13	(risperdal* or risperidal* or belivon* or rispolin* or risperin* or rispolept* or sequinan* or zyprexa* or olansek* or seroquel* or clozaril* or clorazil* or fazaclo* or iprox* or leponex* or abilify* or abilitat* or invega* or geodon* or zeldox* or saphris*).ti,ab.
14	((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 antipsychotic*).ti,ab.
15	((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 anti-psychotic*).ti,ab.
16	((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 neuroleptic*).ti,ab.
17	(106266-06-2 or 132539-06-1 or 111974-69-7 or 129722-12-9 or 5786-21-0 or 144598-75-4 or 146939-27-7 or 85650-56-2).rn.
18	or/4-17
19	3 and 18
20	drug combinations/
21	exp drug therapy, combination/
22	polypharmacy/
23	(augmentation or add-on or adjunctive or adjunct or adjuvant or added or polypharmac* or polytherap* or combination* or combined or combining or co-therap* or cotherap* or co-administration or coadministration or (dual adj2 therap*) or concomitant or concurrent or monotherap* or monotreatment or mono-therap* or mono-treatment* or mono-administration).ti,ab.
24	or/20-23
25	dose-response relationship, drug/

26	drug dosage calculations/
27	no-observed-adverse-effect level/
28	maximum tolerated dose/
29	drug dosages/
30	(dose or doses or dosage* or dosing).ti,ab.
31	or/25-30
32	24 or 31
33	19 and 32
34	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
35	Randomized Controlled Trial/
36	Randomized Controlled Trials as Topic/
37	Controlled Clinical Trial/
38	Controlled Clinical Trials as Topic/
39	Randomization/
40	Random Allocation/
41	Double-Blind Method/
42	Double Blind Procedure/
43	Double-Blind Studies/
44	Single-Blind Method/
45	Single Blind Procedure/
46	Single-Blind Studies/
47	Placebos/
48	Placebo/
49	Control Groups/
50	Control Group/
51	(random* or sham or placebo*).ti,ab,hw.
52	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
53	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
54	(control* adj3 (study or studies or trial*)).ti,ab.
55	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
56	"allocated to".ti,ab,hw.
57	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
58	or/34-57
59	33 and 58
60	33 use cctr
61	59 or 60
62	exp animals/

63	exp animal experimentation/
64	exp models animal/
65	exp animal experiment/
66	nonhuman/
67	exp vertebrate/
68	animal.po.
69	or/62-68
70	exp humans/
71	exp human experiment/
72	human.po.
73	or/70-72
74	69 not 73
75	61 not 74
76	limit 75 to english language [Limit not valid in CCTR; records were retained]
77	75 and french.la,lg.
78	76 or 77

EMBASE	
Line #	**Strategy**
1	exp *schizophrenia/
2	(schizophreni* or schizoaffect* or schizo affect* or hebephreni* or schizophreniform or dementia praecox or dementia precox or shared paranoid disorder* or (delusional adj2 disorder*) or (brief psychotic adj2 disorder*) or first psychotic episode* or first episode psychos*).ti,ab.
3	or/1-2
4	*risperidone/ or *clozapine/ or *aripiprazole/ or *olanzapine/ or *quetiapine/ or *paliperidone/ or *ziprasidone/ or *asenapine/
5	(risperidone* or clozapine* or aripiprazole* or olanzapine* or quetiapine* or 9-hydroxy-risperidone* or paliperidone* or ziprasidone* or ziprazidone* or asenapine*).ti,ab.
6	(risperdal* or risperidal* or belivon* or rispolin* or risperin* or rispolept* or sequinan* or zyprexa* or olansek* or seroquel* or clozaril* or clorazil* or fazaclo* or iprox* or leponex* or abilify* or abilitat* or invega* or geodon* or zeldox* or saphris*).ti,ab.
7	((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 antipsychotic*).ti,ab.
8	((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 anti-psychotic*).ti,ab.
9	((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 neuroleptic*).ti,ab.
10	or/4-9

11	3 and 10
12	drug combination/
13	polypharmacy/
14	add-on therapy/
15	adjuvant therapy/
16	drug mixture/
17	monotherapy/
18	(augmentation or add-on or adjunctive or adjunct or adjuvant or added or polypharmac* or polytherap* or combination* or combined or combining or co-therap* or cotherap* or co-administration or coadministration or (dual adj2 therap*) or concomitant or concurrent or monotherap* or monotreatment or mono-therap* or mono-treatment* or mono-administration).ti,ab.
19	or/12-18
20	dose response/
21	dose calculation/
22	maximum permissible dose/
23	maximum tolerated dose/
24	dosage schedule comparison/
25	drug dose comparison/
26	drug dose escalation/
27	drug dose increase/
28	drug dose reduction/
29	drug dose regimen/
30	drug dose sequence/
31	drug dose titration/
32	drug megadose/
33	maintenance drug dose/
34	multiple drug dose/
35	optimal drug dose/
36	recommended drug dose/
37	(dose or doses or dosage* or dosing).ti,ab.
38	or/20-37
39	19 or 38
40	11 and 39
41	Randomized Controlled Trial/
42	Randomized Controlled Trials as Topic/
43	Controlled Clinical Trial/
44	Controlled Clinical Trials as Topic/

45	Randomization/
46	Random Allocation/
47	Double-Blind Method/
48	Double Blind Procedure/
49	Double-Blind Studies/
50	Single-Blind Method/
51	Single Blind Procedure/
52	Single-Blind Studies/
53	Placebos/
54	Placebo/
55	Control Groups/
56	Control Group/
57	(random* or sham or placebo*).ti,ab,hw.
58	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
59	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
60	(control* adj3 (study or studies or trial*)).ti,ab.
61	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
62	allocated.ti,ab,hw.
63	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
64	or/41-63
65	40 and 64
66	exp animals/
67	exp animal experimentation/
68	exp models animal/
69	exp animal experiment/
70	nonhuman/
71	exp vertebrate/
72	or/66-71
73	exp humans/
74	exp human experiment/
75	or/73-74
76	72 not 75
77	65 not 76
78	limit 77 to english language
79	77 and french.la.
80	78 or 79

OTHER DATABASES	
PubMed	Same MeSH and keywords as per MEDLINE search, with appropriate syntax used. Search limited to publisher in the status field.
CINAHL	Same keywords used as per MEDLINE search. CINAHL subject headings added. Search limited to clinical trial in publication type field. Syntax adjusted for CINAHL database.

Search Strategy for Systematic Reviews, Meta-Analyses, and Clinical Practice Guidelines

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) <1950 to present>
Alerts:	Monthly until publication of report
Study Types:	Systematic reviews; meta-analyses; technology assessments; clinical practice guidelines; review articles
Limits:	Publication dates: 2004 to present. Review articles: 2009 to present

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process

Line #	Strategy
1	meta-analysis.pt.
2	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
3	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
4	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
5	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
6	(data synthes* or data extraction* or data abstraction*).ti,ab.
7	(handsearch* or hand search*).ti,ab.
8	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
9	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
10	(meta regression* or metaregression* or mega regression*).ti,ab.
11	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
12	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
13	(cochrane or health technology assessment or evidence report).jw.
14	(meta-analysis or systematic review).md.
15	or/1-14

16	risperidone/
17	clozapine/
18	aripiprazole.rn.
19	olanzapine.rn.
20	quetiapine.rn.
21	9-hydroxy-risperidone.rn.
22	ziprasidone.rn.
23	asenapine.rn.
24	(risperidone or clozapine or aripiprazole or olanzapine or quetiapine or 9-hydroxy-risperidone or paliperidone or ziprasidone or asenapine).ti,ab,nm.
25	(risperdal or risperidal or belivon or rispolin or risperin or rispolept or sequinan or zyprexa or olansek or seroquel or clozaril or clorazil or fazaclo or iprox or leponex or abilify or abilitat or invega or geodon or zeldox or saphris).ti,ab.
26	((atypical or new generation or second generation or 2nd generation or novel) adj2 antipsychotic*).ti,ab.
27	((atypical or new generation or second generation or 2nd generation or novel) adj2 anti-psychotic*).ti,ab.
28	((atypical or new generation or second generation or 2nd generation or novel) adj2 neuroleptic*).ti,ab.
29	(106266-06-2 or 132539-06-1 or 111974-69-7 or 129722-12-9 or 5786-21-0 or 144598-75-4 or 146939-27-7 or 85650-56-2).rn.
30	or/16-29
31	drug combinations/
32	exp drug therapy, combination/
33	polypharmacy/
34	(augmentation or add-on or adjunctive or adjunct or adjuvant or added or polypharmac* or polytherap* or combination* or combined or combining or co-therap* or cotherap* or co-administration or coadministration or (dual adj2 therap*) or monotherap* or monotreatment or mono-administration).ti,ab.
35	or/31-34
36	dose-response relationship, drug/
37	drug dosage calculations/
38	no-observed-adverse-effect level/
39	maximum tolerated dose/
40	(dose or doses or dosage* or dosing).ti,ab.
41	or/36-40
42	35 or 41
43	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
44	(guideline* or standards or consensus* or recommendat*).ti.
45	(practice parameter* or position statement* or policy statement* or CPG or CPGs or best

	practice*).ti.
46	(care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard or standards)).ti.
47	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti.
48	(algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti.
49	(algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.
50	or/43-49
51	exp schizophrenia/
52	(schizophreni* or schizoaffect* or schizo affect* or hebephreni* or schizophreniform or dementia praecox or dementia precox or shared paranoid disorder* or (delusional adj2 disorder*) or (brief psychotic adj2 disorder*) or first psychotic episode*).ti,ab.
53	or/51-52
54	53 and 30 and 42 and 15
55	limit 54 to yr="2004 -Current"
56	50 and 53 and 30
57	limit 56 to yr="2004 -Current"
58	55 or 57

Additional schizophrenia guidelines that do not specifically mention atypical antipsychotic drug names

Line #	Strategy
59	50 and 53
60	59 not 56
61	limit 60 to yr="2004 -Current"

Review articles

Line #	Strategy
62	53 and 30 and 42
63	review.pt,ti
64	62 and 63
65	limit 64 to yr="2009 -Current"

Grey Literature and Hand-Searches

Keywords: Atypical antipsychotics, second generation antipsychotics, novel antipsychotics, schizophrenia

This section lists the main agencies, organizations, and websites searched; it is not a complete list.

Health Technology Assessment Agencies

Institut national d'excellence en santé et en services sociaux (INESSS) [succeeded AETMIS]
http://www.inesss.qc.ca/

Canadian Agency for Drugs and Technologies in Health (CADTH)
http://www.cadth.ca

Health Technology Assessment International (HTAi)
http://www.htai.org

International Network of Agencies for Health Technology Assessment (INAHTA)
http://www.inahta.org

National Institute for Health Research (NIHR) Health Technology Assessment programme
http://www.hta.ac.uk/

NHS National Institute for Health and Clinical Excellence (NICE)
http://www.nice.org.uk

University of York NHS Centre for Reviews and Dissemination (NHS CRD)
http://www.york.ac.uk/inst/crd

Agency for Healthcare Research and Quality (AHRQ)
http://www.ahrq.gov/

United States Department of Veterans Affairs Research & Development (general publications)
http://www.research.va.gov/resources/pubs/default.cfm

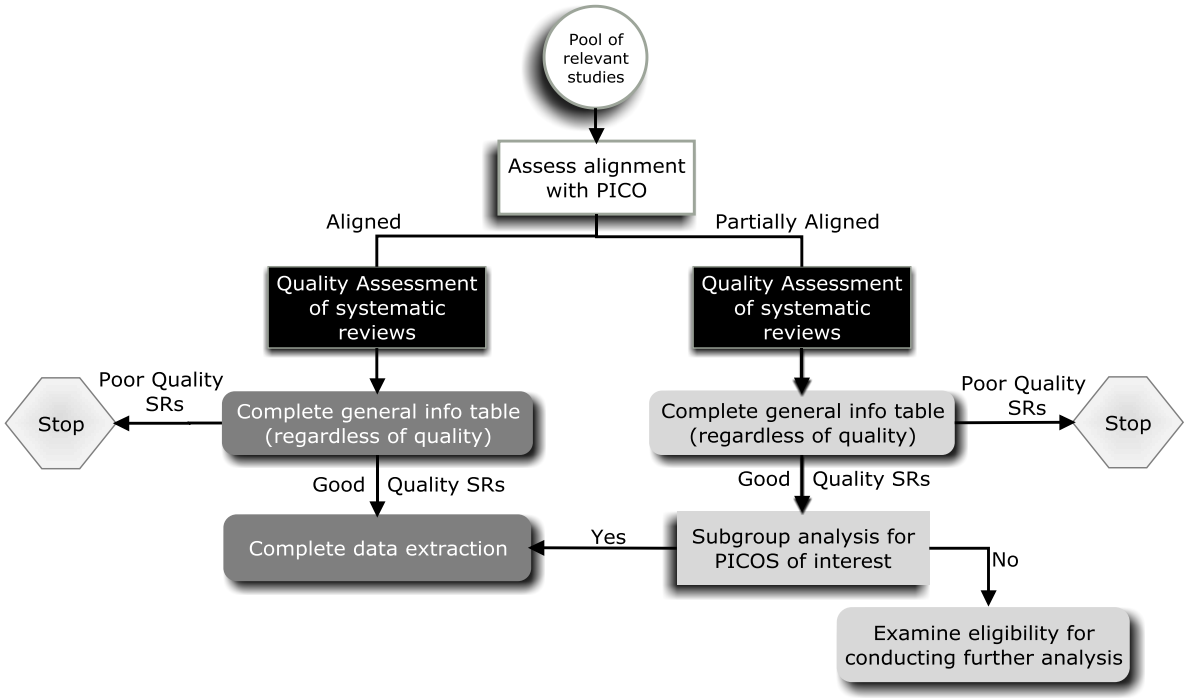
United States Department of Veterans Affairs VA Technology Assessment Program (VATAP)
http://www.va.gov/vatap/

ECRI
http://www.ecri.org/

Search Engines

Google
http://www.google.ca/

APPENDIX 2: Overview of Process for Assessing the Applicability of Existing Systematic Reviews and Meta-analyses



PICO = population, intervention, comparators, and outcome; SRs = systematic reviews.

APPENDIX 3: SIGN 50* — Randomized Controlled Trial Quality Assessment Tool

Project: Test Strips	Statement #:	Author:
Title:		
Reviewer:	Date:	**RefMan #:**

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		In this study this criterion is:		
1.1	The study addresses an appropriate and clearly focused question.	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.2	The assignment of subjects to treatment groups is randomised	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.3	An adequate concealment method is used	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.4	Subjects and investigators are kept 'blind' about treatment allocation	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.5	The treatment and control groups are similar at the start of the trial	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.6	The only difference between groups is the treatment under investigation	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.7	All relevant outcomes are measured in a standard, valid and reliable way	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?			
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed

1.10	Where the study is carried out at more than one site, results are comparable for all sites	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
SECTION 2: OVERALL ASSESSMENT OF THE STUDY				
2.1	How well was the study done to minimise bias? Code ++, +, or –		-	
SECTION 3: OTHERS				
3.1	How was this study funded? *List all sources of funding quoted in the article, whether government, voluntary sector, or industry.*			

**SIGN 50: A guideline developers' handbook*.[13]