Drug Class Review

Agents for Overactive Bladder

Final Report Update 4

March 2009

Update 3 Report date: December 2005
Update 2 Report date: May 2005
Update 1 Report date: January 2004
Original Report date: February 2003
A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Marian S. McDonagh, PharmD
Dana Selover, MD, MPH
John Santa, MD
Sujata Thakurta, MPA:HA

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

TABLE OF CONTENTS

Note:
The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Prior versions of this report can be accessed at the DERP website.

Suggested citation for this report:
McDonagh M, Selover D, Santa J, Thakurta S. Drug class review: Agents for overactive bladder. Update 4. http://www.ohsu.edu/drugeffectiveness/reports/final.cfm

Acknowledgments:
Leah Williams and Arkady Mak, PhD, MD, contributed to this report by formatting and editing the manuscript. Sarah Lopez, MS, Trish Thieda, MA, and Miranda Walker, MA, assisted with data abstraction and quality assessment of studies. Theresa Nguyen assisted through article retrieval and assistance with formatting.

Funding:
The Drug Effectiveness Review Project, made up of 15 organizations including 14 state Medicaid agencies, commissioned and funded this report. These organizations selected the topic of the report and had input into its Key Questions. Content and conclusions of the report were determined entirely by researchers at the Evidence-based Practice Center. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in the report.

INTRODUCTION

Overactive bladder is defined by the International Continence Society as a syndrome of urinary frequency and urgency, with or without urge incontinence, appearing in the absence of local pathological factors.[1] Nocturia is also commonly present.[1] Urinary continence relies heavily upon control and coordination of the smooth muscle found in the wall of the bladder. The effective storage of urine relies on detrusor muscle relaxation, and contraction of internal and external sphincters found within the neck of the bladder while voiding is controlled through the contraction of the bladder's detrusor muscle and relaxation of its internal and external sphincters.[2] Bladder contraction is mediated via cholinergic muscarinic receptors in bladder smooth muscle. The most common cause of overactive bladder syndrome is detrusor overactivity. Detrusor overactivity may be either idiopathic or neurogenic in origin. A subset of patients with an overactive bladder may complain of urge urinary incontinence, involuntary leakage accompanied by or immediately preceded by urgency.[3, 4]

While urge incontinence is not inevitable, its incidence does increase with age.[5] Overactive bladder has been estimated to affect 20% of community-dwelling senior citizens and around 50% of institutionalized elderly persons.[2, 5] Independent risk factors for the development of overactive bladder include neurologic impairment, immobility, female gender, and history of hysterectomy. It is common for urge incontinence to coexist with stress incontinence, especially in women.

Treatment of overactive bladder syndrome first requires a clear diagnosis. In patients with incontinence, multiple forms can be present and it is important to determine which form is dominant. Non-pharmacologic, non-surgical treatment consists of behavioral training (prompted voiding, bladder training, pelvic muscle rehabilitation), transcutaneous electrical nerve stimulation, catheterization, and use of absorbent pads.[6] Pharmacologic treatment for overactive bladder syndrome includes darifenacin, flavoxate hydrochloride, hyoscyamine, oxybutynin chloride, tolterodine tartrate, trospium chloride, scopolamine transdermal, and solifenacin succinate. Flavoxate hydrochloride acts as a direct spasmolytic on smooth muscle and maintains anticholinergic as well as local analgesic properties.[2, 7] Oxybutynin chloride has direct antispasmodic action on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle.[2, 7, 8] Tolterodine tartrate acts as a competitive muscarinic receptor antagonist.[2, 7, 9] Trospium chloride is a quaternary ammonium derivative with predominantly muscarinic action.[10] Darifenacin and solifenacin are competitive muscarinic receptor antagonists.[11, 12]

Anticholinergic agents have been included in a number of expert-opinion based reviews of drugs with high risk of adverse effects in the elderly. Two well known reviews by Beers et al. discuss the potential for anticholinergic drugs to cause adverse events, particularly central nervous system effects, the older patients.[13, 14] These papers include oxybutynin as an *example* of an anticholinergic drug with this potential, but evidence linking oxybutynin to adverse events is not presented. Because these reviews are not systematic, and do not make comparisons to any of the other drugs included in this report, we do not include these papers here.

The purpose of this systematic review is to compare the benefits and harms of drugs used to treat overactive bladder syndrome.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. A systematic review focuses on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with a careful formulation of research questions. The goal is to select questions that are important to patients and clinicians, then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are emphasized over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in both groups, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant across groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than the absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat, often referred to as the NNT, is the number of patients who would have to be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of evidence, allowing a greater contribution from studies that meet high methodological standards that reduce the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed, randomized, controlled trials are considered better evidence than results of cohort, case-control, or cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, cohort designs are preferred when conducted well and for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to the generalizability of *efficacy studies* performed in controlled or academic settings. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including antipsychotic drugs, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that may be impractical in typical practice settings. And these studies often restrict options that are of value in actual practice, such as combination therapies or switching to other drugs. Efficacy studies

also often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. Results of effectiveness studies are more applicable to the "average" patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling each study as either an efficacy or an effectiveness study, while convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies across the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision-makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how much of it there is, may have limited applicability to practice. Clinicians can judge the relevance of the study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for many patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an

evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide committee of experts. Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to clinicians and patients. The scope of the current review was approved in June 2008. The participating organizations approved the following key questions to guide this review:

1. For adult patients with overactive bladder, do anticholinergic drugs differ in effectiveness?
    a. Is there a difference in effectiveness between long-acting and short-acting formulations?

2. For adult patients with overactive bladder, do anticholinergic drugs differ in safety or adverse effects?
    a. Is there a difference in safety or adverse effects between long-acting and short-acting formulations?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or comorbidities for which one anticholinergic drug is more effective or is associated with fewer adverse effects?
    a. Are there differences in adverse event profiles in older patients between the drugs, particularly long-acting compared with short-acting, and newer drugs compared with the older drug oxybutynin?

METHODS

Inclusion Criteria

Populations

Adult patients with symptoms of urge incontinence/overactive bladder (urgency, frequency, leakage, dysuria).

Interventions

Included interventions are listed in Table 1.

Table 1. Included interventions

Active ingredient	Form	Brand name
Darifenacin	Oral Extended-release tablet	Enablex
Flavoxate hydrochloride	Oral tablet	Urispas
Hyoscyamine sulfate	Oral tablet	Levsin
Oxybutynin chloride	Oral tablet and syrup	Ditropan
Oxybutynin chloride	Extended release oral tablet	Ditropan XL
Oxybutynin	Transdermal system	Oxytrol
Scopolamine (hyoscine) butylbromide	Oral tablet	Buscopan
Solifenacin succinate	Oral tablet	Vesicare
Tolterodine tartrate	Oral tablet	Detrol
Tolterodine tartrate	Extended release oral capsule	Detrol LA
Trospium chloride	Oral tablet	Sanctura (USA), Trosec (Canada)
Trospium chloride	Extended release oral capsule	Sanctura XR[a]

[a] Not available in Canada.

Effectiveness outcomes

- Change in mean number of incontinence episodes per 24 hours
- Change in mean number of micturitions per 24 hours
- Change in mean number of pads per 24 hours
- Subjective patient assessments of symptoms (severity of 'problems' caused by bladder symptoms, severity of urgency, global evaluation of treatment)
- Quality of life

Safety outcomes

- Overall adverse effects
- Withdrawals due to overall adverse effects
- Serious adverse events reported
- Specific adverse events or withdrawals due to specific adverse events (dry mouth, effects on cognition, blurred vision, and cardiac conduction abnormalities)

Study Designs

For effectiveness, the study is a randomized controlled trial or good-quality systematic review of an anticholinergic incontinence drug compared with another anticholinergic incontinence drug, another drug, or placebo. For adverse effects, the study is a controlled clinical trial or observational study of at least 6 months' duration.

Literature Search

To identify articles relevant to each key question for each version of this report, we searched Medline, the Cochrane Library, and reference lists of review articles. For the original report we also searched EMBASE (1980-July week 3 2005). For the current update, we searched Medline and the Cochrane Library through December 2008. In electronic searches, we used broad searches, only combining terms for drug names with terms for relevant research designs. (See Appendix B for complete search strategy). We have attempted to identify additional studies through searches of reference lists of included studies and reviews, the US Food and Drug Administration website, and dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (EndNote XI).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by 2 reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form were not included because lack of detail prevented quality assessment.

Trials that evaluate one anticholinergic drug against another provide direct evidence of comparative effectiveness and adverse event rates. In theory, trials that compare these drugs with placebos or with other drugs used to treat overactive bladder can also provide evidence about efficacy. However, the efficacy of drugs in different trials can be difficult to interpret because of significant differences in key characteristics of the patient populations. Comparison of results across trials (direct comparisons or indirect comparisons) is difficult due to differing outcome measures.

Data Abstraction

The following data were abstracted from included trials: study design; setting; population characteristics (including sex, age, ethnicity, diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results if they were available and the trial did not report high overall loss to follow-up. Data were abstracted by one reviewer and checked for accuracy by a second.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix C. These criteria were based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria for assessing study quality. In rating the internal validity of each trial we assessed the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated poor-quality; trials that met all criteria were rated good-quality. The remainder were rated fair-quality. As the fair-quality category was broad, studies with this rating varied in their strengths and weaknesses; the results of some fair-quality studies were likely to be valid, while others were only possibly valid. Poor-quality trials were not valid: The results were at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items on the quality assessment checklist.

Appendix C also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of study design that are particularly important for assessing adverse event rates. We rated observational studies as good-quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair-quality if they met 3 to 5 criteria, and poor-quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality based on predefined criteria (see Appendix C), which assessed the research questions(s) and inclusion criteria, adequacy of search strategy and validity assessment, adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

The overall strength of evidence for a particular key question or outcome reflected the risk of bias of the studies (based on quality and study design) and the consistency, directness, and precision of the studies relevant to the question. Strength of evidence was graded as insufficient, low, moderate, or high.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy-of-evidence approach, in which the best evidence was the focus of our synthesis for each question, population, intervention, and outcome addressed. Data reported on a ‘per 24 hour’ basis were converted to ‘per week’ to allow comparison to other data.

In addition to qualitative discussion of studies’ findings, meta-analyses were conducted, where possible. Forest plots of the risk difference for efficacy measures or adverse events are presented (where possible) to display data comparatively. Forest plots were created using StatsDirect (CamCode, UK) software. Results are reported as differences between drugs in mean change in number of micturitions or episodes of incontinence per day or per week. Differences in rates of adverse events and withdrawals due to adverse events are expressed as the “percent risk difference,” which is the difference between the proportions with the event in 2 groups of patients at a given time-point. For example, if 20% of patients in group A and 25% of patients in group B report an adverse event, then the groups show a 5% risk difference. The 95% confidence

interval (CI) is reported as a measure of the variance around the estimate of risk difference. If the 95% CI includes 0, then the difference is not statistically significant. Risk differences are plotted on forest plots, always presenting the difference of the first drug minus the second named drug. The size of the box indicating the point estimate is determined by the variance, such that larger studies generally have larger boxes relative to smaller studies.

Peer Review and Public Comment

The Original report underwent a review process that involved solicited peer review from 3 clinical experts. Their comments were reviewed and, where possible, incorporated into the final document. The comments received and the author's proposed actions were reviewed by the representatives of the participating organizations of the Drug Effectiveness Review Project prior to finalization of the report. Names of peer reviewers for Drug Effectiveness Review Project reports are listed at www.ohsu.edu/drugeffectiveness.

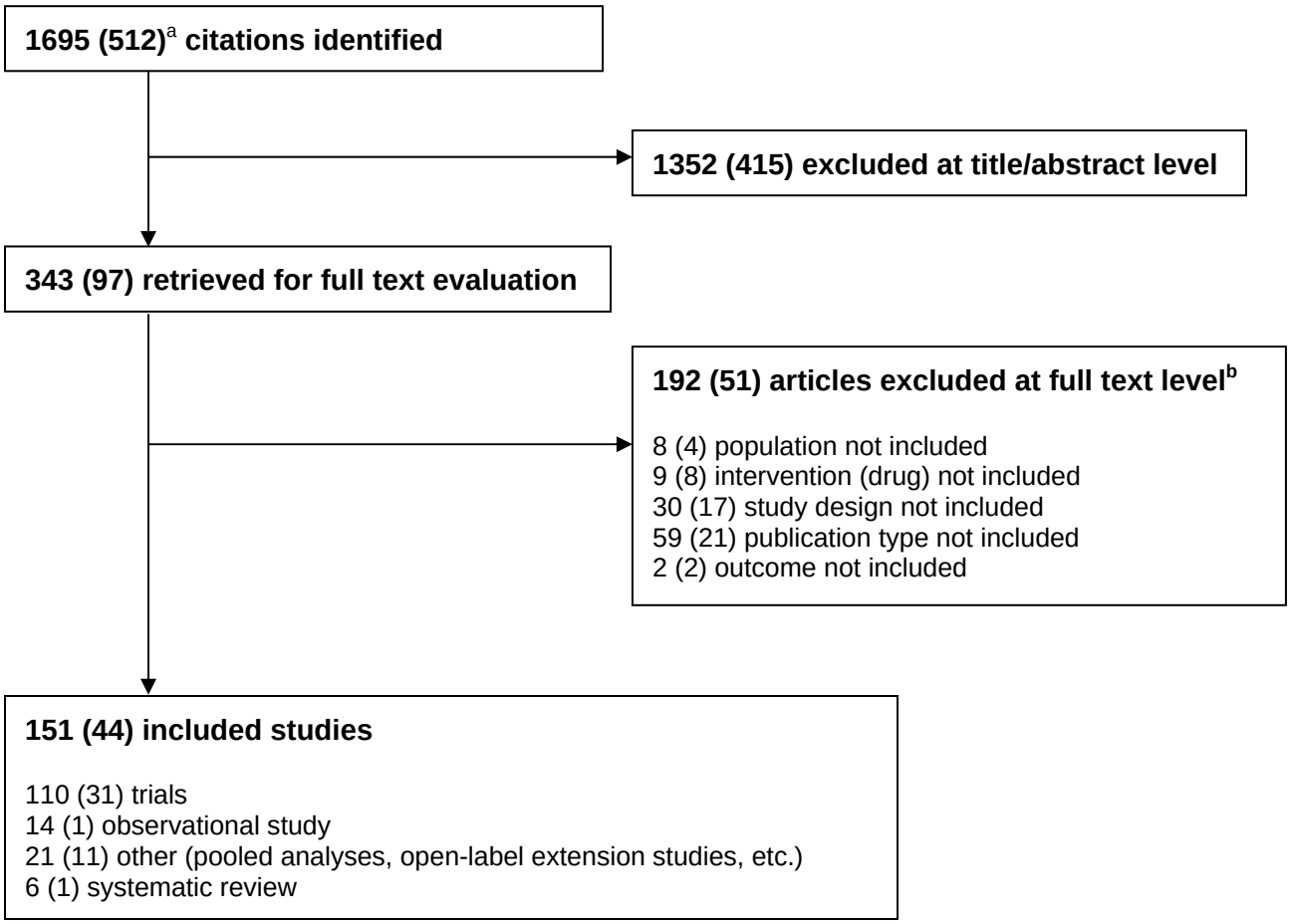
Each version of the report has been posted in draft form to the Drug Effectiveness Review Project website for public comment. Key stakeholders were notified of these postings. For Update 4 we received comments from 3 stakeholders (Novartis, Pfizer, and Orth-McNeil Janssen). The comments received and the author's proposed actions were reviewed by the representatives of the participating organizations of the Drug Effectiveness Review Project prior to finalization of the report.

RESULTS AND DISCUSSION

Overview

Previous versions of this report (the original report, Update 1, Update 2, and Update 3) included 128 randomized controlled trials, 3 systematic reviews, and 5 observational studies. For Update 4, our literature search resulted in 512 new citations, of which 335 were from Medline; 3 citations came from the dossier submitted by Novartis. Of these, 44 met the inclusion criteria for this update (4 head-to-head trials, 9 active-control trials, 18 placebo-controlled trials, 11 pooled analyses or extension studies of trials, 1 systematic review, and 1 observational study). Figure 1 shows the study selection process for Update 4. Appendix D lists the excluded studies.

Figure 1. Results of literature search



[a] Numbers in parentheses are results of the literature search new to Update 4.
[b] Two additional studies unobtainable after exhaustive library searches.

Summary

Comparative efficacy

- When extended-release and immediate-release formulations of the same drug were compared, no differences in efficacy were found.
    - For example, no difference was found between oxybutynin extended-release and oxybutynin immediate-release (4 studies) or tolterodine extended-release and tolterodine immediate-release (1 study).
- Comparisons of different drugs in extended-release and immediate-release formulations more often found the extended-release drug to be superior, but not in all cases.
    - One study comparing oxybutynin extended-release with tolterodine immediate-release found oxybutynin superior, and 1 study comparing tolterodine extended-release with oxybutynin immediate-release found tolterodine superior.
    - Comparison of darifenacin extended-release with oxybutynin immediate-release did not identify differences in efficacy.
- Solifenacin (a long-acting drug) showed greater efficacy over tolterodine (immediate-release and extended-release) for some, but not all, outcomes in 2 short-term studies.
- No difference among immediate-release products was found.
    - The evidence supports no difference in efficacy between oxybutynin immediate-release and tolterodine immediate-release (4 studies) or between trospium immediate-release and oxybutynin immediate-release (1 study).
- For oxybutynin extended-release compared with tolterodine extended-release the better of 2 studies found them equal.

Adverse events

- In longer-term observational studies, dry mouth was the most common adverse event for all the drugs.
    - The only comparative study assessing the discontinuation rate of tolterodine immediate-release and oxybutynin immediate-release over a 6-month period found more and earlier withdrawal with oxybutynin, but rates for both drugs were high.
- Short-term trials making direct comparisons indicate a higher incidence of adverse events overall and specifically dry mouth with oxybutynin than with the other drugs. Differences in adverse event profiles between long-acting products and short-acting products are unclear.
    - Comparisons of extended-release and immediate-release formulations tended to find higher rates of adverse events, particularly dry mouth, with the immediate-release formulations, but differences in discontinuation rates were not found.
        - Short-term head-to-head comparisons of oxybutynin immediate-release with oxybutynin extended-release found a higher rate of overall adverse events and dry mouth with the immediate-release form; withdrawal due to adverse event was similar for both.
        - Trospium immediate-release had lower rates of severe dry mouth than oxybutynin immediate-release, although overall incidences of dry mouth and short-term adverse events were similar to those of oxybutynin immediate-release.

- A short-term head-to-head comparison of tolterodine immediate-release with tolterodine extended-release found a higher rate of dry mouth with the immediate-release form. Withdrawal due to adverse event was similar for both.
- A trial comparing solifenacin with tolterodine extended-release found a lower rate of dry mouth for tolterodine extended-release. The difference between drugs based on withdrawals is less clear: 2 trials comparing solifenacin with tolterodine found similar rates of adverse events overall.

Subpopulations

- Evidence from 5 studies was not consistent in identifying differences between men and women in response to tolterodine.
- Older patients were found to respond to oxybutynin, tolterodine extended-release, darifenacin, or solifenacin in post hoc subgroup analyses. Adverse event profiles were similar to those found in the overall trial populations.
- Oxybutynin immediate-release and tolterodine immediate-release resulted response and adverse event rates that were similar for Chinese women and for primarily white populations of other studies. Solifenacin was found to have response and adverse event rates in a Hispanic subgroup that were similar to those of the overall trial population in 1 study. Tolterodine extended-release and tolterodine immediate-release were found to be similarly effective in Japanese and Korean women, with fewer adverse events in the tolterodine extended-release group. The Japanese patients were shown to have improved quality of life in both groups; no such analysis was undertaken for the Korean patients.
- Two studies of men taking an alpha-adrenergic antagonist for symptoms associated with benign prostatic hypertrophy with residual symptoms of overactive bladder found that adding tolterodine extended-release to the alpha-adrenergic antagonist significantly improved symptoms related to both overactive bladder and benign prostatic hypertrophy compared with tolterodine extended-release alone, placebo, or an alpha-adrenergic antagonist alone.
    - Patient Perception of Bladder Condition was not improved in 1 study.
- One head-to-head trial comparing trospium immediate-release with oxybutynin immediate-release in patients with spinal cord injury found that the drugs had a similar rate of overall adverse events, although trospium appeared to cause less severe dry mouth than oxybutynin.

Flavoxate, scopolamine, and hyoscyamine

- Head-to-head comparisons with flavoxate were poor quality and there were no head-to-head comparisons of scopolamine, or hyoscyamine to another drug for OAB.
    - Flavoxate was not superior to placebo in 2 quality trials.
    - Scopolamine was superior to placebo in a small (N=20) 2-week trial in women diagnosed with detrusor instability who showed greater improvement in diurnal frequency, nocturia, urgency, and urge incontinence with scopolamine than placebo.
    - There were no placebo-controlled trials of for hyoscyamine.

Detailed Assessment

We found no effectiveness trials of drugs for overactive bladder syndrome. The included trials assessed outcome measures related to efficacy and the trials were primarily short (8-12 weeks). Most of the randomized trials had fair internal validity but their applicability to community practice was difficult to determine. The studies generally excluded patients who would have been at risk of serious adverse events from anticholinergic drugs. Most of the treatment and control groups received standard doses of anticholinergic drugs but some studies compared doses at the higher end of the range of one drug with the lower end of the range of another. Of studies that stated their source of funding, all were funded by the pharmaceutical industry and industry employees often served as coauthors.

While several fair- and good-quality systematic reviews examined aspects of treating patients with overactive bladder, only a few directly examined the questions posed here. We include the results of only 2 published systematic reviews in the sections below. One is a good-quality 2005 Cochrane review focused on comparing the effects of different anticholinergic drugs for overactive bladder syndrome using randomized controlled trials that compared 1 anticholinergic drug to another or 2 different doses of the same drug.[15] The other was a fair-quality systematic review of the differences in tolerability, safety, and efficacy between oxybutynin, tolterodine, trospium, darifenacin, and solifenacin.[16] Both of these reviews have been updated since their original publications;[16 17] here we use only the most recent versions.[15, 16] Three other reviews address questions similar to ours but these results are not discussed below because they do not address the question of *comparative* effectiveness and harms. The first is a 2008 broad systematic review of nonsurgical treatments for urinary incontinence in women. Oxybutynin immediate-release and tolterodine extended-release were compared to placebo, but conclusions could not be drawn about the comparison.[18] Another is more than 5 years old and as a result includes almost exclusively placebo-controlled trials.[19] Finally, a systematic review of anticholinergic drugs in patients with lower urinary tract symptoms suggestive of overactive bladder and bladder outlet obstruction includes drugs and study designs not included here.[20]

Key Question 1. For adult patients with urinary urge incontinence/overactive bladder, do anticholinergic drugs differ in effectiveness?

We found 28 head-to-head trials of oxybutynin, tolterodine, trospium, flavoxate, solifenacin, and/or darifenacin.[21-48] All included studies and their respective post hoc analyses are summarized in Evidence Table 1. Quality assessments of the studies are presented in Evidence Table 2.

No good-quality study was found. One study comparing oxybutynin immediate-release and tolterodine immediate-release,[33] 2 studies comparing oxybutynin immediate- and extended-release,[41, 42] and the only 2 flavoxate studies[40, 48] were assessed as poor-quality, and all others were fair-quality. The poor-quality studies suffered from lack of detail about randomization, allocation concealment, and baseline characteristics; lack of randomization; and differences in potentially important baseline characteristics. Eleven studies used an intention-to-treat analysis overall and 3 studies used an intention-to-treat analysis for adverse events, but not for efficacy. The poor-quality studies are not discussed here (see Evidence Tables 1 and 2). Since no fair- or good-quality head-to-head study of flavoxate was found, no results are presented for that drug.

The included studies had similar eligibility and exclusion criteria, largely enrolling patients with urge incontinence. One trial involving trospium and oxybutynin included only patients with a spinal cord injury.[39] Some studies enrolled patients with combined stress and urge incontinence, with symptoms of urge predominant. The studies enrolled significantly more women than men, and although the age ranges of enrolled patients were wide, the mean age for most studies was approaching 60 years. These gender and age trends reflect the typical characteristics of the population with urge incontinence. Ten of 17 fair-quality studies were conducted at least in part in the US, while the others were conducted primarily in European countries, except for a few that were conducted in Asia and Canada.

We found 6 fair-quality studies comparing an immediate-release formulation of one anticholinergic overactive bladder syndrome drug to another.[21, 34, 37-39, 49] Four of these studies compared oxybutynin to tolterodine and all were sponsored by Pharmacia, the maker of tolterodine. Tolterodine was dosed at 2 mg twice daily in all studies while oxybutynin was dosed at 5 mg twice daily in 2 studies[37, 38] and 5 mg 3 times daily in 2 studies.[21, 49] Two studies compared immediate-release formulations of oxybutynin to trospium. One trial was sponsored by a company that makes trospium while the other did not report sponsorship. The study durations ranged from 2 to 54 weeks.

Two studies comparing extended-release formulations of oxybutynin and tolterodine were found.[31, 44] The OPERA trial enrolled 790 women to take either tolterodine extended-release 4 mg or oxybutynin extended-release 10 mg daily for 12 weeks.[31] The manufacturer of oxybutynin extended-release provided the funding for this study. In the second study, the ACET trial, oxybutynin was dosed at 5 to 10 mg once daily and tolterodine at 2 to 4 mg once daily.[44] Funding for this study was not reported. The study design was unusual and problematic in that it consisted of 2 separate trials. One trial randomized patients to 1 of 2 doses of tolterodine in an open label (unblinded) fashion. The other randomized patients to 1 of 2 doses of oxybutynin. Other than the 2 drugs, the same protocol was used at each center. However, the choice of which trial (drug) each center was assigned appears to have been at the discretion of the investigators. Therefore, this cannot be considered a purely randomized trial. The authors state that centers were assigned based on geographic location and prescribing patterns for both drugs, with an effort to produce balance.

The transdermal form of oxybutynin, which received US Food and Drug Administration approval in late February 2003, was studied compared to oxybutynin immediate-release and tolterodine extended-release in separate studies.[30, 32] The study of oxybutynin transdermal compared with oxybutynin oral immediate-release allowed dose titration via patch from 1.3 to 5.2 mg daily or orally from 5 to 15 mg daily.[30] The other study randomized patients to oxybutynin transdermal 3.9 mg daily or tolterodine extended-release 4 mg daily. The manufacturer of the oxybutynin transdermal system funded both studies.

Two studies comparing trospium chloride with oxybutynin immediate-release were found. The first trial conducted in multiple German centers compared trospium 20 mg twice daily (plus a mid-day placebo dose) to oxybutynin immediate-release 5 mg 3 times daily. All the subjects in this trial had spinal cord injuries. No included outcomes for Key Question 1 were reported. The trial is discussed in the section on subpopulations (Key Question 3).[39] The second trial was conducted in multiple European centers comparing trospium 20 mg twice daily with oxybutynin immediate-release 5 mg twice daily. One author of this study was from a pharmaceutical company that manufactures trospium in Europe. Data were collected over an average of 54 weeks at multiple intervals.[34]

One fair-quality systematic review[16] using clinical outcomes reported differences in efficacy between antimuscarinics (oxybutynin, tolterodine, trospium, darifenacin, and solifenacin). The review concluded that solifenacin resulted in significantly greater reductions in episodes of urgency and frequency of micturition compared with tolterodine immediate-release. The original study[50] compared the drugs with placebo in the primary analysis and conducted only "exploratory" analyses comparing tolterodine with solifenacin. The systematic review also concluded that oxybutynin extended-release caused a significantly greater mean reduction in episodes of incontinence and a significant increase in the number of patients who returned to continence than tolterodine extended-release. This difference in episodes of incontinence was not reported as statistically significant in the original OPERA trial[31] and the authors of the systematic review appear to have used a per protocol analysis to calculate relative risk, resulting in a significant difference. The proportion of patients returned to continence was not an outcome measure included to assess efficacy in this systematic review.

Episodes of incontinence and frequency of micturition

Immediate-release compared with immediate-release

The objective measures in these studies were mean change in numbers of episodes of incontinence per 24 hours or micturitions per 24 hours. Four studies compared immediate-release formulations of oxybutynin with tolterodine. One study[38] did not report the actual data for these outcomes but reported that by analysis of variance there were no significant differences between the groups. In the other 3 studies, the range of mean change in micturitions per day in the tolterodine groups was –1.7 to –2.7 and in the oxybutynin groups –1.7 to –2.3. The range of mean change in number of incontinence episodes per day for tolterodine was –1.3 to –2.2 and for oxybutynin was –1.4 to –1.8. One study compared immediate-release formulations of trospium with oxybutynin. Significant differences were not found for frequency of micturition, incontinence, or urgency.[34] No significant differences were found between drugs by intention-to-treat analysis in any study.

Extended-release compared with extended-release

The OPERA trial[31] randomized 790 patients to extended-release oxybutynin 10 mg daily or extended-release tolterodine 4 mg daily for 12 weeks. Forty-seven percent of patients had prior anticholinergic drug therapy for urge incontinence. There was no difference between the groups in the mean change in frequency of urge incontinence (–26.3 compared with –25.5 per week, oxybutynin compared with tolterodine), which was the primary outcome measure. Also, no difference was found in mean change in total number of incontinence episodes. Differences were found in the proportion of patients with no incontinence (23% compared with 17%; $P=0.03$) and in the mean change in micturitions per week (28.4% compared with 25.2%; $P=0.003$) at week 12, in favor of oxybutynin. This study was fair-quality and used the last-observation-carried-forward technique to conduct an intention-to-treat analysis on these efficacy measures.

The other study comparing the 2 extended-release formulations did not report these outcomes.[44]

A fair-quality systematic review evaluated differences in tolerability, safety, and efficacy between oxybutynin and tolterodine extended release formulations.[16] This review found that based on 1 short-term trial, oxybutynin extended-release caused a greater number of patients to return to continence and a greater mean reduction in incontinent episodes than tolterodine

extended-release. In contrast, we concluded, as did the original study,[31] that there is no significant difference in mean reduction of number of incontinent episodes between oxybutynin extended-release and tolterodine extended-release. It appears that this 2005 review found this difference to be statistically significant using a per protocol analysis to calculate relative risk values.

Transdermal compared with immediate-release

A 6-week study comparing transdermal oxybutynin with immediate-release oxybutynin assigned the starting dose depending on the previous dose of oxybutynin (patients were required to have been on oxybutynin for at least 6 weeks and to have had symptomatic improvement).[30] Dose was then titrated to effect or to side effects over the 6-week study period. Seventy-six patients were enrolled. No significant differences were found in this small study in the percent change in mean number of incontinence episodes (66.7% compared with 63.9%) or the proportion of patients with no incontinence during week 6 (21% compared with 26%).

Transdermal compared with extended-release

One study randomized 361 patients to transdermal oxybutynin 3.9 mg daily, extended-release tolterodine 4 mg daily, or placebo.[32] All patients had been taking an anticholinergic drug for incontinence with symptomatic improvement prior to enrollment. The distribution of those taking oxybutynin (oral) and tolterodine prior to enrollment was about even in all groups. No significant differences were found between these drugs on the basis of mean change in number of incontinence episodes per day at 12 weeks (oxybutynin transdermal –2.9, tolterodine extended-release –3.2; P=0.5878) or mean decrease in frequency of micturition (oxybutynin transdermal –1.9 per day, tolterodine extended-release per day –2.2; P=0.2761).

Symptoms and overall assessment of benefit

Immediate-release compared with immediate-release

All 4 studies comparing immediate-release oxybutynin and immediate-release tolterodine reported success based on subjective patient assessments. Two studies[21, 49] used a 6-point scale of symptom severity (0 = no problems, 6 = severe problems). The proportion of patients improving by 1 point or more on this scale was reported in both studies. In the study comparing tolterodine 2 mg twice daily to oxybutynin 5 mg twice daily for 8 weeks,[49] 45% reported improvement on tolterodine and 41% on oxybutynin. In the study comparing tolterodine 2 mg twice daily to oxybutynin 5 mg 3 times daily,[21] 50% of patients taking tolterodine and 49% of patients taking oxybutynin reported improvement at 12 weeks. These findings were not statistically significant.

We also reviewed a study comparing immediate-release tolterodine with immediate-release oxybutynin in Chinese women.[38] Two visual analog scales were used; 1 assessed overall severity of symptoms (0 = no symptoms, 10 = maximum severity), and the other assessed change in symptoms from baseline (–5 = maximum improvement, +5 = maximum deterioration). Overall symptom severity improved by 0.2 for tolterodine and 0.7 for oxybutynin, although the oxybutynin group had a higher baseline score (worse symptoms) than the tolterodine group. Patients' perceived improvement in symptoms from baseline was 1 point for oxybutynin and 2 points for tolterodine. These differences were not statistically significant by intention-to-treat analysis (all randomized patients). However, the assessment of change in symptoms was

statistically significant by a per protocol analysis of patients who completed the study and attended all visits (P=0.047).

In a study of tolterodine 2 mg twice daily compared with oxybutynin 5 mg twice daily, patients were asked if they felt that the study drug had benefited them (yes/no) and if yes, whether it was of little or much benefit.[37] In a per protocol analysis, 45% of tolterodine patients and 46% of oxybutynin patients reported much benefit at 8 weeks.

A study comparing trospium 20 mg twice daily to oxybutynin 5 mg twice daily reported subjective appraisal of efficacy by investigators and patients using a 5 category scale: cure, definite improvement, slight improvement, no improvement, and deterioration. After 52 weeks of treatment physicians rated trospium as "cure" in 29% of cases and oxybutynin immediate-release in 17% of cases. Patients were reported as providing "practically identical figures."[34]

Extended-release compared with extended-release

The OPERA[31] study of extended-release tolterodine and extended-release oxybutynin did not measure frequency of incontinence or micturition.

The other study of extended-release formulations of tolterodine and oxybutynin[44] assessed symptoms at baseline and 8 weeks using the 6-point scale described above. Again, a change of 1 point on the scale was considered "improved." Patients and physicians were also asked to rate the benefit of the assigned study drug at 8 weeks (no, yes–a little, or yes–very much). The proportion reporting improvement on the 6-point scale was 60% on tolterodine 2 mg, 70% on tolterodine 4 mg, 59% on oxybutynin 5 mg, and 60% on oxybutynin 10 mg. Significantly more patients noted improvement on tolterodine 4 mg a day compared with all other groups (P<0.01). An analysis of the degree of change for tolterodine 4 mg and oxybutynin 10 mg indicated that patients reported greater improvement on tolterodine (P<0.01). However, this finding appears to be influenced by the number of subjects in the oxybutynin group with no change. Subgroup analysis indicated that patients with moderate to severe symptoms at baseline also did better on tolterodine 4 mg (77% were improved) than those on oxybutynin 10 mg (65% were improved). The authors reported that there were no statistically significant differences in response between the treatment arms in subgroups of patients who were drug naive or drug experienced at enrollment; however, the proportion with improvement on tolterodine 4 mg was 75% and on oxybutynin 10 mg 54%. By chi-square analysis, this difference is statistically significant (P=0.02). No differences among the 4 groups were found by patient or physician assessment of benefit, although the data were not presented.

This study used an unusual and potentially problematic study design: Centers were chosen by the investigators and assigned to either tolterodine or oxybutynin. Enrolled patients were then randomized to 1 of 2 doses of the assigned drug. Differences between the groups were present at baseline, including race (a higher proportion were white in tolterodine groups), age (younger in oxybutynin groups), and proportion of patients who had previously received anticholinergic drug therapy for overactive bladder syndrome (higher proportion in oxybutynin groups). These differences were not accounted for in the analysis. Considering these differences, the finding of a significant difference in the proportion of patients with prior drug therapy experience who improved with tolterodine 4 mg compared with oxybutynin 10 mg may actually reflect confounding factors or selection bias. Without knowing which drug patients received (and presumably failed) prior to enrollment, it is not possible to rule out important effects on the results. For example those that had received oxybutynin prior to enrollment and were subsequently enrolled to oxybutynin may respond differently to those who were randomized to

tolterodine. Although the authors stated that an intention-to-treat analysis was performed using the last observation carried forward, they also stated that to be included in the analysis patients were required to have been assessed in at least once after randomization. The protocol mentioned only 2 visits, randomization and assessment at 8 weeks, so patients lost to follow-up would have been excluded, and in fact 89 patients were excluded from the analysis due to withdrawal from study between visit 1 and 2.

Transdermal compared with immediate-release

A small, 6-week study comparing transdermal oxybutynin with immediate-release oxybutynin assessed patients' perception of overall treatment efficacy by using visual analog scales at baseline and 6 weeks.[30] No difference was found between the groups, with a change in score of 5.8 for the transdermal group and 6.0 for the immediate-release group.

Transdermal compared with extended-release

A study of 361 patients assigned to transdermal oxybutynin 3.9 mg daily or extended-release tolterodine 4 mg daily used the Incontinence Impact Questionnaire and the Urogenital Distress Inventory to measure quality of life and visual analog scales to measure treatment efficacy "periodically during the trial."[32] It is not clear when these were measured, other than at baseline. There was no significant difference in score for the global assessment of disease state or the 2 quality-of-life instruments used.

Quality of life

Quality of life in patients with urge incontinence has been shown to be significantly lower than quality of life of the general US population.[51-53] However, instruments used to measure quality of life, such as the SF-36, are general and not considered sensitive enough to evaluate changes in quality of life due to treatment of urge incontinence. Measures specific to urinary incontinence have been developed and are used in combination with one of the more general tools. Examples of these are the King's Health Questionnaire and the Incontinence Quality of Life Index, a tool developed for women with urge incontinence.

The effect on quality of life of treatment with tolterodine compared with oxybutynin has been assessed in 2 head-to-head trials,[23, 54] 1 with an open-label extension study of tolterodine.[55] Quality of life also was assessed in 1 randomized trial and 1 open-label extension study comparing immediate-release and extended-release tolterodine with placebo.[56-59] All of these studies assessed patients who completed the study. One also attempted to assess changes in those who withdrew from the trial,[54] but the number of subjects in each arm was not sufficient to allow a comparative analysis. Five studies used the King's Health Questionnaire as the urinary incontinence-specific quality-of-life tool.[54, 56-59]

A 12-week study comparing immediate-release oxybutynin with extended-release oxybutynin measured quality of life with 2 validated questionnaires, the Incontinence Impact Questionnaire and the Urogenital Distress Inventory.[24] Although investigators mentioned significant improvement on these 2 disease-specific quality-of-life scales with both treatments, there are no precise results reported.

A clinical trial comparing immediate-release tolterodine, extended-release tolterodine, and placebo also assessed quality of life during the trial and during an open-label extension. To date, the quality-of-life results comparing immediate-release tolterodine to placebo and

comparing extended-release tolterodine to placebo have been published, but not the comparison of tolterodine immediate-release to extended-release.[56-59] The 12-week trial showed a statistically significant improvement in the tolterodine groups compared with placebo. Differences in mean change on individual domain scores ranged from –0.2 to –8.36. These differences were maintained, and became greater after 3 months and 12 months of open-label treatment.[58] The comparison of extended-release tolterodine to placebo also favored tolterodine on 6 of 10 domains on the King's Health Questionnaire.[57] An analysis of data from a 12-month open-label extension study indicated that patients continued to have similar benefit after 3 and 12 months.[56] In comparisons of results of the King's Health Questionnaire reported for the immediate-release and extended-release forms (in 2 publications), no overall difference is apparent, with differences on individual domains ranging from –1.88 to +1.68.[57, 59]

One 12-week trial compared sexual quality of life in younger women with overactive bladder taking either tolterodine extended-release or placebo. Patients taking tolterodine showed significantly greater improvement of total score on 2 quality-of-life questionnaires, the Sexual Quality of Life Questionnaire-Female and the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire.[60]

A pooled analysis of three 12-week trials comparing darifenacin with placebo found that patients taking darifenacin had significantly greater improvements in the six domains of King's Health Questionnaire relevant to overactive bladder.[61]

In a 12-week study comparing tolterodine and oxybutynin the SF-36 and the Incontinence Quality of Life Index were used to assess quality of life.[62] There were no significant changes from baseline on the SF-36 and no differences between the drug groups. This continued to be true in a 12-month open-label extension study. The experimental Incontinence Quality of Life Index (assessing women only) showed that all groups improved significantly over 12 weeks, but no significant differences were seen between the groups.

A systematic review of antimuscarinic drugs for overactive bladder syndrome included global and disease-specific quality-of-life assessments reported in placebo-controlled trials only.[16] The review found significant differences in quality of life in comparisons of trospium, solifenacin, immediate-release tolterodine, extended-release tolterodine, and transdermal oxybutynin with placebo. Analyses of differences between the drugs were limited with no differences identified.

Indirect evidence

This review uses placebo-controlled trials where direct comparative evidence is unavailable. Most drugs for overactive bladder syndrome are supported by evidence from head-to-head trials. In a 2008 broad systematic review of nonsurgical treatments for urinary incontinence in women, oxybutynin immediate-release and tolterodine extended-release were found superior to placebo in improving continence rates, but conclusions could not be drawn about how the drugs might compare to each other.[18] Another fair-quality systematic review used almost exclusively placebo-controlled trials to evaluate effectiveness of anticholinergic drugs for overactive bladder syndrome; its included trials were published before January 2002. The review concluded that the statistically significant differences between anticholinergic drugs and placebo were small.[19]

Four drugs, flavoxate, scopolamine, hyoscyamine, and trospium extended-release, had no or poor-quality direct comparative evidence, thus their placebo evidence, where available, is reviewed in detail. There was no placebo evidence for hyoscyamine. We also reviewed the

effects of solifenacin and transdermal oxybutynin in pooled analysis of subgroups of patients with different manifestations of overactive bladder (for example, with and without incontinence).

Overall, we found 37 placebo-controlled trials (including 1 unpublished study provided by the manufacturer)[27, 50, 57, 63-96] and 4 systematic reviews[15-18] of drugs used to treat overactive bladder syndrome. A summary of efficacy results, change in frequency of micturition and episodes of incontinence, can be found in Evidence Table 5.

It is important to remember that although all the placebo trials measure similar outcomes, the trials vary greatly in methodological aspects and clinical characteristics of patients enrolled. The patient populations also sometimes differ substantially among trials. Comparing results from these placebo studies is no substitute for a well designed head-to-head trial.

Only 1 included study compared flavoxate[68] with placebo; other studies did not meet the inclusion criteria. This trial compared flavoxate 200 mg 3 times daily to placebo. The difference between flavoxate and placebo in the mean change in frequency of micturitions was not statistically significant (–0.292 times per day; P=0.95).

Six trials compared trospium with placebo.[63, 64, 81, 85, 92, 94] Four of them reported mean change in frequency of micturition and episodes of incontinence, with 3 finding significant differences compared with placebo (Evidence Table 5).[81, 85, 92, 94] Two studies investigated the new extended-release formulation of trospium.[85, 94] Both were 12-week trials comparing trospium 60 mg once daily with placebo, and both found that trospium had better efficacy as measured by mean reduction in frequency of micturition and episodes of incontinence per day. One of the trials reported a mean reduction in number of daily incontinence and micturition episodes compared with placebo, –2.48 compared with –1.93 (P=0.0022) and –2.81 compared with –1.99 (P<0.001), respectively.[94] Similarly, the other placebo trial found a mean reduction in number of daily incontinence episodes and micturitions compared with placebo, –2.4 compared with –1.6 (P<0.001) and –2.5 compared with –1.8 (P<0.001), respectively.

A very small placebo-controlled 2-week trial evaluating transdermal scopolamine in 20 women with detrusor instability showed greater improvements in daytime urinary frequency, nocturia, urgency, and urge incontinence with scopolamine than placebo.[76]

A series of pooled analyses of subgroups of patients from 4 placebo-controlled trials studied the effects of solifenacin in patients with incontinence, without incontinence (dry overactive bladder), polyuria or nocturia, mixed urinary incontinence, or severe symptoms of overactive bladder.[97-101] In the subgroup with incontinence (n=1873), the proportions achieving continence at 12 weeks were 34% with placebo, 51% with solifenacin 5 mg daily, and 52% with 10 mg daily; the actual mean change in the number of incontinence episodes per day were –1.1 with placebo, –1.5 with 5 mg daily, and –1.8 with 10 mg daily (P<0.001 for each drug group compared to placebo).[100] The authors also analyzed subgroups (age <65 or >65) within this subgroup, finding solifenacin to be superior to placebo in most cases. In patients without incontinence (n=975), the mean percent change in the number of urgency episodes per day was 46% with placebo and 75% with either 5 or 10 mg daily solifenacin, and the mean change in actual urgency episodes per day was –2.1 with placebo and –3.2 with solifenacin 5 or 10 mg daily (P<0.001 for each drug group compared with placebo). Micturition frequency was also significantly lower in the drug groups, with a mean percent change of 13% with placebo, 19% with solifenacin 5 mg daily, and 23% with solifenacin10 mg daily.

An analysis of the effect of solifenacin on severe overactive bladder symptoms used 3 definitions of severity: more than 3 incontinence episodes per day (n=599), more than 8 urgency episodes per day (n=741), and more than 13 micturitions per day (n=789).[99] With all 3

definitions, the 10 mg daily dose of solifenacin was superior to placebo in the resolution of incontinence or urgency, normalization of micturition, and reduction in number of episodes of incontinence, micturition, or urgency per day. In contrast, the 5 mg dose was superior to placebo only for percent reduction in incontinence episodes per day and only among the patients who began with more than >13 micturitions per day. The impact on nocturia was not a reported outcome in this analysis.

In the subgroup of patients with a history of mixed urinary incontinence (mixed stress and urge symptoms; n=1041), significantly more patients taking solifenacin achieved continence at 12 weeks (33% with placebo and 43% and 49% with solifenacin 5 and 10 mg daily, respectively)[98] These symptom improvements were associated with improvement in quality of life. Nocturia was not an outcome measured in this analysis.

Two of these pooled subgroup analyses found that only the 10 mg dose of solifenacin was statistically superior to placebo in reducing episodes of nocturia.[101] A separate pooled analysis of only patients reporting nocturia at baseline (n=2534) found that solifenacin was superior to placebo in reducing nocturia in patients without polynocturia (unusually large volumes of urine produced during sleep hours, as defined by Weiss and Blaivis).[97] In this subgroup, 62% had polynocturia, with 602 patients who had data available for the analysis. The mean change from baseline was –0.6 with either dose of solifenacin and –0.4 with placebo (*P*=0.026 for 5 mg, *P*=0.006 for 10 mg compared with placebo). Similarly, more patients in the drug groups than the placebo group achieved less than 1 episode of nocturia per night at 12 weeks; this difference was statistically significant.

An analysis that pooled the results of the 2 placebo-controlled trials of transdermal oxybutynin confirmed the efficacy finding of the individual trials.[102] Median daily number of incontinence episodes was reduced by 3 with oxybutynin and by 2 with placebo patch; frequency of micturition was reduced by 2 with oxybutynin and by 1 with placebo. Dry mouth was experienced by 7% of patients using oxybutynin transdermal and by 5% using placebo.

A post hoc subgroup analysis of a placebo-controlled trial of tolterodine extended-release [90] examined the subgroups of patients with and without incontinence at baseline.[103] For both subgroups, this analysis found similar improvement of urgency symptoms with tolterodine over placebo. Among patients incontinent at baseline (40%), incontinence outcomes also were improved compared with placebo.

1a. Is there a difference in effectiveness between long-acting and short-acting formulations?

We found 8 fair-quality studies comparing the efficacy of an extended-release formulation of an anticholinergic drug for overactive bladder with an immediate-release formulation.[22, 24, 25, 36, 46, 47, 104, 105] Four studies compared extended-release oxybutynin with immediate-release oxybutynin,[22, 24, 25, 47] 1 compared extended-release tolterodine with immediate-release tolterodine,[46] 1 compared extended-release oxybutynin with immediate-release tolterodine,[23] 1 compared extended-release tolterodine with immediate-release oxybutynin,[36] and 1 compared darifenacin with immediate-release oxybutynin.[105] In these studies oxybutynin doses ranged from 5 mg to 30 mg daily, tolterodine was dosed at 4 mg daily, and the darifenacin dose was either 15 mg or 30 mg daily.

Of the 4 studies comparing extended-release oxybutynin with immediate-release oxybutynin, 1 was 6 weeks in duration and compared oxybutynin 10 mg daily, either as

extended-release 10 mg once daily or immediate-release 5 mg twice daily.[25] The other 3 studies[22, 24, 47] used a dose titration up to the threshold of either intolerable side effects (in which case the dose was reduced by 5 mg per day) or maximum efficacy. In 1 study the efficacy analysis was performed with only patients who completed ≥ 2 weeks at the optimal dose and had no major protocol violations.[24] All 4 studies were funded by or had authors from the companies that make the extended-release formulations.

We found only 1 study comparing tolterodine extended-release (4 mg once daily) with immediate-release (2 mg twice daily). A placebo arm was also included in this 12 week-study.[46] This large study included over 500 patients per treatment arm, and it used an intention-to-treat analysis. A study comparing extended-release tolterodine with immediate-release oxybutynin included 600 Japanese or Korean patients.[36] Patients received daily doses of either tolterodine 4 mg or oxybutynin 9 mg. The manufacturer of extended-release tolterodine provided funding; the formulation of immediate-release oxybutynin used in this study is not available in the United States.

One study compared extended-release oxybutynin (10 mg once daily) with immediate-release tolterodine (2 mg twice daily) for 12 weeks.[23] The funding was provided by Alza, the manufacturer of the extended-release form of oxybutynin, and the company employed one of the authors.

Two studies compared solifenacin with tolterodine (one immediate-release and the other extended-release). The first, a fair-quality study, compared solifenacin 5 mg, solifenacin 10 mg, immediate-release tolterodine 2 mg twice daily, and placebo.[50] This study was not powered to show treatment differences between the active treatment arms. Thus, the authors did not conduct a statistical analysis of comparisons between drugs; however, they did perform statistical analyses of each drug compared with placebo. A fair-quality systematic review evaluated differences in tolerability, safety, and efficacy between oxybutynin, tolterodine, trospium, darifenacin, and solifenacin and concluded that based on 1 short-term trial, solifenacin had greater efficacy for some clinical outcomes than tolterodine.[16]

The second study, the STAR trial,[28] was designed as a non-inferiority trial with respect to frequency of micturition; claims of superiority were not intended to be drawn from these data. The trial compared extended-release tolterodine 4 mg with a "flexible" dose of solifenacin (5 mg or 10 mg) over a total of 12 weeks. Patients were randomized to either tolterodine extended-release 4 mg or solifenacin 5 mg for the first 4 weeks. At week 4, solifenacin patients were allowed to increase their dose if they were not satisfied with treatment efficacy. The final dose was maintained for the remaining 8 weeks of the study. The investigators stated that use of flexible dosing allowed the trial to mirror clinical practice as closely as possible. One problem with this trial's analysis should be noted: Data for both doses of solifenacin were combined in the analyses of efficacy and safety outcomes. Thus, it is not possible to determine which dose of solifenacin provided greater efficacy or whether the different doses caused a difference in rates of adverse events. Because the authors did not conduct a statistical analysis of the difference in adverse events between solifenacin and tolterodine, we did a statistical analysis of the adverse event rates of the STAR trial ourselves using the StatsDirect program. The investigators did a post hoc analysis of the STAR trial data to determine which drug most quickly led to improvement.[106] The analysis compared tolterodine with the initial dose of solifenacin (tolterodine extended-release 4 mg compared with solifenacin 5 mg over the first 4 weeks of the trial).

In the final included study, darifenacin (15 mg and 30 mg doses) was compared with immediate-release oxybutynin in a crossover study with 2 weeks in each treatment arm.[105]

Episodes of incontinence and frequency of micturition

Short-acting compared with long-acting drugs

Two fair-quality studies[22, 47] that titrated extended-release or immediate-release oxybutynin to adverse events or efficacy reported no significant difference between groups in the mean change in number of incontinence episodes per week. Converted to mean change in incontinence episodes per day, the mean change in the extended-release groups was -3.2 and -2.2 and in the immediate-release groups was -2.9 and -2.2 in the first and second studies, respectively. Time period from baseline to assessment was not reported. Neither study used an intention-to-treat analysis. Alza, the manufacturer of the extended-release formulation, funded both studies.

A study comparing extended-release oxybutynin (10 mg once daily) with immediate-release oxybutynin (5 mg twice daily)[25] used an extended-release formulation that is not available in the United States. It also used different outcome measures than the other studies: proportion of patients with daytime and nighttime *continence*, day/night micturition, and day/night incontinence. For these reasons, we did not evaluate this study any further.

An additional study comparing titrated "optimal" doses of 10 to 30 mg oxybutynin extended-release once daily (increasing in 5 mg increments) or 5 mg oxybutynin immediate-release twice daily (also maximum of 30 daily) showed that the mean titrated doses were similar, with 15.2 mg for the controlled release version and 14.0 mg for the immediate-release formulation.[24] Baseline reductions in incontinence episodes per 24 hours were 2.0 and 2.4 for the controlled release and immediate-release forms, respectively. Similarly, reductions in micturitions per 24 hours at the end of treatment were 1.8 and 2.4 for extended-release and immediate-release forms, respectively. These differences were not statistically significant. This was a study of an extended-release product introduced into the Canadian market by Purdue Pharma and is currently not available in the United States.

The OPERA study compared extended-release tolterodine 4 mg once daily with immediate-release tolterodine 2 mg twice daily[46] and found no significant difference in mean change (absolute) in frequency of micturition or episodes of incontinence over one week. Converted to per day, the mean change in frequency of micturition was –3.5 times per day (extended-release) and –3.3 (immediate-release), and the mean change in incontinence was –1.6 episodes per day (extended-release) and –1.5 (immediate-release). Mean change in the number of urinary pads used per day was –3.3 in both groups. The median percent change in incontinence episodes was also reported. The percent reduction was 71% for extended-release, 60% for immediate-release, and 33% for placebo. The authors stated that they used the median rather than the mean, and the percent reduction, because the data were positively skewed and they believed the relative change was more relevant than the absolute change. Because few other studies report data in this way, the comparability of these results to other trials is somewhat limited. Overall withdrawal was 12%, with similar rates in the 2 drug treatment groups. In a post hoc analysis of the OPERA trial, women who were anticholinergic drug naïve, efficacy and tolerability outcomes were not different between the drugs, with the exception that oxybutynin extended-release was associated with a lower frequency of micturition (P=0.035).[107] The post hoc analysis did however find differences among the women with anticholinergic experience. Extended-release oxybutynin was associated with significantly reduced micturition frequency compared

with extended-release tolterodine (*P*=0.052). Significantly more women reported no urge incontinence at study endpoint in the oxybutynin extended-release group compared with the tolterodine extended-release group (23.6% compared with 15.1%; *P*=0.038).

Extended-release oxybutynin was compared with immediate-release tolterodine in 1 study.[23] On the basis of an analysis of covariance, with adjustment for baseline and severity of symptoms, oxybutynin extended-release was significantly more effective at reducing the number of incontinence episodes per week (*P*=0.03) and frequency of micturition during the week (*P*=0.02). This analysis was not intention-to-treat; the proportions of patients excluded from the analysis were 14% in the oxybutynin extended-release group and 11% in the tolterodine group. Therefore, due to dropouts, the analysis may not reflect actual reductions in efficacy. Insufficient data were presented for us to calculate the mean change in incontinence or micturitions based on intention-to-treat.

Extended-release tolterodine was compared with immediate-release oxybutynin in Japan and Korea.[36] No significant differences were found in percent change in median number of incontinence episodes, pad use, or frequency of micturition. The median percent change in incontinence episodes was 78.6% for tolterodine and 76.5% for oxybutynin. The absolute change was not reported and again the data were reported to be skewed. The changes in frequency of micturition were –2.1 and –2.0 times per day for tolterodine and oxybutynin, respectively. There was no change in pad use, however.

A study of solifenacin 5 mg or 10 mg once daily and immediate-release tolterodine 2 mg twice daily demonstrated that both doses of solifenacin and tolterodine produced significantly lower mean frequency of micturition than placebo.[50] Solifenacin at both doses, but not tolterodine, resulted in statistically significant improvements in urge and number of incontinence episodes per 24 hours and episodes of urgency. Only solifenacin 10 mg was better than tolterodine for reducing frequency of micturition.

The STAR trial[28] examined the difference between a "flexible" dose of solifenacin 5 mg or 10 mg daily and extended-release tolterodine 4 mg daily using a noninferiority design. Patients administered solifenacin had significantly decreased urgency, incontinence, urge incontinence, and pad usage.[28] However, the study did not demonstrate statistically significant between-treatment differences in the primary endpoint, frequency of micturition, or in nocturia episodes, thus solifenacin was non-inferior to extended-release tolterodine for these measures. Data for both doses of solifenacin were combined for analysis of outcomes.

A post hoc analysis of only solifenacin 5 mg and extended-release tolterodine 4 mg in the initial 4 weeks of the STAR trial showed a significantly greater mean reduction in number of incontinence episodes per 24 hours for solifenacin (–1.30 compared with –0.90; *P*=0.0181).[106]

A head-to-head trial used a crossover design to compare darifenacin (15 mg or 30 mg once daily) with immediate-release oxybutynin (5 mg 3 times daily). Darifenacin (both doses) and oxybutynin were significantly better than placebo for reducing the number of incontinence episodes per day and reducing the frequency of micturition, but no significant difference in efficacy was found between the drugs.[105]

Symptoms and overall assessment of benefit

Short-acting compared with long-acting drugs

One study comparing immediate-release oxybutynin with extended-release tolterodine in Japanese and Korean women assessed subjective outcome measures.[36] Patients were asked to

assess their perception of bladder condition (on a 6-point scale), urinary urgency (on a 3-point scale), overall treatment benefit (on a 3-point scale), and quality of life (measured by the King's Health Questionnaire) at baseline and 12 weeks. There was no difference between the groups based on the change in the patients' perception of bladder condition (improved, extended-release tolterodine 72% compared with immediate-release oxybutynin 73%; the deterioration rate for both treatments was 5% and was 8% for placebo). The patients' assessment of urinary urgency was also similar between the groups (improved ability to hold urine, extended-release tolterodine 49% compared with immediate-release oxybutynin 57%). The treatment benefit was rated "much" by 42% on extended-release tolterodine compared with 53% on oxybutynin. Although both treatments showed a difference in quality of life compared with placebo, no significant differences between treatments were found in any domain of the quality-of-life assessment.

The STAR trial,[28] which compared a "flexible" dose of solifenacin (5 mg daily for 4 weeks followed by either 5 mg or 10 mg daily for 8 weeks) with extended-release tolterodine (4 mg daily), reported that Perception of Bladder Condition scores were significantly better in patients receiving solifenacin than patients on tolterodine. Perception of Bladder Condition is a validated 6-point categorical scale used by patients. A decrease in score signifies improvement in perceived bladder condition. The change in score from baseline was –1.51 for solifenacin and –1.33 for tolterodine. While the difference between drugs was statistically significant (P=0.006), it is only a 3% change on the 6-point scale and the clinical significance is not known.

The post hoc analysis of solifenacin 5 mg and tolterodine 4 mg in only the initial 4 weeks of the STAR trial found a significantly greater mean reduction in pad use for solifenacin (–1.21 compared with –0.80; P=0.0089).[106] The remaining efficacy outcomes included frequency of micturition, incontinence, and nocturia and showed no significant difference between the 2 drugs at 12 weeks.

The head-to-head trial that compared darifenacin (15 mg or 30 mg once daily) with immediate-release oxybutynin (5 mg 3 times daily) found no significant difference in reductions of mean severity of urgency episodes between the drugs.[105]

Key Question 2. For adult patients with urinary urge incontinence/overactive bladder, do anticholinergic incontinence drugs differ in safety or adverse events?

Long-term studies

No long-term head-to-head studies assessed adverse events associated with tolterodine, darifenacin, solifenacin, or flavoxate. We found 1 head-to-head study[34] comparing adverse events for trospium and oxybutynin over an average of 54 weeks (mean follow-up). This study compared trospium 20 mg twice daily with oxybutynin immediate-release 5 mg twice daily. Significant differences were found favoring trospium for adverse events taken as a whole, adverse events having probable or possible connection with trial medications, and for dryness of the mouth. Subjective appraisal of tolerability also favored trospium at 26 and 52 weeks. Overall rates of adverse events were high in both groups (65% for trospium and 77% for oxybutynin).

We found 3 studies of prescription claims data that evaluated the discontinuation rate of new prescriptions for tolterodine or oxybutynin (see Evidence Table 8).[108-110] One study evaluated the proportion of patients discontinuing treatment (not refilling prescription) in a 6-month period in 1998.[108] Thirty-two percent of patients who were prescribed tolterodine,

compared with 22% on oxybutynin, were still refilling their prescriptions at 6 months ($P<0.001$; this difference remained significant after adjusting for age and copayment). The mean time to discontinuation was 59 days for tolterodine and 45 days for oxybutynin; 55% on tolterodine never refilled the original prescription compared with 68% on oxybutynin. While the differences are significant, the numbers apparently discontinuing treatment are high in both groups.

In another study of a pharmacy claims database, patient records were evaluated over a 12-month period following the initial prescription for tolterodine extended-release or oxybutynin extended-release or immediate-release.[110] Inpatients were included. The researchers identified 33 067 patient records for the study, with 50% showing tolterodine extended-release and 25% and 26% showing oxybutynin extended-release and immediate-release, respectively. Compliance (based on prescription refills) was not found to be different between tolterodine extended-release and oxybutynin extended-release, but oxybutynin immediate-release was stated to be lower (no statistical analysis presented). Persistence rates were low overall but highest for tolterodine extended-release (mean 139 days) followed by oxybutynin extended-release (mean 115 days) and then oxybutynin immediate-release (mean 60 days). The difference was statistically significant at months 1, 2, 3, and 12 ($P< 0.001$) for the comparison of tolterodine extended-release to either formulation of oxybutynin. Differences at other months were presumed by the study authors to be nonsignificant (data not reported).

The third study used a Medicaid claims database, excluding records of patients eligible for Medicare or in institutions.[109] The researchers identified 1637 patient records for the study. In this study, only 11% were taking tolterodine extended-release, 13% were taking oxybutynin extended-release, and 76% were taking oxybutynin immediate-release. Notably, 30% of oxybutynin immediate-release users were under 18 years old. In this study, only 32% of patients on oxybutynin immediate-release and 44% of those on either tolterodine or oxybutynin extended-release continued to take the drugs after 30 days ($P<0.001$). The 1-year persistence rates were 5%, 9%, and 6% for oxybutynin immediate-release, tolterodine extended-release, and oxybutynin extended-release, respectively ($P=0.086$). In a Cox regression model adjusting for age, sex, and race, persistence was not different between oxybutynin immediate-release and tolterodine extended-release. In this analysis, oxybutynin extended-release had a higher risk of nonpersistence after 30 days than tolterodine extended-release (no difference in the first 30 days). An analysis of risk for nonpossession (similar to compliance measures based on days' supply provided) indicated no difference between the drugs. Similarly, an analysis of switching from the index drug showed "little difference," with 6% switching drug.

We found 5 open-label studies of tolterodine: one 12-week uncontrolled study[111] and four 9-to-12-month extension studies following randomized controlled trials.[55, 112-114] Overall adverse event reporting was high (see Evidence Table 8). Dry mouth was the most common adverse event reported, occurring in 13% to 41% of patients. In the short-term study 8% of cases were classified as severe while longer-term studies reported severe dry mouth in 2% to 3% of patients. Other reported adverse events included urinary tract infection, headache, and abdominal pain. The longer studies reported 3 to 5 serious adverse events and classified them as possibly or probably related to tolterodine. These included urinary retention, worsening of multiple sclerosis, pulmonary edema, tachycardia, hernia, abdominal pain, constipation, and dyspepsia/reflux. Between 8% and 15% of enrolled patients withdrew because of adverse reactions. Two studies[55, 114] reported that dry mouth accounted for only 1% to 2% of patients withdrawing overall.

An uncontrolled 12-month open-label extension of 4 randomized placebo-controlled trials for tolterodine immediate-release evaluated a total of 714 patients.[113] The number of

withdrawals due to adverse events was 105 (15%) with dry mouth reported by 41% of all patients. Dose reduction was offered for patients with tolerability problems. In a 12-month open-label extension of the previously cited head-to-head comparison of tolterodine extended-release and oxybutynin immediate-release, all patients were offered tolterodine extended-release 4 mg.[113] The most frequent adverse event in this extension was dry mouth, reported by 33.5% of patients during the 12 months, which was lower than levels (36.8%) found in the 12-week original study. There was a 1% withdrawal rate due to adverse events over the 1ong-term study. It is not clear whether patients in either of these 2 studies were also included in previously reported studies that also combine data from patients followed after participating in randomized controlled trials.[112, 113]

In addition to these open-label prospective studies, we reviewed 2 uncontrolled studies identifying patients by new tolterodine prescriptions.[115, 116] One study evaluated adverse events and tolerability over 12 weeks.[116] Only 4% of patients reported any adverse event, with dry mouth being the most common (2%). The other study[115] identified all new prescriptions for tolterodine in the United Kingdom in a 6-month period and asked the prescribing general practitioners to retrospectively complete a standard form assessing adverse events at 3 and 9 months. Overall, the physicians reported 3634 events, 13% classified as an adverse drug reaction. Dry mouth was the most common, accounting for 2.9% of all events and 0.5% of all adverse drug reactions. Dry mouth was followed by unspecified adverse events, headache or migraine, and urinary tract infection. Withdrawals due to adverse events occurred in 4.8% overall, with 1.7% due to dry mouth.

One observational study evaluating implementation of a toileting program that included tolterodine for nursing home residents who did not respond to a drugless protocol did not meet our criteria for efficacy but did report adverse events data.[117] This study found that 4% (2 patients) of participating residents had their dosage of tolterodine reduced due to dry mouth (1 patient) and nausea (1 patient). One patient was taken off tolterodine because of increased confusion and increased back and leg pain.

An open-label 12-week study of oxybutynin reported 59% of patients with dry mouth, moderate to severe in 23%.[118] Similar to the open-label tolterodine studies, withdrawals due to adverse events were 8.0% overall, 1.6% due to dry mouth.

Solifenacin safety and tolerability was studied in a long-term, 40-week open-label extension study[119] that included patients who had completed 1 of 2 different trials: a placebo-controlled 12-week trial that compared solifenacin 5 mg and 10 mg to placebo[66] or a placebo-controlled trial[50] that compared solifenacin 5 mg, solifenacin 10 mg, tolterodine immediate-release 2 mg twice daily, and placebo. In the extension study, 81% of patients who began the study completed all 40 weeks; 4.7% of patients withdrew due to adverse events. Of the patients who completed this study, 20.7% reported dry mouth, 9.6% reported constipation, and 6.9% reported blurred vision.

A 2-year open-label extension study of 2 previous placebo trials[70, 78] assessed the tolerability of darifenacin 7.5 or 15 mg[120] in 716 patients. Results showed 343 (47.9%) patients with treatment-related adverse events: dry mouth in 166 (23.3%), constipation in 142 (19.8%), urinary tract infection in 8 (1.1%), dyspepsia in 37 (5.2%), and headache in 14 (2%). There was 1 serious adverse event, 64 patients (8.9%) withdrew due to adverse events, and 46 (6.4%) withdrew due to treatment-related adverse events.

Open-label extension studies are only generalizable to the patient populations included in the trials and to patients who responded adequately to the drug used in the extension study.

Two poor-quality observational studies of tolterodine and oxybutynin are not discussed here.[121, 122]

Short-term trials

Adverse events reported in short-term head-to-head trials are summarized in Evidence Table 10. The overall adverse event rate was high in all the studies, ranging from 49% to 97%. The most common adverse event in all studies was dry mouth. The risk of dry mouth was 28% lower with tolterodine immediate-release than with oxybutynin immediate-release (pooled risk difference –0.28, 95% CI –0.34 to –0.21). Two of these studies[37, 123] reported the incidence of severe dry mouth with tolterodine and oxybutynin: 1% compared with 5% (not significant) in one study[124] and 4% compared with 15% (P=0.01) in the other.[123] The other study reported that more patients on oxybutynin than on tolterodine reported severe dry mouth, but numbers were not reported. One additional study[38] assessed dry mouth using a xerostomia questionnaire. It found significant deterioration on all measures of the scale (except denture fit) for both drugs, with no difference between them.

A Cochrane review of this evidence suggests that there may be fewer withdrawals due to adverse events and lower risk of dry mouth with tolterodine than oxybutynin.[15] The authors also conclude that although there is insufficient evidence to claim differences in withdrawals due to adverse events for the extended- compared with the immediate-release forms of oxybutynin and tolterodine, there is less risk of dry mouth with the extended-release drugs.

One short-term trial comparing trospium with oxybutynin immediate-release found a higher incidence of severe dry mouth in oxybutynin immediate-release, 23% compared with 4%, though overall adverse events were comparable.[39] Overall incidence of adverse events was high.

The 4 studies comparing oxybutynin immediate-release and oxybutynin extended-release showed inconsistent results. Two studies using an extended-release formulation available in the US reported lower incidence of dry mouth and adverse events with the extended-release than immediate-release formulation.[22, 47] These studies also reported a higher incidence of severe dry mouth with the immediate-release formulation, especially as doses increased. Both studies showed a larger difference in moderate to severe dry mouth at 10 and 15 mg levels than at 5 mg daily levels. But at a dose of 20 mg daily one study[47] showed a small difference and the second[22] showed a much larger difference. This second study also allowed 25 and 30 mg daily doses of the extended-release formulation; these two higher doses resulted in similarly higher proportions of patients with moderate to severe dry mouth than lower doses.

Two studies used extended release products that are not available in the United States and found results that were somewhat different to those in the studies above in that the immediate-release product was not consistently inferior to the extended-release product in terms of adverse events.[24,25] A study conducted in the UK using an extended-release formulation made in Finland reported higher rates of dry mouth but lower rates of overall adverse events in the extended-release group.[25] A study conducted in Canada, using a product not available in the United States, showed a slightly higher withdrawal rate due to adverse events for the immediate-release form compared to the extended-release form (20% compared with 17%, nonsignificant) but reported numbers of patients with dry mouth that were similar for the formulations.[24] Most other adverse events in this study were reported in greater numbers for oxybutynin immediate-release, but again differences were not statistically significant.

Differences between tolterodine extended-release and immediate-release in overall adverse event rates were not found in a large 12-week study, but a slightly lower rate of dry mouth (risk difference –7%, 95% CI –12% to –2%) with the extended-release form.[46]

The study of tolterodine extended-release compared with oxybutynin immediate-release found significantly fewer patients reporting dry mouth with tolterodine extended-release (33.5%) than with oxybutynin immediate-release (53.7%, $P<0.001$).[36] Overall adverse events were not reported in a way that could be directly compared.

The study of oxybutynin extended-release compared with tolterodine immediate-release found no difference in overall reports of adverse events and a nonsignificant reduction in the proportion of dry mouth.

In the better-quality study of the extended-release formulations of oxybutynin and tolterodine (OPERA study), dry mouth was the most common adverse event noted and was significantly more frequent in the oxybutynin extended-release group than the tolterodine extended-release group (29.7% compared with 22.3%; $P=0.02$).[31] While not reaching statistical significance, the number of patients with dry mouth (mild to severe) was greater in the oxybutynin group. A post hoc analysis of the OPERA study looked more closely at the incidence, severity, and tolerability of dry mouth.[125] When dry mouth was stratified by severity (mild, moderate, or severe), there was no significant difference between the drugs. This is important because more severe cases of dry mouth are very relevant from the patient perspective and these cases may be more inclined to discontinue use. But for dry mouth of any severity there was a significantly higher frequency of dry mouth with oxybutynin extended-release than tolterodine extended-release (28.1% compared with 21.6%; $P=0.039$).

The other study comparing the extended-release formulations of tolterodine and oxybutynin used visual analog scale to assess change in adverse event severity.[44] The authors reported a dose-dependent change for both drugs but a statistically significant increase only for oxybutynin 10 mg once daily, not tolterodine 4 mg once daily ($P=0.03$). Other reported adverse events included headache, abdominal pain, constipation, micturition disorders, urinary tract infections, dizziness, somnolence, and vision disturbances. The rates of occurrence of these events and the overall rate of adverse events varied from study to study, reflecting differences in the identification and classification of adverse events.

A small 6-week study comparing transdermal with immediate-release oxybutynin found a much higher rate of dry mouth in the immediate-release group (39% compared with 82%, $P<0.001$), the highest incidence reported in any study.[30] On an unvalidated questionnaire the severity of dry mouth appeared worse in the immediate-release group, but few patients rated the dry mouth as "intolerable." All patients had been taking immediate-release oxybutynin before enrollment and 67% on transdermal reported a reduction in dry mouth compared to 33% on immediate-release. However, overall adverse event rates were not reported.

A 12-week study comparing transdermal oxybutynin with extended-release tolterodine found fewer systemic adverse events among patients in the transdermal oxybutynin group, including dry mouth, but the difference did not reach statistical significance.[32] Application site reactions were reported in 26% of the transdermal oxybutynin group and 5.7% in the placebo patch group.

In a comparison of varying doses of extended-release darifenacin and immediate-release oxybutynin, visual nearpoint (a measure of the anticholinergic effect on vision) was not statistically different between the drugs.[26]

The STAR trial, which was designed as a noninferiority trial, compared solifenacin (5 mg or 10 mg) with tolterodine extended-release (4 mg). Data from the solifenacin groups were combined in reporting of adverse events. Because the authors did not do a statistical analysis comparing the rates of the adverse events for the two drugs, we conducted our own statistical analysis. The most commonly reported adverse events with both drugs were dry mouth (30% for solifenacin, 24% for tolterodine; $P<0.05$), constipation (6.4% for solifenacin, 2.5% for tolterodine; $P=0.009$), and blurred vision (0.7% for solifenacin, 1.7% for tolterodine; NS).[28] Withdrawals due to adverse events did not differ significantly between groups (3.5% of patients receiving solifenacin, 3.0% for tolterodine). A subanalysis of the STAR trial compared only the 5 mg dose of solifenacin (the "no dose increase" subgroup) with tolterodine extended-release over 12 weeks.[106] Solifenacin was associated with slightly higher incidence of dry mouth (27.6 % compared with 24.0%) and constipation (4.0% compared with 2.4%, significance not reported), while the tolterodine group had a somewhat higher incidence of blurred vision (0.3% compared with 2.4%, significance not reported).

A trial comparing solifenacin 5 mg, solifenacin 10 mg, and tolterodine immediate-release 4 mg to placebo reported incidence of dry mouth as follows: 14% of the solifenacin 5 mg group, 21.3% of the solifenacin 10 mg group, 18.6% of the tolterodine group, and 4.9% of the placebo group.[50] These differences were not statistically significant by chi-square analysis. The incidence of constipation was 7.8% for solifenacin 10 mg, 7.2% for solifenacin 5 mg, 2.6% for tolterodine, and 1.9% for placebo. The comparisons of tolterodine with each solifenacin dose were statistically significant and favored tolterodine ($P<0.05$ for both). Similarly, blurred vision was reported by 5.6% of solifenacin 10 mg patients, 3.6% of solifenacin 5 mg patients, 1.5% of tolterodine patients, and 2.6% of placebo patients. The comparison of tolterodine and solifenacin 10 mg is statistically significant by chi-square analysis ($P=0.0115$). The percentage of patients withdrawing due to adverse events was lowest for tolterodine (1.9%), followed by solifenacin 10 mg (2.6%), solifenacin 5 mg (3.2%), and, lastly, placebo (3.7%), all not statistically significant by chi-square analysis.

Darifenacin 15 mg and 30 mg were compared with oxybutynin immediate-release 5 mg and with placebo in an 8-week, 4-way crossover study (2 weeks each drug).[105] This study found significantly higher incidence of dry mouth with oxybutynin than darifenacin 15 mg (36.1% compared with 13.1%) and of constipation with darifenacin 30 mg than oxybutynin (21.3% compared with 8.2%). No other between-drug differences in adverse events were significant, including for blurred vision and dizziness.

A fair-quality systematic review evaluated differences in tolerability, safety, and efficacy between oxybutynin, tolterodine, trospium, darifenacin, and solifenacin.[16] This review found that tolterodine extended-release had significantly lower all-cause withdrawals compared with placebo and no significant difference for solifenacin and darifenacin. Patients treated with oxybutynin immediate-release had a greater risk of withdrawing from treatment than patients on placebo. Mixed results were reported for adverse event profiles. For instance, the authors found that compared with placebo, oxybutynin immediate-release (based on a single study) and tolterodine immediate-release and extended-release showed the most favorable adverse event profile. However, the active-control trials showed that oxybutynin immediate-release had high rates of moderately to severely dry mouth. Oxybutynin immediate-release was found to have a greater rate of dry mouth compared with oxybutynin extended-release, oxybutynin transdermal, and tolterodine extended-release and immediate-release in the meta-analysis. Further, there was evidence that oxybutynin transdermal had a lower rate of dry mouth and, in one study, greater

rate of withdrawal due to adverse event (skin reactions at application site) than tolterodine extended-release. It should be noted that this fair-quality review excluded observational studies which can be relevant for evaluation of safety and tolerability in more broadly inclusive populations and over longer time periods.

Central nervous system adverse events

Adverse events of the central nervous system, such as confusion and reduced cognition, can occur with anticholinergic and antimuscarinic drugs for incontinence, but we found only very limited comparative evidence on the relative incidence or severity of these adverse events. A subanalysis of central nervous system adverse events in the OPERA trial (tolterodine extended-release compared with oxybutynin extended-release) showed a similar low incidence of these specific adverse events in both drugs.[29] The incidence of withdrawal from the study due to central nervous system adverse events was 0.15% for oxybutynin extended-release and 0.005% for tolterodine extended-release (no significant difference). No other studies of comparative central nervous system adverse events were found.

Withdrawal from studies due to adverse events

Withdrawals due to adverse events may be a better indicator of drug tolerability than overall incidence of adverse events. And of course a large number of withdrawals also negatively impact the overall effectiveness of a drug. In 3- to 12-month open-label extension studies of tolterodine (extended-release or immediate-release) the rate of withdrawal due to adverse event ranged from 8% to 15%, with the higher rates in the longer studies. Observational studies reported much lower rates of withdrawal due to adverse event (3% to 5%), reflecting a less sensitive measure of reason for withdrawal. The one 3-month open-label extension study of oxybutynin extended-release reported a withdrawal rate of 8%. A 54-week trial comparing oxybutynin immediate-release with trospium reported an overall withdrawal rate of 25.0% for trospium and 26.7% for oxybutynin immediate-release, with all adverse-event-related withdrawals at 5.9% for trospium and 10.0% for oxybutynin immediate-release.[34] Withdrawals related to adverse events felt associated with the drugs were higher for oxybutynin, 6.7% compared with 3.7% for trospium.

Three 12-month extensions of randomized controlled trials looking at tolterodine immediate-release (2 mg twice daily), tolterodine extended-release (4 mg once daily), and solifenacin (5 mg or 10 mg once daily) reported withdrawal rates due to adverse events of 15%,[113] 10.1%,[126] and 4.7%,[119] respectively for the tolterodine groups. The extension study of tolterodine extended-release (4 mg once daily),[126] with a withdrawal rate of 10%, included somewhat older patients (mean 64 years) while the other 2 studies[113, 119] included slightly younger patients (mean 56 to 60 years). In the study of solifenacin,[119] which had the lowest rate of withdrawal, 22% of participants were men, whereas the tolterodine extended-release and immediate-release studies had 34.6% and 32.5% men, respectively.

In short-term head-to-head trials, the rate of withdrawal due to adverse event with tolterodine immediate-release ranged from 5% to 15%, with oxybutynin immediate-release ranged from 4% to 17%, and with trospium was 6%.[127] The rates of withdrawal due to adverse event for tolterodine extended-release ranged from 5% to 6%; for oxybutynin extended-release, 3% to 14%; and for transdermal oxybutynin, 3% to 11%. Six of 7 studies comparing tolterodine

with oxybutynin in any formulation found a lower rate of withdrawal with tolterodine that reached statistical significance in 4 studies.[21, 32, 36, 44]

An additional 9-week study comparing oxybutynin immediate-release with oxybutynin extended-release showed slightly higher withdrawal rates due to adverse events for the immediate-release form (20% compared with 17%).[24]

The single short-term trospium trial reported 16% all-cause withdrawal with oxybutynin immediate-release and 6% withdrawal with trospium.[39]

One study[23] found no difference between tolterodine immediate-release and oxybutynin extended-release but in this study reporting of withdrawals due to adverse events included used a different definition by including patients who withdrew due to intercurrent illnesses and therefore may not be accurate. In another study, withdrawals due to adverse events were lower in the tolterodine extended-release group (5.0% compared with oxybutynin immediate-release 17.1%, $P<0.001$), as were withdrawals due to dry mouth (tolterodine extended-release 0.4% compared with oxybutynin immediate-release 9.4%).[36] Three studies[22, 46, 47] comparing immediate-release to extended-release forms of one drug (tolterodine or oxybutynin) found no significant difference in the rate of withdrawals based on the formulation used.

In a fair-quality study of tolterodine extended-release and oxybutynin extended-release (OPERA trial),[31] withdrawal from the study due to adverse events did not differ between the groups (5.1% compared with 4.8%), although the number of patients withdrawing due to dry mouth was higher in the oxybutynin extended-release group (7 compared with 4 in the tolterodine extended-release group). In addition, the number lost to follow-up was noticeably higher in the oxybutynin extended-release group than the tolterodine extended-release group (13 compared with 3).

Subanalysis of the OPERA trial showed that withdrawal due to adverse events of the central nervous system occurred in 0.15% and 0.005% of oxybutynin extended-release and tolterodine extended-release groups, respectively (not significantly different).[29] An additional post hoc analysis of the OPERA study showed a non-significant difference in withdrawal due to dry mouth.[125]

A study of transdermal oxybutynin compared with extended-release tolterodine found a significantly higher rate of withdrawal in the transdermal oxybutynin group (11% compared with 1.7%), mostly due to application site reactions.[32] A small study comparing transdermal with immediate-release oxybutynin found no difference in withdrawal rate, with only 1 withdrawal per group in the 6-week study.

A fair-quality systematic review found that tolterodine extended-release was associated with significantly fewer all-cause withdrawals than placebo.[16] This review also reported significant differences in the active-control comparisons, which favored oxybutynin extended-release, tolterodine immediate-release, and tolterodine extended-release over oxybutynin immediate-release.

A very short trial comparing darifenacin with oxybutynin reported 3 treatment-related withdrawals due to adverse events overall.[26] The study, designed as a crossover, included a total of only 65 participants, who were divided into 3 cohorts; not all members of each cohort participated in all of the measurements.

The STAR trial, comparing the difference between solifenacin (5 mg or 10 mg) and tolterodine extended-release (4 mg) reported withdrawals due to adverse events for all patients receiving solifenacin (3.5%) and for patients receiving tolterodine (3.0%).[28] Our statistical analysis found that this difference was not significant. A post hoc analysis comparing solely the

5 mg dose of solifenacin (the "no-dose-increase" subgroup) with tolterodine extended-release found that over 12 weeks both groups had a comparable incidence of withdrawal due to adverse events (1.3% solifenacin compared with 2.8% tolterodine).[106]

One placebo-controlled trial[50] reported an apparently lower rate of withdrawal due to adverse events among patients receiving tolterodine immediate-release (1.9%) than those receiving either solifenacin 10 mg (2.6%) or solifenacin 5 mg (3.2%); the rate was the highest for patients taking placebo (3.7%). These differences were not statistically significant.

2a. Is there a difference in adverse events between long-acting and short-acting formulations?

Immediate-release compared with extended-release tolterodine

Short-term studies

In a 12-week head-to-head placebo-controlled trial of extended-release and immediate release formulations of tolterodine, rate of dry mouth was 23% for extended-release tolterodine, 30% for immediate-release, and 8% for placebo. Rate of constipation was 6% for extended-release, 7% for immediate-release, and 4% for placebo.[46] Withdrawal due to adverse event was almost identical: for extended-release, 5.3%; for immediate-release, 5.5%; and for placebo, 6.5%. These rates differ statistically significantly.

There were 2 additional short-term observational trials, one each measuring tolerability of tolterodine immediate-release and extended-release.[111, 116] All observational trials are summarized in Evidence Table 8. The study of varying doses of the short-acting formulation reported 4.1% of patients had an adverse event, 2% had dry mouth, and 3% withdrew due to one or more adverse events.[116] It is not entirely clear how adverse events were assessed. In the trial of tolterodine extended-release 4 mg, authors reported that16% of patients had dry mouth and 8% withdrew from the study due to adverse events.[111]

Long-term studies

We found 5 longer-term observational studies, 3 for tolterodine extended-release and 2 for the immediate-release formulation.[55, 113, 114, 121, 126] All trials reported rates of dry mouth ranging from 7.8 % to 33.5% for tolterodine extended-release and from 28% to 41% for tolterodine immediate-release. The withdrawal rates due to adverse events were more consistent, ranging from 2.8% to 10% for tolterodine extended-release and from 9% to 15% for tolterodine immediate-release. Overall rates of adverse events were inconsistently reported and were spread from 10% to 77%, thus not useful for conclusions. It is essential to note that trial designs varied from frequent provider visits and elicitation of adverse events to phone or postal surveys of experience with drugs; design could have substantially influenced the outcome of reported adverse events.

Immediate-release compared with extended-release oxybutynin

Short-term studies

There were 4 studies comparing long-acting with short-acting formulations of oxybutynin.[22, 24, 25, 47] The data are summarized in Evidence Table 10. Two of these trials have an unclear duration

of follow-up[22, 47] but report significantly more dry mouth with oxybutynin immediate-release than with oxybutynin extended-release (48% compared with 59%; *P*=0.007[22] and 68% compared with 87%; *P*=0.04).[47] Adverse event rates for extended-release and immediate-release formulations were 28% and 17% for blurred vision, 28% and 38% for dizziness, and 30% and 31% for constipation. Rate of withdrawal due to adverse event was 3% for extended-release and 6% for immediate-release in one trial and 4% for both groups in the other trial, overall very low. Without reporting statistical significance, another 4-week trial found that dry mouth was somewhat more frequent with oxybutynin immediate-release (72%) than extended-release (68%). For dry mouth considered moderate-to-severe, the incidence was 45% with immediate-release oxybutynin and 38% with extended-release.[24] Withdrawals due to adverse events were similar between formulations (immediate-release, 20%; extended-release, 17%). Another 4 week trial did not find higher rates of dry mouth in the immediate-release group (17%) than the extended-release group (23%); however, overall adverse events were higher for oxybutynin immediate-release (67%) than extended-release (55%). Statistical significance was not reported for these comparisons.[25] It is important to note that this trial included a run-in phase to establish tolerability, during which patients with adverse events were excluded. All of the above oxybutynin immediate-release compared with extended-release studies included some type of dose titration for both long- and short-acting formulations, which may have affected the adverse occurrences and made it difficult to make any conclusions about better tolerability.

We found a 12-week observational trial of various doses of oxybutynin extended-release that reported dry mouth in 59% of patient and withdrawal due to adverse event by 8%.[118]

Long-term studies

There was only 1 longer-term study of oxybutynin immediate-release. No details of adverse events were contained, but an overall adverse event rate was reported as 34.8% and withdrawal due to adverse event occurred in 43.2% of patients.[122] Although the longest observational trial, it was administered as a single phone or postal questionnaire 2 years after baseline, limiting its value for conclusions.

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or comorbidities for which one anticholinergic incontinence drug is more effective or is associated with fewer adverse effects?

The included studies generally enrolled ambulatory populations in the 50 to 60 year-old age range (mean), with more women than men.

Age

No head-to-head or observational studies conducted in long-term care facilities met inclusion criteria. A placebo-controlled study of oxybutynin added to a program of prompted voiding in a long-term facility found a statistically significant reduction in incontinence episodes in the oxybutynin group (-2.0) compared to the placebo group (- 0.9).[128] A 12-week, randomized, placebo-controlled trial[82] found no significant difference in efficacy, safety, or tolerability

between younger (<65 years) and older (≥65 years) women taking tolterodine extended-release 4 mg.

Two studies examined effects of darifenacin in older adults with overactive bladder syndrome: a pooled analysis of data from the subgroups of patients ≥65 years old in 3 placebo-controlled trials[129] and an open-label extension study of patients ≥65 years from 2 of these trials.[130] Patients enrolled in the trials (pooled N=317, mean age 72 years) were highly functioning, ambulatory adults, although with numerous comorbidities. The difference in the median change in the number of incontinence episodes per week was statistically significantly greater with darifenacin 7.5 mg or 15 mg than placebo, with median differences of –5.9 (95 % CI -9.1 to -2.2) and –4.1 (95% CI -6.4 to -1.6) times per week, respectively. While statistical analyses were not performed, in darifenacin 7.5 mg, darifenacin 15 mg, and placebo groups the incidence of dry mouth was 21%, 31%, and 5%, respectively; of constipation was 19%, 24%, and 6%; and of new treatment for constipation was 4%, 10%, and 2%. The incidences of dry mouth, constipation, and dyspepsia were highest in the 15 mg group but cardiovascular and central nervous system adverse events were rare in all groups. From 2 of these trials, 217 patients entered a 2-year extension study where the dose was started at 7.5 mg daily and could be adjusted to 15 mg daily. The incidence of dry mouth (23.4%) and constipation (22.4%) were high, although withdrawals due to adverse events remained low (2% to 4%).

Similarly, post hoc analyses of patients from 4 placebo-controlled trials (N=1045) and an extension study (N=509) of solifenacin 5 mg or 10 mg daily were done to examine effects in patients ≥65 years old.[131] The mean age in these subgroups was 72 years. The difference in the median change in the number of incontinence episodes per week compared with placebo was –2.1 for solifenacin 5 mg daily and –5.6 for 10 mg daily (both statistically significant). In this analysis, the incidence of dry mouth was also greater in the drug groups: 14% with 5 mg daily, 32% with 10 mg daily, and 4.5% with placebo. Rates of constipation were 9%, 18%, and 4% for 5 mg daily, 10 mg daily, and placebo, respectively. The incidence of urinary tract infection was higher in the 10 mg group (7%) than the 5 mg group (4%) and placebo (3%) group. Rates of these adverse events in the 40-week extension study were similar, with the exception of a somewhat lower rate of dry mouth with the 10 mg dose (22%).

Gender

Little is known about potential differences between men and women in the efficacy or adverse events related to drug therapy for overactive bladder syndrome. Three studies provide some evidence comparing effects in men and women.[43, 45, 132] A subgroup analysis of a study comparing tolterodine immediate-release with tolterodine extended-release assessed the subgroup of 1235 women in the study population. Women had a statistically significant benefit favoring tolterodine extended-release in the mean change in incontinence episodes per week; however, the absolute difference was very small (extended-release, –11.8; immediate-release, –10.1; P=0.036). Differences found in the overall trial sample (including both men and women) were not statistically significant. In the subgroup of women, dry mouth was slightly higher in the immediate-release group (extended-release 25.3% compared with immediate-release 31.2%) but rate of withdrawal due to adverse events was not different.

A subanalysis of data from women in atrial comparing oxybutynin extended-release to tolterodine immediate-release (known as the OBJECT trial) demonstrated that oxybutynin extended-release was significantly more effective with regard to urge incontinence, episodes of

incontinence, and frequency of micturition in women age 64 years or younger. These findings are not meaningfully different from those found in the overall study population including both men and women, which was largely women in this age group.[43]

In a post hoc pooled analysis of data from 2 placebo-controlled trials of tolterodine extended-release, data regarding urgency of micturition was analyzed separately for men and women.[132] Using data on the degree of urgency recorded by patients for each micturition, the authors assigned an urgency using a scale of 1 to 5. Urgency of 1 to 2 was "nonoveractive bladder syndrome," 3 to 5 was "overactive bladder syndrome," and 4 to 5 was "severe overactive bladder syndrome." The overlap between overactive bladder syndrome and severe overactive bladder syndrome is not explored or explained. Compared with placebo, tolterodine extended-release was superior in reducing frequency of micturition overall, micturition associated with urgency of 3 to 5, and with urgency of 4 to 5 during the 24-hour period in both men and women, and during the daytime in women. During the night, tolterodine was *not* superior to placebo in reducing the overall frequency of micturition (number of micturition episodes in 24 hours, the primary outcome measure in the trials) in men or women. Data for men indicated that tolterodine extended-release was superior in reducing only overall frequency of micturition, micturition associated with severe overactive bladder syndrome, and less frequent nocturnal micturition associated with overactive bladder syndrome compared to placebo. In women less frequent nocturnal micturition associated with overactive bladder syndrome and severe overactive bladder syndrome compared to placebo was found. Limitations in the design of this study preclude conclusions about gender differences in response to tolterodine extended-release.

While a few included studies enrolled only women, they do not provide information on differences in response based on gender, and thus are reported only in key question(s) 1 and 2.

Gender and Age

One open-label, 3-month observational study of 2250 patients prescribed tolterodine analyzed data to assess the effect of age and gender on efficacy and adverse events.[116] A multiple logistic regression analysis of 1930 patients with complete urinary diary information (not an intention-to-treat analysis) was conducted using age, gender, baseline symptom severity, global tolerability, efficacy ratings, and tolterodine dose as the variables. In this study, mean age was 61 years and 77% of the patients were female. Age was associated with a decrease in efficacy in reducing frequency, urgency, incontinence, and global efficacy rating ($P \leq 0.0001$). While these effects were significant statistically, the differences were small. Male gender was associated with greater reduction in incontinence ($P=0.02$), but not frequency or urgency, and was also associated with a *lower* global efficacy rating ($P=0.0002$). Gender and age were not shown to be associated with the global tolerability rating.

An observational study of tolterodine over a 6-month period assessed the effect of age and gender on the incidence of hallucinations and palpitations/tachycardia.[115] In this study, physicians were asked to retrospectively report adverse events occurring during the first 6 months of treatment. The number of patients reported to have hallucinations (23) or palpitations/tachycardia (42) was small compared with the total in the group (14 536). However, older patients and female patients were each associated with a significantly higher incidence of hallucinations and palpitations/tachycardia. Patients over 74 years old were at the highest risk of hallucinations (*P* value not reported). Because of the retrospective nature of this study and the

absence of controls for potential confounders such as comorbidity, its results must be interpreted with caution.

Ethnicity

A study of male and female patients from Japan and Korea[36] compared tolterodine extended-release with oxybutynin immediate-release. This study found similar efficacy but fewer adverse events with tolterodine extended-release. There are no other studies of these 2 formulations so making assessments across races is not possible. A recent subanalysis of only the Japanese patients in this trial used the King's Health Questionnaire results to show that both medications improved overall quality of life in Japanese patients with overactive bladder syndrome, though the results of the drugs were only statistically significant compared to placebo but were not compared to one another.[35, 36]

A fair-quality trial that enrolled only Chinese women compared the immediate-release forms of tolterodine and oxybutynin.[38] The efficacy and adverse event findings and rate of withdrawals due to adverse events for this study were similar to the findings of the other 2 studies[37, 49] of the immediate-release formulations, which included both men and women.

In a subgroup analysis of an unblinded, uncontrolled study of solifenacin, 94 enrolled patients (out of 2205 total) were Hispanic.[133] While this study is not comparative, improvements reported in overactive bladder symptoms and quality of life over the 12-week study were similar in the overall study group and in the subgroup of Hispanic patients. Rates of adverse events and withdrawal due to adverse events were also similar.

Tolterodine is metabolized to an active metabolite by the CYP2D6 liver enzyme. Approximately 7% of white persons have a CYP2D6 polymorphism that results in poor metabolism through this enzyme. Theoretically, persons who are poor metabolizers would have a lower serum concentration of the active metabolite and in situations where the active metabolite is important for clinical results these people would be expected to have poorer outcomes. Studies in healthy subjects have shown that there are pharmacokinetic differences between "poor" and "extensive" CYP2D6 metabolizers but that these differences are not clinically important because the parent compound and active metabolite have similar actions.[134-138]

Comorbidity

Tolterodine has been studied in men whose symptoms were attributed to a combination of bladder outlet obstruction related to benign prostatic hypertrophy and overactive bladder syndrome.[139-141] Two of these 3 studies required that the enrolled men take an alpha-adrenergic antagonist. Both were 12-week studies randomizing patients to placebo or tolterodine extended-release 4 mg per day.[139, 140] The trials showed that in men with residual symptoms consistent with overactive bladder, in comparison with placebo the addition of tolterodine improved symptoms of both overactive bladder and benign prostatic hypertrophy, as measured on the International Prostate Symptom Score scale.

The larger study (N=879), known as the TIMES study,[139] similarly added tolterodine to an alpha-blocker; it also randomized patients to an alpha-blocker alone (tamsulosin) or tolterodine alone. At least 4 publications are associated with this study, reporting a variety of efficacy outcomes.[139, 142-144] For the purposes of this review, the comparison of the group receiving tamsulosin alone with the group receiving combination therapy (the benefit of adding a

drug for overactive bladder) is the most relevant. The primary outcome measure was patient perception of benefit at 12 weeks: The combination was superior to tamsulosin alone (80% compared with 71%; 95% CI, 1 to 19). Using a more conservative analysis, in which for patients missing data at 12 weeks, zero benefit—not the last available data point—was assumed, this difference becomes nonsignificant (76% compared with 68%; 95% CI, 0 to 18). Other efficacy measures were reported only as comparisons with placebo, where the combination was superior to placebo at 12 weeks in improving urgency urinary incontinence, urgency, micturition frequency per 14 hours, and nighttime frequency. Tamsulosin alone was not superior to placebo at 12 weeks on any of these measures. In a subgroup analysis based on prostate size, the combination therapy was superior to placebo for improving frequency of micturition (per 24 hours and at night) regardless of prostate size but did not significantly improve urge incontinence (episodes per 24 hours), regardless of prostate size.[142] For the combination, urgency (episodes per 24 hours) was improved compared with placebo only in men with prostate size >29 mL. Tamsulosin alone, on the other hand, was not significantly different from placebo on any of these measures in men with prostate size >29 mL. However, tamsulosin did improve urge incontinence and nocturnal micturition (number of episodes per night) compared with placebo in men with prostate size <29 mL. In a separate publication reporting solely on urgency, the combination was found to be superior to tamsulosin alone in reducing episodes of daytime micturition-related urgency ($P<0.05$) and improving the frequency-urgency sum (the sum of urgency scores on a 5-point scale) at 12 weeks ($P<0.01$), but not nighttime episodes of micturition-related urgency (*P* value not reported).[143]

The other study enrolled 652 men who were >40 years of age and who still had symptoms of overactive bladder despite taking an alpha-blocker for at least a month.[140] The men were randomized to add placebo or tolterodine extended-release 4 mg daily to their alpha-blocker. No significant difference was found in improvement on the Patient Perceived Bladder Condition, the primary outcome measure, or in episodes of urgency-related urinary incontinence after 12 weeks. However, other outcomes related to overactive bladder were significantly reduced in the tolterodine group: 24-hour micturition (–1.8 episodes compared with –1.2; $P=0.0079$), daytime micturition (–1.3 episodes compared with –0.8; $P=0.0123$); 24-hour urgency (–2.9 episodes compared with –1.8; $P=0.0010$), daytime urgency (–2.2 episodes compared with –1.4; $P=0.0017$), and nocturnal urgency (–0.5 episodes compared with –0.3; $P=0.0378$).

A third study compared tolterodine immediate-release (2 mg twice daily) with placebo but reported efficacy outcome measures that are not included here.[133] It is also unclear whether the men in this study were allowed to take an alpha-blocker, although the use of 5-alpha-reductase inhibitors was excluded.

No studies looked thoroughly at the effect of non-urological comorbidity. The head-to-head trials allowed inclusion of patients with comorbidities other than renal, hepatic, and psychiatric illnesses, and some allowed a broader range of comorbidity, but none of the trials analyzed the effect of comorbidity on efficacy or adverse events in a comparative way. One study[38] reported that coexisting illness was significantly associated with withdrawal from the study but did not stratify by drug.

One study included patients with spinal cord injury.[39] This study randomized patients to a 2-week treatment of oxybutynin immediate-release 5 mg 3 times daily or trospium 20 mg twice daily with a placebo at midday. The overall rate of side effects including dry mouth was similar in the two groups. Severity of dry mouth was graded on a 4-point scale. “Severe” dry mouth occurred in 23% of oxybutynin immediate-release group and in 4% of the trospium group.

Withdrawal occurred more commonly with oxybutynin immediate-release (16%) than trospium (4%). There were differences in demographic and urodynamic variables between the 2 groups at baseline and the numbers of randomized patients were unbalanced (more in one group than the other). While small differences in the number of patients randomized to each group is to be expected, large differences indicate a problem with the randomization process. Type or level of spinal cord injury was not provided, nor was information about other medications.

Table 2. Summary of the evidence

Key question	Quality of body of evidence[a]	Findings
Key question 1: Comparative efficacy		
In head-to-head trials what is the comparative efficacy of anticholinergic incontinence drugs?	Oxy IR vs Tol IR: Fair Tros IR vs Oxy IR: Fair Tros IR vs Oxy ER: Fair Tros ER vs Oxy ER: Poor Flav: Poor Sol vs Tol IR: Fair Sol vs Tol ER: Fair Dar vs Oxy IR: Fair	Four studies of Oxy IR vs Tol IR found no difference in efficacy. One study of Tros IR vs Oxy IR found no difference in efficacy. Mixed results were found with Oxy ER vs Tol ER; the better study found them equal. No studies of Fla. Sol showed greater efficacy over Tol (IR and ER) for some outcomes in 2 short-term studies. No difference in efficacy found between Dar and Oxy IR.
What is the comparative efficacy of long-acting vs short-acting anticholinergic incontinence drugs?	Fair	Four studies of Oxy ER vs Oxy IR and 1 of Tol ER vs Tol IR found no difference in efficacy. One study of Oxy ER vs Tol IR found Oxy superior, and 1 study of Tol ER vs Oxy IR found Tol ER superior.
Key question 2: Adverse events		
	Long-term studies: Poor	One comparative study assessing the discontinuation rate of Tol and Oxy over a 6-month period found a higher rate and earlier withdrawal with Oxy, but rates for both drugs were high. Uncontrolled studies reported dry mouth as the most common adverse event and found similar rates of adverse events and withdrawals between the drugs.
	Short-term studies: Fair	Head-to-head trials indicate a higher incidence of adverse events overall and specifically dry mouth with Oxy. The ER form had less frequent adverse events overall and, specifically, less dry mouth than the IR form. Tros less often causes severe dry mouth than Oxy, although overall incidence of dry mouth and short-term adverse events are similar to those of Oxy IR. A Sol vs Tol ER trial found a lower rate of dry mouth for Tol ER. The difference between drugs based on withdrawals is less clear: 2 Sol vs Tol trials found similar rates of adverse events overall.
What is the difference in adverse events between long-acting and short-acting formulations of anticholinergic incontinence drugs?	Tol IR vs Tol ER: Fair Oxy IR vs Oxy ER: Fair	A short-term head-to-head comparison of Tol IR vs Tol ER found a higher rate of dry mouth with the IR form. Withdrawal due to adverse event was similar for both. Short-term head-to-head comparison of Oxy IR vs Oxy ER found a higher rate of dry mouth with the IR form. Withdrawal due to adverse event was similar for both.

Key question	Quality of body of evidence[a]	Findings
Key question 3: Subpopulations		
	Gender: Poor (inconsistent) Age: Fair Racial groups: Fair Comorbidity: Fair	Evidence limited to 5 studies was not consistent in identifying differences between men and women in response to tolterodine. Older patients were found to respond to Oxy, Tol ER, darifenacin or solifenacin in post-hoc subgroup analyses. Adverse event profiles were similar to those found in the overall trial populations. Oxy IR and Tol IR resulted in similar response and adverse event rates in Chinese women compared to other studies with primarily White populations. Solifenacin was found to have similar response and adverse event rates in a Hispanic subgroup compared to the overall trial population in one study. Tol ER and Tol IR were found to be similarly effective in Japanese and Korean women, with fewer adverse events in the Tol ER group. The Japanese patients were shown to have improved quality of life in both groups, no such analysis was undertaken for the Korean patients. Two studies of men taking an alpha antagonist for symptoms associated with benign prostatic hypertrophy with residual symptoms of overactive bladder found that adding Tol ER resulted in significant improvement in symptoms related to both overactive bladder and benign prostatic hypertrophy compared to Tol ER, placebo or an alpha antagonist alone. Patient Perception of Bladder Condition was not improved in one study. One head-to-head trial of Tros vs Oxy in patients with spinal cord injury found the drugs had a similar rate of overall adverse events. Tros appeared to cause less severe dry mouth than Oxy.

[a] Quality of the *body* of evidence ratings based on criteria developed by the Third US Preventive Services Task Force.

Abbreviations: Dar, Darifenacin; ER, extended-release; Flav, Flavoxate; IR, immediate-release; Oxy, Oxybutynin; Sol, Solifenacin; Tol, Tolterodine; Tros, Trospium.

REFERENCES

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology.* 2003;61(1):37-49.

2. Koda-Kimble, et al., eds. *Applied therapeutics: the clinical use of drugs, 7th ed.* Baltimore, MD: Lippincott Williams & Wilkins; 2001.

3. Fantl JA, Newman DK, Colling J, et al. *Urinary incontinence in adults: acute and chronic management. Clinical Practice Guideline #2 AHCPR Publication No. 96-0682.* Rockville, MD: Agency for Healthcare Policy and Research; 1996.

4. Garnett S, Abrams P. The natural history of the overactive bladder and detrusor overactivity. A review of the evidence regarding the long-term outcome of the overactive bladder. *Journal of Urology.* 2003;169(3):843-848.

5. Couture JA, Valiquette L. Urinary incontinence. *Annals of Pharmacotherapy.* 2000;34(5):646-655.

6. Schmidt RA, Zermann DH, Doggweiler R. Urinary incontinence update: old traditions and new concepts. *Advances in Internal Medicine.* 1999;44:19-57.

7. McEvoy, et al., eds. *AHFS Drug Information 2002*. Bethesda, MD: Society of Health System Pharmacists, Inc.; 2002.

8. Ortho McNeil Janssen. Ditropan XL package insert. 2008.

9. Pharmacia and Upjohn. Detrol LA package insert. 2008.

10. Trospium chloride (Sanctura): another anticholinergic for overactive bladder. *Medical Letter on Drugs & Therapeutics.* 2004;46(1188):63-64.

11. Novartis. Enablex (darifenacin) package insert; 2008.

12. Astellas. VESIcare (solifenacin) package insert; 2008.

13. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Archives of Internal Medicine.* 1997;157(4):1531-1537.

14. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. *Archives of Internal Medicine.* 1991;151(9):1825-1832.

15. Hay-Smith J, Herbison P, Ellis G, Morris A. Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database of Systematic Reviews.* 2005;3.

16. Chapple C, Khullar V, Gabriel Z, Dooley JA. The effects of antimuscarinic treatments in overactive bladder: a systematic review and meta-analysis. *European Urology.* 2005;48(1):5-26.

17. Hay-Smith J, Herbison P, Ellis G, Moore K. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. *Cochrane Database of Systematic Reviews.* 2002;3.

18. Shamliyan TA, Kane RL, Wyman J, et al. Systematic review: randomized, controlled trials of nonsurgical treatments for urinary incontinence in women. *Annals of Internal Medicine.* Mar 18 2008;148(6):459-473.

19. Herbison P, Hay-Smith J, Ellis G, Moore K. Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: Systematic review. *British Medical Journal.* 2003;326(7394):841-844.

20. Novara G, Galfano A, Ficarra V, Artibani W. Anticholinergic drugs in patients with bladder outlet obstruction and lower urinary tract symptoms: A systematic review. *European Urology.* Oct 2006;50(4):675-683.
21. Abrams P, Freeman R, Anderstrom C, Mattiasson A. Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. *British Journal of Urology.* 1998;81(6):801-810.
22. Anderson RU, Mobley D, Blank B, Saltzstein D, Susset J, Brown JS. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. *Journal of Urology.* 1999;161(6):1809-1812.
23. Appell RA, Sand P, Dmochowski R, et al. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. *Mayo Clinic Proceedings.* 2001;76(4):358-363.
24. Barkin J, Corcos J, Radomski S, et al. A randomized, double-blind, parallel-group comparison of controlled- and immediate-release oxybutynin chloride in urge urinary incontinence. *Clinical Therapeutics.* Jul 2004;26(7):1026-1036.
25. Birns J, Lukkari E, Malone-Lee JG, et al. A randomized controlled trial comparing the efficacy of controlled-release oxybutynin tablets (10 mg once daily) with conventional oxybutynin tablets (5 mg twice daily) in patients whose symptoms were stabilized on 5 mg twice daily of oxybutynin. *BJU International.* 2000;85(7):793-798.
26. Chapple CR, Abrams P. Comparison of darifenacin and oxybutynin in patients with overactive bladder: assessment of ambulatory urodynamics and impact on salivary flow. *European Urology.* 2005;48(1):102-109.
27. Chapple CR, Arano P, Bosch JHR, De Ridder D, Kramer A, Ridder A. Solifenacin appears effective and well tolerated in patients with symptomatic idiopathic detrusor overactivity in a placebo- and tolterodine-controlled phase 2 dose-finding study.[erratum appears in BJU Int. 2004 May;93(7):1135]. *BJU International.* 2004;93(1):71-77.
28. Chapple CR, Martinez-Garcia R, Selvaggi L, et al. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: Results of the STAR trial. *European Urology.* 2005;48(3):464-470.
29. Chu FM, Dmochowski RR, Lama DJ, Anderson RU, Sand PK. Extended-release formulations of oxybutynin and tolterodine exhibit similar central nervous system tolerability profiles: a subanalysis of data from the OPERA trial. *American Journal of Obstetrics & Gynecology.* 2005;192(6):1849-1854.
30. Davila GW, Daugherty CA, Sanders SW. A short-term, multicenter, randomized double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. *Journal of Urology.* 2001;166(1):140-145.
31. Diokno AC, Appell RA, Sand PK, et al. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: Results of the OPERA trial. *Mayo Clinic Proceedings.* 2003;78(6):687-695.
32. Dmochowski RR, Sand PK, Zinner NR, et al. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology.* 2003;62(2):237-242.

33. Drutz HP, Appell RA, Gleason D, Klimberg I, Radomski S. Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. *International Urogynecology Journal.* 1999;10(5):283-289.
34. Halaska M, Ralph G, Wiedemann A, et al. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World Journal of Urology.* 2003;20(6):392-399.
35. Homma Y, Kawabe K. Health-related quality of life of Japanese patients with overactive bladder treated with extended-release tolterodine or immediate-release oxybutynin: a randomized, placebo-controlled trial. *World Journal of Urology.* Aug 2004;22(4):251-256.
36. Homma Y, Paick JS, Lee JG, Kawabe K, Japanese, Korean Tolterodine Study G. Clinical efficacy and tolerability of extended-release tolterodine and immediate-release oxybutynin in Japanese and Korean patients with an overactive bladder: a randomized, placebo-controlled trial. *BJU International.* 2003;92(7):741-747.
37. Lee JG, Hong JY, Choo M-S, et al. Tolterodine: As effective but better tolerated than oxybutynin in Asian patients with symptoms of overactive bladder. *International Journal of Urology.* 2002;9(5):247-252.
38. Leung HY, Yip SK, Cheon C, et al. A randomized controlled trial of tolterodine and oxybutynin on tolerability and clinical efficacy for treating Chinese women with an overactive bladder. *BJU International.* 2002;90:375-380.
39. Madersbacher H, Stohrer M, Richter R, Burgdorfer H, Hachen HJ, Murtz G. Trospium chloride versus oxybutynin: a randomized, double-blind, multicentre trial in the treatment of detrusor hyper-reflexia. *British Journal of Urology.* 1995;75(4):452-456.
40. Milani R, Scalambrino S, Milia R, et al. Double-blind crossover comparison of flavoxate and oxybutynin in women affected by urinary urge syndrome. *Int Urogynecol J.* 1993;4(1):3-8.
41. Nilsson CG, Lukkari E, Haarala M, Kivela A, Hakonen T, Kiilholma P. Comparison of a 10-mg controlled release oxybutynin tablet with a 5-mg oxybutynin tablet in urge incontinent patients. *Neurourology & Urodynamics.* 1997;16(6):533-542.
42. Radomski S, Caley B, Reiz JL, Miceli PC, Harsanyi Z, Darke AC. Preliminary evaluation of a new controlled-release oxybutynin in urinary incontinence. *Current Medical Research and Opinion.* 2004;20(2):249-253.
43. Sand PK, Miklos J, Ritter H, Appell R. A comparison of extended-release oxybutynin and tolterodine for treatment of overactive bladder in women. *International Urogynecology Journal.* Jul-Aug 2004;15(4):243-248.
44. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: The Antimuscarinic Clinical Effectiveness Trial (ACET). *Current Medical Research & Opinion.* 2002;18(4):177-184.
45. Swift S, Garely A, Dimpfl T, Payne C, Tolterodine Study G. A new once-daily formulation of tolterodine provides superior efficacy and is well tolerated in women with overactive bladder. *International Urogynecology Journal.* 2003;14(1):50-54; discussion 54-55.
46. Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A, Tolterodine Study G. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology.* 2001;57(3):414-421.

47. Versi E, Appell R, Mobley D, Patton W, Saltzstein D. Dry mouth with conventional and controlled-release oxybutynin in urinary incontinence. *Obstetrics & Gynecology.* 2000;95(5):718-721.
48. Zeegers AGM, Kiesswetter H, Kramer A, Jonas U. Conservative therapy of frequency, urgency and urge incontinence: A double-blind clinical trial of flavoxate hydrochloride, oxybutinin chloride, emepronium bromide and placebo. *World Journal of Urology.* 1987;5(1):57-61.
49. Malone-Lee JG. The efficacy, tolerability and safety profile of tolterodine in the treatment of overactive/unstable bladder. *Reviews in Contemporary Pharmacotherapy.* 2000;11(1):29-42.
50. Chapple CR, Rechberger T, Al-Shukri S, et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. *BJU International.* 2004;93(3):303-310.
51. Badia X, Ibarz R. Health-related quality of life issues in urinary urge incontinence. *Expert Review of Pharmacoeconomics & Outcomes Research.* 2002;2(4):357-365.
52. Kobelt G, Kirchberger I, Malone-Lee J. Review. Quality-of-life aspects of the overactive bladder and the effect of treatment with tolterodine. *BJU International.* 1999;83(6):583-590.
53. O'Conor RM, Johannesson M, Hass SL, Kobelt-Nguyen G. Urge incontinence. Quality of life and patients' valuation of symptom reduction. *Pharmacoeconomics.* 1998;14(5):531-539.
54. Malone-Lee J, Eriksson M, Olofsson S, Lidberg. The comparative tolerability and efficacy of tolterodine 2 mg bid versus oxybutynin 2.5/5 mg bid in the treatment of the overactive bladder. *Neurourology & Urodynamics.* 1998;17(4):163-164.
55. Appell RA, Abrams P, Drutz HP, Van Kerrebroeck PE, Millard R, Wein A. Treatment of overactive bladder: long-term tolerability and efficacy of tolterodine. *World Journal of Urology.* 2001;19(2):141-147.
56. Kelleher CJ, Kreder KJ, Pleil AM, Burgess SM, Reese PR. Long-term health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. *American Journal of Managed Care.* 2002;8(19 Suppl):S616-630.
57. Kelleher CJ, Reese PR, Pleil AM, Okano GJ. Health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. *American Journal of Managed Care.* 2002;8(19 Suppl):S608-615.
58. Okano GJ, Pleil AM, Reese PR, al. e. Effects of long-term tolterodine treatment on physical and symptom aspects of health-related quality of life in overactive bladder patients. *Value in Health.* 2002;5(3):278.
59. Pleil AM, Reese PR, Kelleher CJ, Okano GJ. Health-related quality of life of patients with overactive bladder receiving immediate-release tolterodine. *Hepac Health Economics in Prevention & Care.* 2001;2(2):69-75.
60. Rogers R, Bachmann, G, Jumadilova, Z, Sun, F, Morro, JD, Guan, Z, Bavendam, T. Efficacy of tolterodine on overactive bladder symptoms and sexual and emotional quality of life in sexually active women. *Int Urogynecol J Pelvic Floor Dysfunct.* 2008;19(11):1551-1557.
61. Abrams P, Kelleher C, Huels J, Quebe-Fehling E, Omar MA, Steel M. Clinical relevance of health-related quality of life outcomes with darifenacin. *BJU International.* Jul 2008;102(2):208-213.

62. Appell RA. Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. *Urology.* 1997;50(6A Suppl):90-96.
63. Alloussi S, Laval KU, Eckert R, et al. Trospium chloride (Spasmo-lyt(R)) in patients with motor urge syndrome (detrusor instability): a double-blind, randomised, multicentre, placebo-controlled study. *Journal of Drug Assessment.* 1999;2(Part 1):27-40.
64. Cardozo L, Chapple CR, Toozs-Hobson P, et al. Efficacy of trospium chloride in patients with detrusor instability: a placebo-controlled, randomized, double-blind, multicentre clinical trial. *BJU International.* 2000;85(6):659-664.
65. Cardozo L, Dixon A. Increased warning time with darifenacin: a new concept in the management of urinary urgency. *Journal of Urology.* Apr 2005;173(4):1214-1218.
66. Cardozo L, Lisec M, Millard R, et al. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *Journal of Urology.* Nov 2004;172(5 Pt 1):1919-1924.
67. Chancellor M, Freedman S, Mitcheson HD, Antoci J, Primus G, Wein A. Tolterodine, an effective and well tolerated treatment for urge incontinence and other overactive bladder symptoms. *Clinical Drug Investigation.* 2000;19(2):83-91.
68. Chapple CR, Parkhouse H, Gardener C, Milroy EJ. Double-blind, placebo-controlled, cross-over study of flavoxate in the treatment of idiopathic detrusor instability. *British Journal of Urology.* 1990;66(5):491-494.
69. Dmochowski RR, Davila GW, Zinner NR, et al. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. *Journal of Urology.* 2002;168(2):580-586.
70. Haab F, Stewart L, Dwyer P. Darifenacin, an M3 selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. *European Urology.* Apr 2004;45(4):420-429; discussion 429.
71. Jacquetin B, Wyndaele J. Tolterodine reduces the number of urge incontinence episodes in patients with an overactive bladder. *European Journal of Obstetrics, Gynecology, & Reproductive Biology.* 2001;98(1):97-102.
72. Khullar V, Hill S, Laval K-U, Schiotz HA, Jonas U, Versi E. Treatment of urge-predominant mixed urinary incontinence with tolterodine extended release: A randomized, placebo-controlled trial. *Urology.* Vol 64; 2004:269-274.
73. Landis JR, Kaplan S, Swift S, Versi E. Efficacy of antimuscarinic therapy for overactive bladder with varying degrees of incontinence severity. *Journal of Urology.* 2004;171(2 Pt 1):752-756.
74. Malone-Lee JG, Walsh JB, Maugourd MF. Tolterodine: a safe and effective treatment for older patients with overactive bladder. *Journal of the American Geriatrics Society.* 2001;49(6):700-705.
75. Millard R, Tuttle J, Moore K, et al. Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity. *Journal of Urology.* 1999;161(5):1551-1555.
76. Muskat Y, Bukovsky I, Schneider D, Langer R. The use of scopolamine in the treatment of detrusor instability. *Journal of Urology.* Dec 1996;156(6):1989-1990.
77. Rentzhog L, Stanton SL, Cardozo L, Nelson E, Fall M, Abrams P. Efficacy and safety of tolterodine in patients with detrusor instability: a dose-ranging study. *British Journal of Urology.* 1998;81(1):42-48.

78. Steers W, Corcos J, Foote J, Kralidis G. An investigation of dose titration with darifenacin, an M3-selective receptor antagonist. *BJU International.* Mar 2005;95(4):580-586.
79. Szonyi G, Collas DM, Ding YY, Malone-Lee JG. Oxybutynin with bladder retraining for detrusor instability in elderly people: A randomized controlled trial. *Age & Ageing.* 1995;24(4):287-291.
80. Van Kerrebroeck PE, Amarenco G, Thuroff JW, et al. Dose-ranging study of tolterodine in patients with detrusor hyperreflexia. *Neurourology & Urodynamics.* 1998;17(5):499-512.
81. Zinner N, Gittelman M, Harris R, Susset J, Kanellos A, Auerbach S. Trospium chloride improves overactive bladder symptoms: A multicenter phase III trial. *Journal of Urology.* 2004;171(6 I):2311-2315.
82. Zinner NR, Mattiasson A, Stanton SL. Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. *Journal of the American Geriatrics Society.* 2002;50(5):799-807.
83. Chapple C, DuBeau C, Ebinger U, Rekeda L, Viegas A. Darifenacin treatment of patients >or= 65 years with overactive bladder: results of a randomized, controlled, 12-week trial. *Current Medical Research & Opinion.* Oct 2007;23(10):2347-2358.
84. Dmochowski R, Kreder K, MacDiarmid S, et al. The clinical efficacy of tolterodine extended-release is maintained for 24 h in patients with overactive bladder. *BJU International.* Jul 2007;100(1):107-110.
85. Dmochowski RR, Sand PK, Zinner NR, et al. Trospium 60 mg once daily (QD) for overactive bladder syndrome: results from a placebo-controlled interventional study. *Urology.* Mar 2008;71(3):449-454.
86. Hill S, Khullar V, Wyndaele J-J, Lheritier K, Darifenacin Study G. Dose response with darifenacin, a novel once-daily M3 selective receptor antagonist for the treatment of overactive bladder: results of a fixed dose study. *International Urogynecology Journal.* May 2006;17(3):239-247.
87. Kaplan SA, Roehrborn CG, Dmochowski R, Rovner ES, Wang JT, Guan Z. Tolterodine extended release improves overactive bladder symptoms in men with overactive bladder and nocturia. *Urology.* Aug 2006;68(2):328-332.
88. Kelleher C, Cardozo L, Kobashi K, Lucente V. Solifenacin: as effective in mixed urinary incontinence as in urge urinary incontinence. *International Urogynecology Journal.* Jun 2006;17(4):382-388.
89. Nitti VW, Dmochowski R, Appell RA, et al. Efficacy and tolerability of tolterodine extended-release in continent patients with overactive bladder and nocturia. *BJU International.* Jun 2006;97(6):1262-1266.
90. Rackley R, Weiss JP, Rovner ES, Wang JT, Guan Z, Study G. Nighttime dosing with tolterodine reduces overactive bladder-related nocturnal micturitions in patients with overactive bladder and nocturia. *Urology.* Apr 2006;67(4):731-736; discussion 736.
91. Roehrborn CG, Abrams P, Rovner ES, Kaplan SA, Herschorn S, Guan Z. Efficacy and tolerability of tolterodine extended-release in men with overactive bladder and urgency urinary incontinence. *BJU International.* May 2006;97(5):1003-1006.
92. Rudy D, Cline K, Harris R, Goldberg K, Dmochowski R. Multicenter phase III trial studying trospium chloride in patients with overactive bladder. *Urology.* Feb 2006;67(2):275-280.

93. Rudy D, Cline K, Harris R, Goldberg K, Dmochowski R. Time to onset of improvement in symptoms of overactive bladder using antimuscarinic treatment. *BJU International.* Mar 2006;97(3):540-546.
94. Staskin D, Sand P, Zinner N, et al. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. *Journal of Urology.* Sep 2007;178(3 Pt 1):978-983; discussion 983-974.
95. Wein AJ, Khullar V, Wang JT, et al. Achieving continence with antimuscarinic therapy for overactive bladder: effects of baseline incontinence severity and bladder diary duration. *BJU International.* Feb 2007;99(2):360-363.
96. Zinner N, Susset J, Gittelman M, Arguinzoniz M, Rekeda L, Haab F. Efficacy, tolerability and safety of darifenacin, an M(3) selective receptor antagonist: an investigation of warning time in patients with OAB.[erratum appears in Int J Clin Pract. 2006 Jul;60(7):890]. *International Journal of Clinical Practice.* Jan 2006;60(1):119-126.
97. Brubaker L, FitzGerald MP, Brubaker L, FitzGerald MP. Nocturnal polyuria and nocturia relief in patients treated with solifenacin for overactive bladder symptoms. *International Urogynecology Journal.* Jul 2007;18(7):737-741.
98. Staskin DR, Te AE. Short- and long-term efficacy of solifenacin treatment in patients with symptoms of mixed urinary incontinence. *BJU International.* Jun 2006;97(6):1256-1261.
99. Millard RJ, Halaska M. Efficacy of solifenacin in patients with severe symptoms of overactive bladder: a pooled analysis. *Current Medical Research & Opinion.* Jan 2006;22(1):41-48.
100. Cardozo L, Castro-Diaz D, Gittelman M, Ridder A, Huang M. Reductions in overactive bladder-related incontinence from pooled analysis of phase III trials evaluating treatment with solifenacin. *International Urogynecology Journal.* Sep 2006;17(5):512-519.
101. Abrams P, Swift S, Abrams P, Swift S. Solifenacin is effective for the treatment of OAB dry patients: a pooled analysis. *European Urology.* Sep 2005;48(3):483-487.
102. Dmochowski RR, Nitti V, Staskin D, Luber K, Appell R, Davila GW. Transdermal oxybutynin in the treatment of adults with overactive bladder: combined results of two randomized clinical trials. *World Journal of Urology.* Sep 2005;23(4):263-270.
103. Rovner ES, Rackley R, Nitti VW, Wang JT, Guan Z, Study G. Tolterodine extended release is efficacious in continent and incontinent subjects with overactive bladder. *Urology.* Sep 2008;72(3):488-493.
104. Appell RA. Treatment of overactive bladder: the Antimuscarinic Clinical Effectiveness Trial. *Current Urology Reports.* 2002;3(5):343-344.
105. Zinner N, Tuttle J, Marks L. Efficacy and tolerability of darifenacin, a muscarinic M3 selective receptor antagonist (M3 SRA), compared with oxybutynin in the treatment of patients with overactive bladder. *World Journal of Urology.* Sep 2005;23(4):248-252.
106. Chapple CR, Fianu-Jonsson A, Indig M, et al. Treatment outcomes in the STAR study: a subanalysis of solifenacin 5 mg and tolterodine ER 4 mg. *European Urology.* Oct 2007;52(4):1195-1203.
107. Anderson RU, MacDiarmid S, Kell S, Barada JH, Serels S, Goldberg RP. Effectiveness and tolerability of extended-release oxybutynin vs extended-release tolterodine in women with or without prior anticholinergic treatment for overactive bladder. *International Urogynecology Journal.* Sep 2006;17(5):502-511.

108. Lawrence M, Guay DR, Benson SR, Anderson MJ. Immediate-release oxybutynin versus tolterodine in detrusor overactivity: a population analysis. *Pharmacotherapy.* 2000;20(4):470-475.
109. Shaya FT, Blume S, Gu A, Zyczynski T, Jumadilova Z. Persistence with overactive bladder pharmacotherapy in a Medicaid population. *American Journal of Managed Care.* 2005;11(4 Suppl):S121-129.
110. Varadharajan S, Jumadilova Z, Girase P, Ollendorf DA. Economic impact of extended-release tolterodine versus immediate- and extended-release oxybutynin among commercially insured persons with overactive bladder. *American Journal of Managed Care.* 2005;11(4 Suppl):S140-149.
111. Siami P, Seidman LS, Lama D. A multicenter, prospective, open-label study of tolterodine extended-release 4 mg for overactive bladder: The Speed of Onset of Therapeutic Assessment Trial (STAT). *Clinical Therapeutics.* 2002;24(4):616-628.
112. Abrams P. Evidence for the efficacy and safety of tolterodine in the treatment of overactive bladder. *Expert Opinion on Pharmacotherapy.* 2001;2(10):1685-1701.
113. Abrams P, Malone-Lee J, Jacquetin B, Wyndaele JJ, Wein A, et al. Twelve month treatment of overactive bladder: efficacy and tolerability of tolterodine. *Drugs & Aging.* 2001;18(7):551-560.
114. Kreder K, Mayne C, Jonas U. Long-term safety, tolerability and efficacy of extended-release tolterodine in the treatment of overactive bladder. *European Urology.* 2002;41(6):588-595.
115. Layton D, Pearce GL, Shakir SA. Safety profile of tolterodine as used in general practice in England: results of prescription-event monitoring. *Drug Safety.* 2001;24(9):703-713.
116. Michel MC, Schneider T, Krege S, Goepel M. Does gender or age affect the efficacy and safety of tolterodine? *Journal of Urology.* 2002;168(3):1027-1031.
117. Ouslander JG, Maloney C, Grasela TH, Rogers L, Walawander CA. Implementation of a nursing home urinary incontinence management program with and without tolterodine. *Journal of the American Medical Directors Association.* 2001;2(5):207-214.
118. Gleason DM, Susset J, White C, Munoz DR, Sand PK. Evaluation of a new once-daily formulation of oxbutynin for the treatment of urinary urge incontinence. Ditropan XL Study Group. *Urology.* 1999;54(3):420-423.
119. Haab F, Cardozo L, Chapple C, Ridder AM, Solifenacin Study Group. Long-term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome. *European Urology.* Mar 2005;47(3):376-384.
120. Haab F, Corcos J, Siami P, et al. Long-term treatment with darifenacin for overactive bladder: results of a 2-year, open-label extension study. *BJU International.* Nov 2006;98(5):1025-1032.
121. Michel MC, de la Rosette JJ, Piro M, Schneider T. Comparison of symptom severity and treatment response in patients with incontinent and continent overactive bladder. *European Urology.* 2005;48(1):110-115.
122. Salvatore S, Khullar V, Cardozo L, Milani R, Athanasiou S, Kelleher C. Long-term prospective randomized study comparing two different regimens of oxybutynin as a treatment for detrusor overactivity. *European Journal of Obstetrics, Gynecology, & Reproductive Biology.* 2005;119(2):237-241.

123. Malone-Lee J, Shaffu B, Anand C, Powell C. Tolterodine: superior tolerability than and comparable efficacy to oxybutynin in individuals 50 years old or older with overactive bladder: a randomized controlled trial. *Journal of Urology.* 2001;165(5):1452-1456.
124. Lee JG, Hong JY, Choo MS, Kwon HY, Chung DYK, S T. Tolterodine: as effective but better tolerated than Oxybutinin in Asian patients with symptoms of overactive bladder (Abstract). *Proceedings of the International Continence Society.* 2001.
125. Armstrong RB, Luber KM, Peters KM. Comparison of dry mouth in women treated with extended-release formulations of oxybutynin or tolterodine for overactive bladder. *International Urology & Nephrology.* 2005;37(2):247-252.
126. Takei M, Homma Y, The Japanese Tolterodine Study G. Long-term safety, tolerability and efficacy of extended-release tolterodine in the treatment of overactive bladder in Japanese patients. *International Journal of Urology.* 2005;12(5):456-464.
127. Madersbacher H, Knoll M. Lntravesical application of oxybutynine: Mode of action in controlling detrusor hyperreflexia. Preliminary results. *European Urology.* 1995;28(4):340-344.
128. Ouslander JG, Schnelle JF, Uman G, et al. Does oxybutynin add to the effectiveness of prompted voiding for urinary incontinence among nursing home residents? A placebo-controlled trial. *Journal of the American Geriatrics Society.* 1995;43(6):610-617.
129. Hill S, Elhilali M, Millard RJ, et al. Long-term darifenacin treatment for overactive bladder in patients aged 65 years and older: analysis of results from a 2-year, open-label extension study. *Current Medical Research & Opinion.* Nov 2007;23(11):2697-2704.
130. Foote J, Glavind K, Kralidis G, et al. Treatment of overactive bladder in the older patient: pooled analysis of three phase III studies of darifenacin, an M3 selective receptor antagonist. *European Urology.* Sep 2005;48(3):471-477.
131. Wagg A, Wyndaele JJ, Sieber P, Wagg A, Wyndaele J-J, Sieber P. Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: a pooled analysis. *American Journal Geriatric Pharmacotherapy.* Mar 2006;4(1):14-24.
132. Dmochowski R, Abrams P, Marschall-Kehrel D, et al. Efficacy and tolerability of tolterodine extended release in male and female patients with overactive bladder. *European Urology.* Apr 2007;51(4):1054-1064; discussion 1064.
133. Capo JP, Jr., Laramee C, Lucente V, Fakhoury A, Forero-Schwanhaeuser S. Solifenacin treatment for overactive bladder in Hispanic patients: patient-reported symptom bother and quality of life outcomes from the VESIcare Open-Label Trial. *International Journal of Clinical Practice.* Jan 2008;62(1):39-46.
134. Brynne N, Bottiger Y, Hallen B, Bertilsson L. Tolterodine does not affect the human in vivo metabolism of the probe drugs caffeine, debrisoquine and omeprazole. *British Journal of Clinical Pharmacology.* 1999;47(2):145-150.
135. Brynne N, Dalen P, Alvan G, Bertilsson L, Gabrielsson J. Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamic of tolterodine. *Clinical Pharmacology & Therapeutics.* 1998;63(5):529-539.
136. Brynne N, Forslund C, Hallen B, Gustafsson LL, Bertilsson L. Ketoconazole inhibits the metabolism of tolterodine in subjects with deficient CYP2D6 activity. *British Journal of Clinical Pharmacology.* 1999;48(4):564-572.
137. Brynne N, Stahl MM, Hallen B, et al. Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. *International Journal of Clinical Pharmacology & Therapeutics.* 1997;35(7):287-295.

138. Brynne N, Svanstrom C, Aberg-Wistedt A, Hallen B, Bertilsson L. Fluoxetine inhibits the metabolism of tolterodine-pharmacokinetic implications and proposed clinical relevance. *British Journal of Clinical Pharmacology.* 1999;48(4):553-563.

139. Kaplan SA, Roehrborn CG, Rovner ES, et al. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. [erratum appears in JAMA. 2007 Mar 21:297(11):1195]. *JAMA.* Nov 15 2006;296(19):2319-2328.

140. Chapple C, Herschorn, S., Abrams, P., Sun, F., Brodsky, M., Guan, Z. Tolterodine treatment improves storage symptoms suggestive of overactive bladder in men treated with alpha-blockers. *Eur Urol.* 2008.

141. Abrams P, Kaplan S, De Koning Gans HJ, Millard R. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. *Journal of Urology.* Mar 2006;175(3 Pt 1):999-1004; discussion 1004.

142. Roehrborn CG, Kaplan, S.A., Jones, J.S., Wang, J.T., Bavendam, T., Guan, Z. Tolterodine extended release with or without tamsulosin in men with lower urinary tract symptoms including overactive bladder symptoms: effects of prostate size. *Eur Urol.* 2009;55:472-481.

143. Rovner ES, Kreder K, Sussman DO, et al. Effect of tolterodine extended release with or without tamsulosin on measures of urgency and patient reported outcomes in men with lower urinary tract symptoms. *Journal of Urology.* Sep 2008;180(3):1034-1041.

144. Kaplan SA, Roehrborn CG, Chancellor M, Carlsson M, Bavendam T, Guan Z. Extended-release tolterodine with or without tamsulosin in men with lower urinary tract symptoms and overactive bladder: effects on urinary symptoms assessed by the International Prostate Symptom Score. *BJU International.* Nov 2008;102(9):1133-1139.

Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor

for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Search strategy

Search Strategies for Update 4

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
Search Strategy:
---
1 (oxybutinin or tolterodine or flavoxate or darifenacin or scopolamine or hyoscyamine or solifenacin or trospium).ti. (627)
2 limit 1 to yr="2005 - 2008" (91)
3 from 2 keep 1-91 (91)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2008>
Search Strategy:
---
1 (oxybutinin or tolterodine or flavoxate or darifenacin or scopolamine or hyoscyamine or solifenacin or trospium).ti. (1)
2 limit 1 to yr="2005 - 2008" (1)
3 from 2 keep 1 (1)

Database: Ovid MEDLINE(R) <1996 to November Week 3 2008>
Search Strategy:
---
1 flavoxate.mp. or exp FLAVOXATE/ (40)
2 (tolterodine or oxybutinin or darifenacin or scopolamine or hyoscyamine or solifenacin or trospium).mp. (3324)
3 1 or 2 (3352)
4 limit 3 to (english language and humans) (1346)
5 limit 4 to yr="2005 - 2009" (608)
6 limit 5 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial) (285)
7 observational stud$.mp. (16249)
8 exp Cohort Studies/ or cohort$.mp. (464922)
9 exp Retrospective Studies/ or retrospective$.mp. (250000)
10 8 or 7 or 9 (655298)
11 10 and 5 (84)
12 6 or 11 (306)
13 from 12 keep 1-306 (306)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2008>
Search Strategy:---
1 (oxybutinin or tolterodine or flavoxate or darifenacin or scopolamine or hyoscyamine or solifenacin or trospium).ti. (2)
2 from 1 keep 1-2 (2)

Previous Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <2nd Quarter 2005>
Search Strategy:
1 (oxybutinin or tolterodine or flavoxate or darifenacin or scopolamine or hyoscyamine or solifenacin or trospium).ti.
2 from 1 keep 1-105

Database: MEDLINE (1996-2005)
Search Strategy:
---
1 flavoxate.mp. or exp FLAVOXATE/
2 (tolterodine or oxybutinin or darifenacin or scopolamine or hyoscyamine or solifenacin or trospium).mp.
3 1 or 2
4 limit 3 to human
5 limit 4 to english language
6 4 not 5
7 limit 6 to abstracts
8 5 or 7
9 from 8 keep 1-200

Database: EMBASE Drugs & Pharmacology <1980-2005>
Search Strategy:
---
1 oxybutinin.mp. or exp Oxybutynin/
2 tolterodine.mp. or exp TOLTERODINE/
3 flavoxate.mp. or exp FLAVOXATE/
4 darifenacin.mp. or exp DARIFENACIN/
5 scopolamine.mp. or exp SCOPOLAMINE/
6 hyoscyamine.mp. or exp HYOSCYAMINE/
7 solifenacin.mp or exp SOLIFENACIN/
8 trospium.mp. or exp TROSPIUM/
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 limit 9 to human
11 limit 10 to english language
12 10 not 11
13 limit 12 to abstracts
14 11 or 13
15 randomized controlled trial$.mp.
16 randomised controlled trial$.mp.
17 Controlled Study/
18 controlled clinical trial$.mp.
19 15 or 16 or 17 or 18

20 14 and 19
21 exp retrospective study/
22 exp *OXYBUTYNIN/ae, to [Adverse Drug Reaction, Drug Toxicity]
23 exp *TOLTERODINE/ae, to [Adverse Drug Reaction, Drug Toxicity]
24 exp *FLAVOXATE/ae, to [Adverse Drug Reaction, Drug Toxicity]
25 exp *DARIFENCIN/ae, to [Adverse Drug Reaction, Drug Toxicity]
26 exp *SCOPOLAMINE/ae, to [Adverse Drug Reaction, Drug Toxicity]
27 exp *HYOSCYAMINE/ae, to [Adverse Drug Reaction, Drug Toxicity]
28 exp *SOLIFENACIN/ae, to [Adverse Drug Reaction, Drug Toxicity]
29 exp *TROSPIUM/ae, to [Adverse Drug Reaction, Drug Toxicity]
30 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31 21 and 30
32 drug interaction.mp. or exp Drug Interaction/
33 14 and 32
34 exp oxybutinin/it or exp tolterodine/it or exp flavoxate/it or exp darifencin/it or exp scopolamine/it or exp hyoscyamine/it or exp solifenacin/it or exp trospium/it
35 limit 34 to human
36 evaluation studies.mp. or evaluation/ or drug evaluation.mp. or exp drug evaluation/
37 14 and 36
38 20 or 31 or 33 or 35 or 37
39 from 38 keep all

Appendix C. Methods used to assess quality of studies

Study quality was objectively assessed using predetermined criteria for internal validity, which were based on a combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination criteria.

All included studies, regardless of design, were assessed for quality and assigned a rating of "good," "fair," or "poor". Studies that have a fatal flaw were rated poor quality. A fatal flaw was the failure to meet combinations of criteria that may be related to indicate the presence of bias. An example would be inadequate procedures for allocation concealment combined with important differences between groups in prognostic factors at baseline and following randomization. Studies that meet all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category was broad, studies with this rating varied in their strengths and weaknesses: The results of some fair-quality studies were *likely* to be valid, while others were only *possibly* valid. A poor-quality trial was not valid; the results were at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Criteria for assessing applicability (external validity) are also listed, although they were not used to determine study quality.

Systematic Reviews

1. Does the systematic review report a clear review question and clearly state inclusion and exclusion criteria for primary studies?

A good-quality review focuses on a well-defined question or set of questions, which ideally refer to the inclusion/exclusion criteria by which decisions are made about whether to include or exclude primary studies. These criteria would relate to the 4 components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. A good-quality review also includes details about the process of decision-making, that is, how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to find all relevant research?

If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, date restrictions, and language restrictions are presented. In addition, descriptions of hand-searches, attempts to identify unpublished material, and any contact with authors, industry, or research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE is searched for a systematic review about health education, then it is unlikely that all relevant studies will be located.

3. Is the validity of included studies adequately assessed?

If the review systematically assesses the quality of primary studies, it should include an explanation of the basis for determining quality (for example, method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis) and the process by which assessment is carried out (that is, how many reviewers are involved, whether the assessment is independent, and how discrepancies between reviewers are resolved). Authors

may have used either a published checklist or scale or one that they designed specifically for their review.

4. Is sufficient detail of the individual studies presented?

The review should show that the included studies are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. It is usually considered sufficient if a paper includes a table giving information on the design and results of individual studies or includes a narrative description of the studies. If relevant, the tables or text should include information on study design, sample size for each study group, patient characteristics, interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, according to sample size or according to inverse of the variance) so that studies that are thought to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?

Adequate approaches to sequence generation:

Computer-generated random numbers

Random numbers tables

Inferior approaches to sequence generation:

Use of alternation, case record number, birth date, or day of week

Not reported

2. Was the treatment allocation concealed?

Adequate approaches to concealment of randomization:

Centralized or pharmacy-controlled randomization

Serially-numbered identical containers

On-site computer based system with a randomization sequence that is not readable until allocation

Inferior approaches to concealment of randomization:

Use of alternation, case record number, birth date, or day of week

Open random numbers lists

Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (Study should give number for each group.)

Nonrandomized studies

Assessment of Internal Validity

1. Was the selection of patients for inclusion unbiased? (Was any group of patients systematically excluded?)

2. Was there important differential loss to follow-up or overall high loss to follow-up? (Numbers should be given for each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (that is, by independent ascertainers using a validated ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Was the duration of follow-up reasonable for investigated events?

References

1. Center for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. *CRD Report.* 2001(4).

2. Harris RP, Helfand M, Woolf SH. Current methods of the US Preventive Services Task Force: a review of the process. *American Journal of Preventive Medicine.* 2001;20(3 Suppl):21-35.

Appendix D. Excluded trials

Trials in a foreign language

Xia, T., Su, R. S., Tao, X. C., Yan, J. Z., et al. Clinical Evaluation on the Efficacy and Safety of Tolterodine in the Treatment for Overactive Bladder. *The Chinese Journal of Clinical Pharmacology.* 2001;17(2):83-86.

Takayasu, H., Ueno, A., Tsuchida, S., et al. Clinical evaluation of propiverine hydrochloride (P-4) for the treatment of patients with urinary frequency - A double-blind controlled study using flavoxate hydrochloride. *Nishinihon Journal of Urology.* 1990;52(2):248-258.

Trials with an ineligible outcome

Lee, J. Y., Kim, H. W., Lee, S. J., Koh, J. S., Suh, H. J., Chancellor, M. B. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. *BJU Int.* 2004;94(6):817-820.

Giannitsas, K., Perimenis, P., Athanasopoulos, A., Gyftopoulos, K., Nikiforidis, G., Barbalias, G. Comparison of the efficacy of tolterodine and oxybutynin in different urodynamic severity grades of idiopathic detrusor overactivity. *Eur Urol.* Dec 2004;46(6):776-782; discussion 782-773.

Altan-Yaycioglu, R., Yaycioglu, O., Aydin Akova, Y., Guvel, S., Ozkardes, H. Ocular side-effects of tolterodine and oxybutynin, a single-blind prospective randomized trial. *Br J Clin Pharmacol.* 2005;59(5):588-592.

Trials with an ineligible drug or intervention

Robinson, J. M., Brocklehurst, J. C. Emepronium bromide and flavoxate hydrochloride in the treatment of urinary incontinence associated with detrusor instability in elderly women. *Br J Urol.* 1983;55(4):371-376.

Jarvis, G. J. A controlled trial of bladder drill and drug therapy in the management of detrusor instability. *Br J Urol.* 1981;53(6):565-566.

Herschorn, S., Becker, D., Miller, E., Thompson, M., Forte, L. Impact of a health education intervention in overactive bladder patients. *Canadian Journal of Urology.* Dec 2004;11(6):2430-2437.

Guay, D. R., New, K. Pharmacokinetics of oxybutynin transdermal delivery in healthy volunteers and patients with overactive bladder (OAB). *Ashp Midyear Clinical Meeting.* 2002;37(DEC).

Diokno, A. C., Catipay, J. R. C., Steinert, B. W. Office assessment of patient outcome of pharmacologic therapy for urge incontinence. *Int Urogyn J.* 2002;13(5):334-338.

Trials in an ineligible population

Dahm, T. L., Ostri, P., Kristensen, J. K., et al. Flavoxate treatment of micturition disorders accompanying benign prostatic hypertrophy: a double-blind placebo-controlled multicenter investigation. *Urol Int.* 1995;55(4):205-208.

Chancellor, M. B., Appell, R. A., Sathyan, G., Gupta, S. K. A comparison of the effects on saliva output of oxybutynin chloride and tolterodine tartrate. *Clin Ther.* 2001;23(5):753-760.

Chancellor, M., Appell, R. A., Sathyan, G., Gupta, S. Effect on salivary output following controlled-release oxybutynin and tolterodine. *Neur Urodyn.* 2000;19(4):28-31.

Benvenuti, C., Cova, A., Simonazzi, I. Urinary kinetics and tolerability of oral flavoxate in man. *Farmaco Ed Prat.* 1977;32(Feb):99-107.

Trials with an ineligible design

Wallace, S. A., Roe, B., Williams, K., Palmer, M. Bladder training for urinary incontinence in adults.[update of Cochrane Database Syst Rev. 2000;(2):CD001308; PMID: 10796768]. *Cochrane Database of Systematic Reviews.* 2004;1.

Schwantes, U., Topfmeier, P. Importance of pharmacological and physicochemical properties for tolerance of antimuscarinic drugs in the treatment of detrusor instability and detrusor hyperreflexia - Chances for improvement of therapy. *Int J Clin Pharmacol Ther.* 1999;37(5):209-218.

Millard, R. J., Asia Pacific Tolterodine Study, G. Clinical efficacy of tolterodine with or without a simplified pelvic floor exercise regimen. *Neur Urodyn.* 2004;23(1):48-53.

Michel, M. C., de la Rosette, J. J., Piro, M., Goepel, M. Does concomitant stress incontinence alter the efficacy of tolterodine in patients with overactive bladder? *J Urol.* 2004;172(2):601-604.

Burton, G. A randomised, cross-over trial comparing oxybutinin taken three times a day or taken 'when needed'. *Neur Urodyn.* 1994;13(4):351-352.

Burgio, K. L., Matthews, K. A., Engel, B. T. Prevalence, incidence and correlates of urinary incontinence in healthy, middle-aged women. *J Urol.* 1991;146(5):1255-1259.

Atan, A., Konety, B. R., Erickson, J. R., Yokoyama, T., Kim, D. Y., Chancellor, M. B. Tolterodine for overactive bladder: time to onset of action, preferred dosage, and 9-month follow-up. *Techniques in Urology.* 1999;5(2):67-70.

Trials with an ineligible duration of study

Milani, R., Scalambrino, S., Carrera, S., Pezzoli, P., Ruffmann, R. Comparison of flavoxate hydrochloride in daily dosages of 600 versus 1200 mg for the treatment of urgency and urge incontinence. *J Int Med Res.* 1988;16(3):244-248.

Milani, R., Scalambrino, S., Carrera, S., Pezzoli, P., Ruffmann, R. Flavoxate hydrochloride for urinary urgency after pelvic radiotherapy: comparison of 600 mg versus 1200 mg daily dosages. *J Int Med Res.* 1988;16(1):71-74.

Hooper, P., Tincello, D. G., Richmond, D. H. The use of salivary stimulant pastilles to improve compliance in women taking oxybutynin hydrochloride for detrusor instability: A pilot study. *Br J Urol.* 1997;80(3):414-416.

Briggs, R. S., Castleden, C. M., Asher, M. J. The effect of flavoxate on uninhibited detrusor contractions and urinary incontinence in the elderly. *J Urol.* 1980;123(5):665-666.

Excluded Studies Update 4

3=Wrong intervention, 4=wrong population, 6=wrong study design

Excluded studies	Exclusion codes
Head-to-head trials	
Armstrong RB, Dmochowski RR, Sand PK, et al. Safety and tolerability of extended-release oxybutynin once daily in urinary incontinence: combined results from two phase 4 controlled clinical trials. International Urology & Nephrology. 2007;39(4):1069-1077.	6
Horstmann M, Schaefer T, Aguilar Y, Stenzl A, Sievert KD. Neurogenic bladder treatment by doubling the recommended antimuscarinic dosage. Neurourology & Urodynamics. 2006;25(5):441-445.	4
Active control trials	
Chapple C, Van Kerrebroeck P, Tubaro A, et al. Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. European Urology. Oct 2007;52(4):1204-1212.	3
Kaplan SA, Roehrborn CG, Rovner ES, et al. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. [erratum appears in JAMA. 2007 Mar 21:297(11):1195]. JAMA. Nov 15 2006;296(19):2319-2328.	3
Robinson D, Cardozo L, Terpstra G, et al. A randomized double-blind placebo-controlled multicentre study to explore the efficacy and safety of tamsulosin and tolterodine in women with overactive bladder syndrome. BJU International. Oct 2007;100(4):840-845.	3
Song C, Park JT, Heo KO, Lee KS, Choo M-S. Effects of bladder training and/or tolterodine in female patients with overactive bladder syndrome: a prospective, randomized study. Journal of Korean Medical Science. Dec 2006;21(6):1060-1063.	6
Wang AC, Chih S-Y, Chen M-C. Comparison of electric stimulation and oxybutynin chloride in management of overactive bladder with special reference to urinary urgency: a randomized placebo-controlled trial. Urology. Nov 2006;68(5):999-1004.	6
Systematic Review	
Tulikangas PK, Ayers A, O'Sullivan DM, Tulikangas PK, Ayers A, O'Sullivan DM. A meta-analysis comparing trials of antimuscarinic medications funded by industry or not. BJU International. Aug 2006;98(2):377-380.	6

Drug Class Review

Agents for Overactive Bladder

Final Report Update 4
Evidence Tables

March 2009

Update 3 Report date: December 2005
Update 2 Report date: May 2005
Update 1 Report date: January 2004
Original Report date: February 2003
A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Marian S. McDonagh, PharmD
Dana Selover, MD, MPH
John Santa, MD
Sujata Thakurta, MPA:HA

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

TABLE OF CONTENTS

Note:
The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Prior versions of this report can be accessed at the DERP website.

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs.Tolterodine (Tol)			
Leung 2002	RCT Multicenter Hong Kong	Women, age ≥18, urodynamically confirmed diagnosis of overactive bladder (phasic detrusor contraction with an amplitude ≥15 cm water, urinary frequency (≥8 voids/24h), urgency or urge incontinence (≥1 incontinence episode/24h))	Diagnosis of stress incontinence, clinically significant voiding difficulty, UTIs, require catheterization, uninvestigated hematuria or bladder cancer, currently on treatment for overactive bladder or on anticholinergic drugs, presence of psychiatric disease or cognitive impairment, contraindications for antimuscarinic drugs. Patients underwent Mini Mental Status Exam and Electrocardiograph testing to rule out psychiatric or cardiovascular disease.
Lee 2002	RCT Multicenter South Korea	Male or female, 18+ yrs, with overactive bladder defined by symptoms of urinary frequency and urgency with or without incontinence.	Significant stress incontinence, any anticholinergic drug treatment within 2 wks, renal or hepatic disease, any contraindication to antimuscarinic therapy, UTI, interstitial cystitis or hematuria, bladder outlet obstruction, behavioral training, any urinary catheterization, and any other treatment started at least 2 months prior to enrollment.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs.Tolterodine (Tol)			
Leung 2002	Tol 2mg twice daily x 10 weeks Oxy 5mg twice daily x 10 weeks	None reported	Visual Analog Scale of patient assessment of severity of symptoms at baseline, 4 and 10 weeks, (0 = no effect, 10 = max severity), perceived changes in symptoms before and after treatment assessed at 4 and 10 weeks (+5 = max improvement, -5 = max deterioration). Voiding diary (1 week) at baseline, 4 and 10 weeks. Urinary pad test* at baseline and 10 weeks.
Lee 2002	Tol 2mg twice daily Oxy 5mg twice daily x 8 wks	estrogen allowed.	Micturition diary assessed at 8 wks Patient assessment of treatment benefits as yes/no; with yes further defined as little or much. Compliance assessed by tablet count at 8 wks

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Immediate Release vs Immediate Release (IR vs IR)				
Oxybutynin (Oxy) vs.Tolterodine (Tol)				
Leung 2002	106 enrolled (number per group not stated)	Age range 43-63 yrs Median age 49.5 female	56% postmenopausal, median parity 3	Withdrawals: Tol: 8 Oxy: 9 Number lost to follow-up not reported Number analyzed not clear
Lee 2002	228 enrolled (Tol 112, Oxy 116)	mean age 52 (range 20 to 86) 77% female	Previous drug therapy: Tol 32%, Oxy 22% mean # micturitions/d: 12 % with incontinence: 39%	41 (Tol 15, Oxy 26) Lost to f/u: 2 228 assessed by ITT, 187 by PP

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Immediate Release vs Immediate Release (IR vs IR)	
Oxybutynin (Oxy) vs.Tolterodine (Tol)	
Leung 2002	Diaries Analysis of variance shows NS between groups on any measure, all groups improved. Symptoms Change in overall severity (from baseline) Oxy: 4 and 10 weeks 0.7 Tol: 4 and 10 weeks 0.2 (NS by intention to treat, per protocol not reported) Perceived change in symptom severity (from baseline) Oxy: 4 and 10 weeks 1.0 Tol: 4 and 10 weeks 2.0 (NS at 4 weeks, at 10 weeks p = 0.053 by intention to treat, 0.047 by per protocol)
Lee 2002	ITT analysis: Mean change in Micturitions/d: Tol -2.6 Oxy -1.8 (NS) Mean change in incontinence/d: Tol -2.2 Oxy -1.4 (NS) PP analysis: Patient perception of benefit: Tol 45% much benefit Oxy 46% much benefit (NS)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Immediate Release vs Immediate Release (IR vs IR)	
Oxybutynin (Oxy) vs.Tolterodine (Tol)	
Leung 2002	Xerostomia Questionnaire at 4 and 10 weeks, independent reporting of other side effects. Significant deterioration on all measures of dryness except denture fit, for both drugs. NS between groups. Side effects reported: Oxy 49% Tol 60% (NS) Reported to be mostly abdominal aches, general malaise and urinary retention
Lee 2002	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, and relationship to study drug. 227 patients assessed Tol: 62 patients reported 101 adverse events Oxy: 94 patients reported 154 adverse events (p = 0.001) Dry mouth: Tol 39 (35%) 72 (63%) (p<0.001) Severe dry mouth: Tol 1 (1%), Oxy 6 (5%) Micturition disorder: Tol 10 (9%), Oxy 16 (14%) Dyspepsia/abdominal pain: Tol 14 (13%), Oxy 12 (10%) Headache: Tol 4 (4%), Oxy 6 (5%)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs.Tolterodine (Tol)		
Leung 2002	Unclear. States that most withdrawals not due to side effects, but that patients withdrawing while on Oxy were more likely to have co-existing illnesses (p<0.012).	Compliance measured. Oxy 87.5% (11 to 99.3) Tol 75% (8.9 to 98.8) (NS)
Lee 2002	29 : Tol 11 (6 dry mouth, 55%) Oxy 18 (16 dry mouth, 88%)	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Abrams 1998	RCT Multicenter UK, Ireland and Sweden	Men or women 18+ yrs, urodynamically confirmed bladder overactivity, increased frequency (8 or more micturitions/24hrs), and urge incontinence (1 or more episodes/24hrs) and/or urgency during a 2 week washout/run-in period.	Clinically significant stress incontinence, detrusor hyper-reflexia, hepatic, renal or hematologic disorders, symptomatic or recurrent UTI, bladder outlet obstruction, bladder training or electrostimulation, indwelling or intermittent catheter
Drutz 1999	RCT Multicenter USA/Canada	Age 18+ with evidence of detrusor overactivity on cystometry, along with urinary frequency, and either urge incontinence or urinary urgency.	Clinically significant stress incontinence, renal or hepatic disease, any disease which the investigator thought would make the patient unsuitable, UTI, interstitial cystitis, hematuria, any catheterization, behavioral training within 14d, unstable dose of any drug with anticholinergic side effects, previous serious adverse effects on Oxy, mean voided volume/d >3L, or risk of urinary retention.
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs Flavoxate (Fla)			

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Abrams 1998	Tol 2mg twice daily Dose could be dropped to 1mg during first 2 weeks if not tolerated Oxy 5mg three times daily Dose could be dropped to 2.5mg during first 2 weeks if not tolerated Pl three times daily Subjects >/= 65 yrs in UK and Ireland could start the dose of Oxy at 2.5mg and increase to 5mg during first 2 weeks Total trial duration 12 weeks	None reported	Micturition diary assessed at 2, 4, 8, and 12 weeks Patient assessment of severity of symptoms based on 6-point scale (0 = no problems, 6 = severe problems) Change between baseline and 12 weeks defined as decrease in score of 1 or more points.
Drutz 1999	Tol 2mg twice daily Oxy 5mg three times daily Placebo three times daily x 12 wks Dose reduction to Tol 1mg or Oxy 5mg twice daily allowed during first 2 wks.	None reported	Change in micturitions/d and incontinence episodes/d at 12 wks, assessed by micturition diary.
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs Flavoxate (Fla)			

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Abrams 1998	Number screened/eligible not stated 293 enrolled (118 Tol, 118 Oxy, 57 Pl)	Age range 19-80 yrs Mean age Tol 55, Oxy 58, Pl 58 76% female	Previous drug therapy: Tol 52%, Oxy 60%, Pl 75% Mean micturitions/24h: 12 Tol, 11 Oxy, 12 Pl Mean incontinence episodes/24h: 2.9 Tol, 2.6 Oxy, 3.3 Pl	37 (10 Tol, 20 Oxy, 7 Pl) reported withdrawing due to adverse effects, no other withdrawals or loss to follow-up reported, but 3 patients missing in 'evaluable patients'.
Drutz 1999	277 enrolled (Tol 109, Oxy 112, Placebo 56)	mean age: Tol 63yrs, Oxy 66 yrs, placebo 62 yrs % female: Tol 81, Oxy 72, Placebo 80 % Caucasian: Tol 87, Oxy 94, Placebo 93	% hyperreflexia: Tol 7, Oxy 7, Placebo 5 % Previous drug therapy: Tol 45, Oxy 45, Placebo 55 % with incontinence: Tol 83, Oxy 92, placebo 89 % Prior Urinary tract surgery: Tol 27, Oxy 45, placebo 34	57withdrew 147 analyzed (70 Tol, 41 Oxy, 36 placebo) 27 excluded due to dose reductions 46 excluded due to protocol violations
Immediate Release vs Immediate Release (IR vs IR)				
Oxybutynin (Oxy) vs Flavoxate (Fla)				

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Abrams 1998	Change in mean number of voids/24 hrs at week 12: -2.7 Tol, -2.3 Oxy, -1.7 Pl (Tol vs. Oxy NS) Change in mean number of incontinence episodes/24 hrs at week 12:(n = 92 Tol, 88 Oxy, 40 Pl) -1.3 Tol, -1.7 Oxy, -0.9 Pl (Tol vs. Oxy NS) Change in subjective assessment of symptoms at week 12: Improved 50% Tol, 49% Oxy, 47% Pl
Drutz 1999	PP analysis: Change in mean micturitions/d: Tol -2.0, Oxy -2.0, placebo -1.1 (NS for Tol vs Oxy) Change in incontinence/d: Tol -1.7, Oxy -1.7, placebo -1.0 (NS for Tol vs Oxy) Other variables: At least 50% reduction in frequency: Tol 63%, Oxy 65% Cure (no incontinence in 7 days prior) Tol 21%, Oxy 22%
Immediate Release vs Immediate Release (IR vs IR)	
Oxybutynin (Oxy) vs Flavoxate (Fla)	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Abrams 1998	All adverse events were recorded and categorized by intensity (mild, moderate, severe). The likelihood of relationship to study drug was evaluated for serious adverse events and patient withdrawn if deemed medically necessary or patient wished withdrawal. At least one adverse event reported: 89% Tol, 97% Oxy, 81% Pl (Tol vs. Oxy p = 0.023) Dry mouth: 50% Tol, 86% Oxy, 21% Pl (Tol vs. Oxy p<0.001) More patients reported dry mouth to be severe on Oxy than on Tol or Pl (numbers not given) 1 serious adverse event (syncope) was considered related to Tol
Drutz 1999	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, at visits at 2, 4, 8 and 12 wks ITT analysis: % reporting adverse events: Tol 78%, Oxy 90, placebo 75 (p = 0.013 Tol vs Oxy) Dry mouth: Tol 30%, Oxy 69%, placebo 15% (p <0.001 Tol vs Oxy) Moderate to severe dry mouth: Tol 9%, Oxy 44%, placebo 7% Other adverse events reported: headache: Tol 15%, Oxy 10% dizziness: Oxy 11% (others not reported) cardiovascular events: Tol 7%, Oxy 8% Dose reduction: Tol 7%, Oxy 23%, placebo 4% (p<0.001 Tol vs Oxy)
Immediate Release vs Immediate Release (IR vs IR)	
Oxybutynin (Oxy) vs Flavoxate (Fla)	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Abrams 1998	Tol 8%, Oxy 17%, Pl 2% Due to dry mouth: Tol 0.8%, Oxy 13%, Pl 3.5%	Dose reductions requested by 8% Tol, 32% Oxy, 2% Pl (Tol vs. Oxy p<0.001)
Drutz 1999	Tol 7 (6%), Oxy 23 (21%), placebo 4 (7%) (p = 0.002 Tol vs Oxy)	Only Allowed dose reductions in protocol, but then excluded these from analysis. Incomplete reporting of adverse events. 46 excluded from analysis due to protocol violations, but which groups assigned not reported.
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs Flavoxate (Fla)		

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Milani 1993	RCT, Crossover Multicenter Italy	Females, 18+, with motor or sensory urgency according to the criteria of the International Continence Society.	Severely ill, overt neurological disease, non-compliant, or taking drugs that could affect urinary symptoms.
Zeegers 1987	RCT, Cross-over study Multicenter Netherlands, Austria	Weight 56-85kg Symptoms: frequent voiding, urgency or urge incontinence (patients with neurogenic bladder may have been included)	Kidney, liver or cardiovascular pathology, obstruction or infection, ongoing anticholinergic therapy, glaucoma or Parkinson's disease

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Milani 1993	Fla 400mg or Oxy 5 mg x 4wks, then crossover after 7 d washout	not given	Diurnal and nocturnal frequency, incontinence, urgency, dysuria and pad use by diary. Symptoms scored 0,1, or 2 with 0 = best, 2 = worst. Evaluated at baseline at 4wks. Patient assessment of results at 4 wks (cured, improved, no change, worse).
Zeegers 1987	Randomized to either: {Fla 200mg three times daily x 3 weeks, Emp 200mg three times daily x 3 weeks, Pl three times daily x 3 weeks} or {Oxy 5mg three times daily x 3weeks, Emp 200mg three times daily x 3 weeks, Pl three times daily x 3 weeks) with the order of drugs also randomized.	None reported	Patient and physician score at end of each 3 week period; 1 = no effect, 5 = excellent effect.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Milani 1993	50 enrolled	mean age 51 (range 19 to 78) 100% female	23 (46% sensory urge, 54% motor urge.	9 withdrawn: Fla: 3 poor compliance Oxy: 1 poor compliance, 5 side effects 41 analyzed
Zeegers 1987	Number screened/eligible not stated; stated to be consecutive patients 60 enrolled (30 in Fla/Emp/Pl, 30 in Oxy/Emp/Pl)	Age range 16-78 yrs Reported by center and by completer/noncompleter status rather than by treatment group. 70% female	None reported	12 withdrawn due to side effects, 5 lost to follow-up, 2 found to have non-urologic pathology 41 completed entire protocol and were analyzed

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Milani 1993	Mean change in scores (0-2): Fla: 0.78, Oxy 0.83 Incontinence: Fla 1.05, Oxy 0.9 Urgency: Fla 0.66, Oxy 0.92 Pads: Fla 0.59, Oxy 0.71 Dysuria: Fla 0.072, Oxy 0.072 Patient assessment (n=38) Fla: 82% cured or improved Oxy: 79% cured or improved (NS) Patient's preference: 61% Fla, 37% Oxy, 2% no preference
Zeegers 1987	NS found between drugs in reduction in urge, instability or incontinence episodes. Patient and Physician scores were combined in results: Average score: 2.25 Pl, 2.28 Emp, 2.02 Fla, 2.95 Oxy (stated Oxy significantly better, no p-value given) Fair/Good/Excellent Score: 41% Pl, 34% Emp, 31% Fla, 61% Oxy

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Milani 1993	Adverse events were elicited at 4 wks, and rated as serious or nonserious and according to intensity. By ITT: Fla 11/50 (22%), Oxy 42/50 (84%), plus 5 patients withdrawn due to adverse events. Dry mouth: Fla 2%, Oxy 78% Abdominal or stomach pain: Fla 24%, Oxy 36%
Zeegers 1987	Combined in score 15% Pl, 26% Emp, 8% Fla, 17% Oxy

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Milani 1993	5 (10%)	
Zeegers 1987	12 withdrawals: 2 Pl, 8 Emp, 0 Fla, 2 Oxy	Analysis of the effect of the previous treatment on scores for current treatment showed no change in Oxy score. Without prior drug treatment scores are: Pl 29%, Emp 18%, Fla 44%, Oxy 63% with fair/good/excellent response

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Immediate Release (ER vs IR)			
Oxybutynin ER vs Oxybutynin IR			
Versi 2000	RCT Multicenter USA	Community dwelling adults, 7 to 45 urge incontinence episodes/wk, at least 4 days of incontinence/wk, previous response to treatment with anti-cholinergic drug	clinically significant medical problems, postvoid residual urine volume over 100ml, other conditions in which oxybutynin is contraindicated
Birns 2000	RCT multicenter UK	Age 18 to 76 yrs, outpatients with voiding problems and currently stabilized on and tolerant to treatment with Oxy 5mg twice daily, with bladder sensation, and able to keep a diary chart	other anticholinergic drugs or drugs with anti-cholinergic effects, contraindication to anti-cholinergic therapy, (myasthenia gravis, glaucoma, functional or organic gastric obstruction), UTI, bladder outlet obstruction, only of nocturnal enuresis

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Extended Release vs. Immediate Release (ER vs IR)			
Oxybutynin ER vs Oxybutynin IR			
Versi 2000	Oxy ER 5-20mg once daily or Oxy IR 5-20mg/d - schedule not reported doses increased in 5mg/day increments every 7 days doses decreased by 5mg if side effects were intolerable Optimal dose identified and taken for 1 week	none reported	7 day urinary diary after maintenance dose determined
Birns 2000	Oxy ER 10mg once daily or Oxy 5mg twice daily x 6 wks	none reported	Urinary diary (micturition and incontinence episodes) reviewed at visits 2, 3, 4

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Extended Release vs. Immediate Release (ER vs IR)				
Oxybutynin ER vs Oxybutynin IR				
Versi 2000	screened 417 eligible/enrolled 226	Mean age 59yrs ER; 60yrs IR % Female: ER 88%, IR 90% Ethnicity: White: 86.5 ER; 90.4 IR Black: 5.4ER; 3.5 IR Asian: 0.9 ER; 0 IR	Urge incontinence episodes/wk: ER 18.6, IR 19.8	withdrawn ER: 6 IR: 9 Lost to f/u ER: 1 IR: 0 analyzed ER 111 IR 115
Birns 2000	162 screened 130 randomized	mean age: 56 yrs % female: 68% (ER 71%, IR 66%)	81% with urge or stress/urge incontinence (ER 78%, IR 84%)	Loss to f/u: 2 (1 each arm) Analyzed: 128 by ITT, 125 by PP

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Extended Release vs. Immediate Release (ER vs IR)	
Oxybutynin ER vs Oxybutynin IR	
Versi 2000	Mean change in urge incontinence episodes/wk: -15.7 ER, -15.4 IR (NS)
Birns 2000	Daytime continence at 4 wks ER 53%, IR 58% (NS) Secondary Criteria No of pts with night-time continence at completion of study median change in the no of voluntary daytime voids voluntary night-time voids daytime episodes of incontinence night-time episodes of incontinence No clinically significant difference between treatment groups Exact information not given

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Extended Release vs. Immediate Release (ER vs IR)	
Oxybutynin ER vs Oxybutynin IR	
Versi 2000	Reports of adverse effects recorded at each pt visit Dry mouth: ER 48%, IR 59% Kaplan Meier analysis moderate or severe dry mouth reports indicates a significant difference (p = 0.007) in favor of ER
Birns 2000	Assessed during visits every two weeks 78 pts reported adverse events (60%) (ER 55%, IR 67%) Dry mouth: ER 23%, IR 17% Dizziness ER 2%, IR 9% Vision abnormality ER 7%, IR 5% Cough ER 3%, IR 5% Headache ER 0, IR 5%

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Extended Release vs. Immediate Release (ER vs IR)		
Oxybutynin ER vs Oxybutynin IR		
Versi 2000	Overall: 10 (8%) ER: 3 (3%) abdominal pain: 1 nausea/dysphagia: 1 edema/rash: 1 IR: 7 (6%) dry mouth: 1 blurred vision: 1 nausea: 1 impaired urination, edema, blood pressure changes, UTI: 1 gastric obstruction: 1 UTI: 1 edema and pain: 1	Mean duration of treatment/follow-up not stated. Only dry mouth reported in detail.
Birns 2000	1 (considered unlikely due to study drug)	Mixed types of incontinence Study included a run-in phase to establish tolerability, patients with adverse events excluded during run-in

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Radomski 2004	Single center Open label pilot crossover trial Canada	Efficacy analysis included all subjects age ≥18 with urodynamically confirmed detrusor instability, frequent micturition (≥ 8/day) and/or urinary incontinence (≥2 incontinence period /day) during washout period. Patients could be on oxybutynin IR prior to study. Safety analysis included all patients receiving at least one dose of medication.	Use of medications other than study meds, primary diagnosis of stress incontinence, allergy to anticholinergics/antispasmodics, conditions contraindicating anticholinergic therapy, large daily fluid intake (>6 liters), hepatic/renal disease, interstitial cystitis, uninvestigated hematuria or hematuria secondary to a malignancy, history of recurrent urinary tract infection, indwelling catheter, bladder training within 14 days of entry, drug/alcohol abuse, recent initiation of estrogen, clinically significant neurological disorder, morbid obesity, pregnant or nursing, child bearing age not using contraceptives
Anderson 1999	RCT multi-center USA	Men or women, community dwelling, in good health with urge incontinence or mixed urge incontinence with primary urge component (6+ urge incontinence episodes/wk)	known treatable cause, greater than 100mL post void residual, prostate symptoms in the past 9 mos, risk for complete urinary retention, taken drugs other than hyoscyamine, oxybutynin, propantheline for incontinence, positive urine drug screen, glaucoma, gastric narrowing or myasthenia gravis
Nilsson 1997	Crossover study Multicenter Finland	Females with a history of urge incontinence and detrusor instability confirmed by cystometry.	Stress incontinence (as measured by questionnaire), use of loop diuretics, prazosin, anticholinergics, or antidepressants with anticholinergic effects.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Radomski 2004	Oxy IR twice daily at dose at discretion of investigator for first two weeks (if on Oxy IR prior same dose continued 3 patients, if deemed obese 5 mg twice daily otherwise 2.5 mg twice daily), followed by two week washout, followed by Oxy CR 15 mg once daily for four weeks	Subjects not permitted to use other medications to alleviate incontinence during the 8 week trial	Satisfaction rating at end of week 2 and week 8 using a four point scale.
Anderson 1999	ER Oxy 5-30mg once daily or IR Oxy 5mg once to four times daily. Doses started at 5mg and adjusted during 4 to 7 day intervals, optimal dose taken for 7 days. dose reductions allowed for adverse effects	not given	7-day voiding diary and incontinence pad use at baseline and after "final dose" achieved Duration of study varied by patient, depending on titration needs.
Nilsson 1997	Oxy ER 10mg once daily Oxy 5mg twice daily 60 days, no washout between arms	none reported	urinary diary, disability questionnaire, and assessment of effect of symptoms on general welfare, work, exercise, urge, symptoms of leakage, and frequency by VAS measured at 7-8 wks

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Radomski 2004	#screened not reported. 12 included for safety analysis. 9 included for efficacy analysis (completed 8 week study)	For efficacy analysis mean age = 69 female 67% For safety analysis mean age not reported, % females same. Ethnicity not reported	Baseline/washout: number of voluntary voids/day 10.4;number of UI episodes/day 2.7. Patients diagnosed for average 10.8 months prior to study entry (SD=6.6).	3/0/9
Anderson 1999	158 screened 105 enrolled 93 analyzed	Mean age: ER 59yrs; IR 60yrs % Female: ER 94%, IR 90%	mean urge incontinence episodes/wk: ER 27.4, IR 23.4 mean voids/wk: ER 48.3, IR 51.5	withdrawn ER 7 IR 6 Lost to F/U not reported analyzed 93 (efficacy analysis)/105 (safety analysis)
Nilsson 1997	17 enrolled	mean age 46yrs (range 37-65) 100% female	none reported	1 "due to the sponsors' request" after first study period 16 analyzed in ER group, 17 in IR group

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Radomski 2004	ER reduced UI episodes from baseline 45% (p=0.13) vs IR 7% (p=0.58). Treatment scores differed by 1.0 UI episode/day (p=0.11) favoring ER. ER reduced daily void frequency by 14 % compared to IR 6% (p=0.41). No significant difference in mean satisfaction scores at end of IR and ER phases.
Anderson 1999	mean reduction in number of Urge Incontinence/wk ER: 22.6 IR:20.3 (NS) mean reduction in total incontinence episodes ER: 23.3 IR: 22.5 (NS)
Nilsson 1997	Mean change in micturitions/d: ER: 2.6, IR 2.8 mean change in degree of disability: ER: 5.1, IR 4.6 Mean change in VAS Scores: general welfare: ER 36, IR 39 work ER 33 IR41 exercise ER 31 IR 35 urge ER 32 IR 35 leakage ER 27 IR 35 frequency ER 36 IR 37 No comparisons were statistically significant

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Radomski 2004	Adverse events collected during scheduled visits and entered in diary. Mild dry mouth most frequent followed by unspecified pain
Anderson 1999	Spontaneously reported and anti-cholinergic effects assessed at each study visit Dry mouth: ER 68%, IR 87% (p = 0.04) Moderate to severe dry mouth: ER 25%, IR 46% (p = 0.03) Somnolence: ER 38%, IR 40% Blurred vision: ER 28%, IR 17% Constipation: ER 30%, IR 31% Dizziness ER 28%, IR 38%
Nilsson 1997	Patients reported on a questionnaire throughout study, classified as mild, moderate, severe 14/16 on ER, 5/17 on IR reported at least one adverse event Dry mouth: ER 69%, IR 82% Headache ER 44%, 41% Dyspepsia ER 31%, IR 12% fatigue ER 13%, 24% Blurred vision 25%, IR 12% % Severe: ER 17%, IR 14% reported that these were NS, but unclear what data being compared.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Radomski 2004	3 withdrawals due to adverse events--stomach pain (1), mild peripheral edema (1), severe vision distortion	Unusual design--different treatment duration for two drugs and dosing for Oxy may have been low
Anderson 1999	2 (4%) in each group due to anticholinergic adverse events	Previously all pts had responded to IR oxy Very high incidence of adverse events - may reflect the aggressive dose titration Duration of study (mean) not reported, very little data on final dose in either group
Nilsson 1997	none reported	Very high numbers of subjects reporting adverse events

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Barkin 2004	RCT Multicenter Canada	Men and women, age ≥18, demonstrated UI (≥ 7 episodes/wk) and urinary frequency (≥8 micturitions/d) during baseline no-treatment period, currently not using any other medication for UI	Post-void residual volume >100mL, unstable dosage of any drug with anticholinergic or diuretic/antidiuretic side effects, allergy or previous life-threatening side effects with anticholinergic/ antispasmodic medications, primary diagnosis of stress UI, conditions contraindicating anticholinergic therapy, daily fluid intake >3L, hepatic/renal disease, diagnosed painful bladder syndrome, uninvestigated voiding difficulty with risk of urinary retention, uninvestigated hematuria or hematuria secondary to malignant disease, UTI or history of recurrent UTI (>3 UTIs/y), in-dwelling catheter or bladder training within 14d of screening, drug/alcohol abuse, untreated psychiatric conditions affecting completion of voiding diaries, bladder outlet obstruction, pregnancy or breast feeding and failure to use reliable contraception in women of childbearing potential

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Barkin 2004	No-treatment baseline period for 3 wks Oxy IR 5mg 3X/day, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks Oxy ER 15mg 1X/day, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks	Subjects not permitted to use other medications to alleviate incontinence during the 9 week trial period	24h-patient diary assessed during final 2 wks of treatment, used the Purdue Urgency Questionnaire to assess severity of urgency and frequency of urgency [severity scored on scale or 1 (no urgency or ability to delay voiding) to 5 (≥ 6 episodes of urgency or inability to delay voiding/urine leakage with urge)], used Incontinence Impact Questionnaire (evaluates effect of incontinence on 8 activities of daily living) and the Urogenital Distress Inventory (evaluates distress associated with 8 urinary symptoms) to assess changes in QoL.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Barkin 2004	NR / NR / 125 enrolled (Oxy IR 60, Oxy ER 65)	Of 94 subjects evaluable for efficacy: Oxy ER: 91% women; mean age 58y (range 26-78y), 38% >65y Oxy IR: 90% women; mean age 60.6y (range 26-83y), 44% >65y	41% of patients were taking ≥4 medications at study entry	Withdrawals: Oxy IR:22 (37%); Oxy ER:13 (20%) Lost to follow-up: Oxy IR: 2; Oxy ER:0 Number analyzed for efficacy: 94 defined as completing ≥2 weeks in the stable-dose phase and did not have major protocol violations/ Reported adverse events were analyzed for all randomized patients

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Barkin 2004	Oxy ER vs Oxy IR for all comparisons (endpoint minus baseline): Mean reduction in incontinence episodes/wk: 13.9 vs 16.9 (p=NS) Mean reduction in episodes of voluntary micturition/day: 1.8 vs 2.4 (p=NS) Mean increase in vol. of urine voided/micturition: 25mL vs 40mL (p=NS) Mean score of urgency decrease: 1.0 vs 1.3 (p=NS) Mean severity score decrease (1: no urgency or ability to delay voiding, to 5: ≥6 episodes of urgency or inability to delay voiding): 1.5 vs 1.4 (p=NS) Mean number of pads/day: 0.6 vs 0.5 (p=NS)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Barkin 2004	AE data collected during scheduled visits and in diary. AE data included tolerable/not tolerable questions, # and severity of the events, lab assessments: clinical chemistry and hematological (at baseline and end of study) <u>Oxy ER vs Oxy IR (%)</u> Dry mouth: overall: 68% vs 72%; moderate or severe: 38% vs 45% Pharyngitis (dry throat): 35% vs 40% Dry skin: 17% vs 12% Diarrhea: 14% vs 5% Headache: 12 % vs 22% Urinary tract infection: 12 % vs 18% Dizziness: 11% vs 18% Dyspepsia: 11% vs 17% Rhinitis: 11% vs 15% Abdominal pain: 9% vs 10% Asthenia: 18% vs 15% Constipation: 8% vs 10% Taste perversion: 8% vs 12% Cough increased: 6% vs 13% Dysphagia: 6% vs 13% Dry eyes: 3% vs 15% Nausea: 5% vs 17%

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Barkin 2004	Oxy IR: 12 (20%) Oxy ER: 11 (17%)	sponsored by Purdue Pharma

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Immediate Release (ER vs IR)			
Tolterodine ER vs Tolterodine IR			
Van Kerrebroeck 2001	RCT Multicenter Multinational	Men or women, age 18+ with urinary frequency (8+ micturitions/24h), urge incontinence (5+ /week), or symptoms of overactive bladder for 6+ months	Stress Incontinence, total daily urine volume 3+ L, contraindications to anticholinergic drugs, hepatic/renal disease, UTI/cystitis, hematuria, bladder outlet obstruction, electrostimulation or bladder training, urinary catheter, taking drugs inhibiting CYP 3A4 liver enzymes,
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	RCT Multicenter International	Subset of above study: women, age 18+ with urinary frequency (8+ micturitions/24h), urge incontinence (5+ /week), or symptoms of overactive bladder for 6+ months	Stress Incontinence, total daily urine volume 3+ L, contraindications to anticholinergic drugs, hepatic/renal disease, UTI/cystitis, hematuria, bladder outlet obstruction, electrostimulation or bladder training, urinary catheter, taking drugs inhibiting CYP 3A4 liver enzymes,

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Extended Release vs. Immediate Release (ER vs IR)			
Tolterodine ER vs Tolterodine IR			
Van Kerrebroeck 2001	Tol ER 4mg once daily or Tol IR 2mg or Placebo twice daily x 12 wks	none reported	micturition diary assessed at baseline and 12 wks 1 week f/u
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Tol ER 4 mg (n=417) once daily vs. Tol IR 2 mg twice daily (n=408) vs. Pla (n=410) for 12 wks.	Other treatments for OAB not permitted, except estrogen treatment commenced >2 months prior.	micturition diary assessed at baseline and 12 wks 1 week f/u

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Extended Release vs. Immediate Release (ER vs IR)				
Tolterodine ER vs Tolterodine IR				
Van Kerrebroeck 2001	1529 randomized into study Tol ER: 507 Tol IR: 514 placebo: 508	median age 60yrs 81% Female	Mean number incontinence episodes/wk: ER 22, IR 23, Placebo 23 Mean number micturitions/d: ER 11, IR 11, Placebo 11 previous therapy for UI ER: 53%, IR 54%, Placebo 52% poor efficacy ER: 3%, IR 38%, Placebo 41%	187 (12%)
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Screened NR Eligible NR Enrolled=1235	Mean age=59 All female 95% white 4% black 1% other	Previous drug therapy for OAB=55% Mean number incontinence episodes/wk ER 22, IR 23, Placebo 24 Mean number voluntary micturitions/d: ER 11, IR 11, Placebo 11 previous therapy for UI ER: 56%, IR 54%, Placebo 55%	143 (12%)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Extended Release vs. Immediate Release (ER vs IR)	
Tolterodine ER vs Tolterodine IR	
Van Kerrebroeck 2001	Mean change in incontinence episodes/wk: ER -11.8, IR -10.6, Placebo -6.9 Mean change in number of micturitions/wk: ER -3.5, IR -3.3, Placebo -2.2 Mean change in number of pads used/d: ER -0.5, IR -0.5, Placebo -0.2 Median Percent Change in Incontinence episodes (time period not stated): ER -70%, IR -60%, Placebo -33% (p< 0.05 ER vs IR)
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Mean change in incontinence episodes/wk: ER -11.8, IR -10.1, Placebo -7.2 (p=0.036 ER vs IR) Mean change in number of voluntary micturitions/wk: ER -1.9, IR -1.7, Placebo -1.2 Mean change in number of pads used/d: ER -0.6, IR -0.5, Placebo -0.2 (all ER and IR vs. Pla statistically significant)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Extended Release vs. Immediate Release (ER vs IR)	
Tolterodine ER vs Tolterodine IR	
Van Kerrebroeck 2001	Spontaneously reported events were categorized and causation assigned dry mouth further categorized Dry mouth: ER 23%, IR 30%, Placebo 8% Constipation: ER 6%, IR 7%, Placebo 4% Headache: ER 6%, IR 4%, Placebo 5%
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Reporting details NR. Tol ER vs. Tol IR vs. Pla: Dry mouth: 105/415 (25.3%) vs. 127/407 (31.2%) vs. 33/410 (8.0%) Dry skin: 2 (0.5%) vs. 5 (1.2%) vs.1 (0.2%) Dizziness: 7 (1.7%) vs. 7 (1.7%) vs. 4 (1.0%) Somnolence: 12 (2.9%) vs. 11 (2.7%) vs. 8 (2.0%) Abnormal vision: 5 (1.2%) vs. 4 (1.0%) vs. 2 (0.5%) Constipation: 27 (6.5%) vs. 27 (6.6%) vs. 14 (3.4%)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Extended Release vs. Immediate Release (ER vs IR)		
Tolterodine ER vs Tolterodine IR		
Van Kerrebroeck 2001	88 (5.7%) ER: 27 (5.3%) IR: 28 (5.5%) placebo 33 (6.5%)	Dry mouth classified as mild/moderate/severe but data only reported for ER
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Tol ER 22/417 (5%) vs. Tol IR 20/408 (5%) vs. Pla 26/410 (6%)	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Immediate Release (ER vs IR)			
Oxybutynin ER vs. Tolterodine IR			
Appell 2001	RCT Multicenter USA	Overactive bladder between 7 and 50 episodes per week of urge incontinence 10+ voids/24 hr mixed stress and urge incontinence if the majority of accidents were related to urinary incontinence	Other causes of incontinence post void residual volume more than 150ml delivered baby pelvic bladder vaginal or prostate symptoms in past 6 months risk of complete urinary retention clinically important medical problems organ abnormalities hematuria positive urine culture narrow angle glaucoma pelvic organ prolapse gastric conditions anticholin drugs must be discontinued known allergy alcohol or drug abuse (current) unable to follow direction or schedules not able to swallow tablets whole

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Extended Release vs. Immediate Release (ER vs IR)			
Oxybutynin ER vs. Tolterodine IR			
Appell 2001	ER Oxy 10mg once daily Tol 2mg twice daily 12 week study	Not given	Safety monitoring patient reporting at each study visit 2,4,8,12 weeks number of urge incontinence episodes at 12 weeks vs. baseline used 7 day urinary diary

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Extended Release vs. Immediate Release (ER vs IR)				
Oxybutynin ER vs. Tolterodine IR				
Appell 2001	378 randomized (Oxy ER 185, Tol 193) 332 completed (Oxy ER 160, Tol 172)	Mean Age: 59 yrs Female: 83% Ethnicity: White 87% African American 6% Hispanic 4% Asian 2% Other 1%	Drug naïve Oxy ER: 109 Tol: 119	Overall: 46 (21 Tol, 25 Oxy ER) Lost to Follow-up Oxy ER: 3 Tol:3

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Extended Release vs. Immediate Release (ER vs IR)	
Oxybutynin ER vs. Tolterodine IR	
Appell 2001	Mean number of urge incontinence episodes/wk Oxy ER -19.5, Tol -16.3 Mean change in micturition frequency Oxy ER -24.7, Tol -20.1

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Extended Release vs. Immediate Release (ER vs IR)	
Oxybutynin ER vs. Tolterodine IR	
Appell 2001	Patient reported dry mouth occurred in equal proportion in each group both groups had similar rates of dry mouth and other adverse effects

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Extended Release vs. Immediate Release (ER vs IR)		
Oxybutynin ER vs. Tolterodine IR		
Appell 2001	Oxy ER 14 Tol 15	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Sand et al. 2004 OBJECT (subanalysis of women only)	RCT Multicenter USA	see Appell, 2001	see Appell, 2001

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Sand et al. 2004 OBJECT (subanalysis of women only)	Oxy ER 10mg once daily Tol 2mg twice daily 12 week study	see Appell, 2001	Subjects completed 7-day voiding diaries at baseline and 12-weeks

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Sand et al. 2004 OBJECT (subanalysis of women only)	315 women enrolled/ 276 completed study	mean age: Oxy 58.4y and Tol 58.8y 100% female	Naïve to anticholinergics: Oxy 60.5% and Tol 60.7%	see Appell, 2001

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Sand et al. 2004 OBJECT (subanalysis of women only)	see Appell, 2001 Decrease in urge incontinence episodes: Oxy ER: -21.9, Tol: -20.4 Mean decrease in micturition frequency episodes Oxy ER: -23.7, Tol: -20.4 Total decrease incontinence episodes Oxy ER: -17.9, Tol: -15.1

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Sand et al. 2004 OBJECT (subanalysis of women only)	see Appell, 2001 Oxy ER vs. Tol Dry mouth: 28.3% vs 33.7% Constipation: 8.6% vs 6.7% Impaired urination/urinary retention: 4.0% vs 1.2% Blurred vision: 2.6% vs 0.6% Dizziness: 3.9% vs 4.3% Somnolence: 3.3% vs 1.8% Insomnia: 0.7% vs 1.8% Nervousness: 0.0% vs 1.2% Headache: 9.2% vs 10.4% Dyspepsia: 5.3% vs 6.1% Nausea: 3.3% vs 1.8% Vomiting: 2.0% vs 1.8%

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Sand et al. 2004 OBJECT (subanalysis of women only)	withdrawals due to AE: Oxy 11 patients and Tol 12 patients	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Immediate Release (ER vs IR)			
Tolterodine ER vs. Oxybutynin IR			
Homma 2003	RCT Multicenter Japan & Korea	Men and women, aged ≥20 with symptoms of urinary urgency, frequency (>/= 8 voids/24h), incontinence (>/= 5 episodes/wk), or overactive bladder for ≥6months.	Demonstrable stress incontinence; total daily urinary volume >3 L, avg volume >200 mL; significant hepatic or renal disease; any contraindication to anticholinergic treatment; symptomatic or recurrent UTI; interstitial cystitis; haematuria or BOO; indwelling catheter or intermittent self-catheterization; electrostimulation or bladder training within 14 days or expected during study.
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	RCT Multicenter Japan & Korea (this subanalysis looked at Japanese pts only)	Men and women, aged ≥20 with symptoms of OAB for ≥ 6 months and urinary urgency, frequency (≥ 8 voids/24h), incontinence (≥ 5 episodes/wk), or overactive bladder for ≥6months.	Korean patients were excluded from analysis due to lack of valid King's Health Questionnaire in Korean language
Darifenacin ER vs. Oxybutynin IR			

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Extended Release vs. Immediate Release (ER vs IR)			
Tolterodine ER vs. Oxybutynin IR			
Homma 2003	Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks	Not allowed within 14 days of trial: anticholinergic drug or unstable dosage of any drug with anticholinergic side-effects, any drug for OAB (except estrogen started >2months), potent CYP3A4 inhibitors, or any investigational drug.	Voiding diary for 7 days at baseline and wk 12. Primary outcome, change in median number of incontinence episodes. Secondary endpoint, median number and volume of voids, number of incontinence pads used. Subjective assessment by 6-pt perception of bladder condition, 3-pt perception of urgency, and 3-pt assessment of treatment benefit. Quality of life measured by KHQ at baseline and 12 wks
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks	See Homma 2003	Micturition diary completed during 7 days of run-in (baseline and the last 7days of treatment (week 12) King's Health Questionnaire (KHQ) was used to determine health related quality of life (HRQoL) at baseline and week 12
Darifenacin ER vs. Oxybutynin IR			

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Extended Release vs. Immediate Release (ER vs IR)				
Tolterodine ER vs. Oxybutynin IR				
Homma 2003	Screened NR Eligible NR Enrolled = 608 Tol ER = 240 Oxy IR = 246 Pla = 122	Tol/Oxy grps Age range 26-84, mean age 59.3 Female 70.2% Ethnicity: Japanese 48.2% Korean 51.8%	Previous OAB drug therapy= 23% "Causes severe problems" or "many severe problems"=52%	3 withdrawn before treatment, not included in ITT Total withdrawn: Tol 25 (10.4%) Oxy 57 (23.2%) Analyzed: 605
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	293 enrolled: Tol 114, Oxy 122, Placebo 57	Mean age: 63.4 y Range: 25-88y % female: 66.5% 100% Japanese	prior drug therapy for OAB: 18.4% of total (Tol 19.3%, Oxy 15.6%, Pla 22.8%) % with ≥5 incontinence episodes/wk: 98.6% % with ≥ 8 micturitions/24h: 97.9% % with mean vol. voided ≤ 200ml: 97.6%	see Homma, 2003, not specifically reported in current article
Darifenacin ER vs. Oxybutynin IR				

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Extended Release vs. Immediate Release (ER vs IR)	
Tolterodine ER vs. Oxybutynin IR	
Homma 2003	<u>Diaries percentage change</u> Median incontinence episodes: Tol -78.6% vs. Oxy -76.5% (p=0.4469)) Median number voids: Tol -2.0 vs. Oxy -2.1 (p=0.3132) Pad usage: median change was 0 in all groups. <u>Subjective measures</u> Improvement in bladder condition: Tol 72% vs. Oxy 73% (NS) Deterioration in bladder condition: Tol and Oxy 5% vs Pla 8% Improved ability to hold urine: Tol 49% vs. Oxy 57% Treatment beneficial (much): Tol 42% vs. Oxy 53% (NS) <u>KHQ quality of life</u> Tol vs. Oxy :no statistically significant differences on any domain
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	HRQoL Tol vs Oxy had no significant differences between the amount of improvement compared to each other on these parts of the KHQ: Incontinence impact, Role limitations, Physical limitations, Social limitations, Personal relationships, Emotions, Sleep and energy, Severity (coping) measure+L23, General health perception, and Symptom severity. The improvements were all significantly different from placebo except in Emotions and General health perceptions.
Darifenacin ER vs. Oxybutynin IR	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Extended Release vs. Immediate Release (ER vs IR)	
Tolterodine ER vs. Oxybutynin IR	
Homma 2003	Directly observed and spontaneously reported at visits 3 through 6, rated as mild, moderate or severe. (Tol vs. Oxy) Dry mouth: 80 (33.5%) vs. 131 (53.7%) p<0.001 Severe dry mouth: 0.4% vs 8.2% Dry eyes: 3 (1.3%) vs. 7 (2.9%) Blurred vision: 3 (1.3%) vs. 8 (3.3%) Constipation: 17 (7.1%) vs. 15 (6.1%) Somnolence: 1 (0.4%) vs. 4 (1.6%) Difficulty in micturition: 3 (1.3%) vs. 21 (8.6%)
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	*Tol ER vs Oxy vs Pla* Dry mouth: 36.9% vs 61.5% vs 5.3% (p=0.002 for Tol vs Oxy) Severity of dry mouth: mild: 31.6% vs 45.1% vs 5.3% moderate: 5.3% vs 13.1% vs 0% severe: 0% 3.3% vs 0%
Darifenacin ER vs. Oxybutynin IR	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Extended Release vs. Immediate Release (ER vs IR)		
Tolterodine ER vs. Oxybutynin IR		
Homma 2003	Dry mouth: Tol 0.4% vs. Oxy 9.4% All events: Tol 5.0% vs. Oxy 17.1% p<0.001 Serious event, possibly drug related: 1 Oxy cardiac failure. No deaths and no clinically significant changes in lab or ECG values.	Compliance ≥75% of medication: Tol 98% vs. Oxy 93%
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	See Homma, 2003 for overall withdrawals due to AE. Withdrawals due to AEs in Japanese pts: Oxy: 16.4% Tol: 5.3%	
Darifenacin ER vs. Oxybutynin IR		

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Zinner, 2005	RCT, DB Crossover Multicenter USA	Male or female, 18-85 years with urge incontinence (>4 sig incontinent episodes/week), urinary frequency (>8 voids/day)	Neurogenic bladder or stress incontinence, contraindications to antimuscarinic therapy, previous bladder or prostate surgery, bladder stones, acute or chronic UTI, sig urinary outflow obstruction, clinically sig concomitant disease

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Zinner, 2005	Dar ER 15, 30mg/day Oxy IR 5mg TID	Placebo	Daily paper voiding diaries

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Zinner, 2005	NR/NR/76	Mean age: 59.9 yrs Range: 33-84 yrs 93.4% females Ethnicity: NR	Mean weight (kg): 75.7 Mean # of incontinence episodes/week: 20.4 Mean # of urgency episodes/day: 9.3 Mean severity of urgency episodes (1=mild; 2=moderate; 3=severe): 2 Mean # of micturitions/day: 10.4	16/NR/58

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Zinner, 2005	Mean change from baseline in # of Incontinence episodes/week Dar ER 15: -10.99 vs Dar ER 30: -12.2 vs Oxy IR: -11.57 vs Pla: -6.38 (p<0.05 for each compared to placebo) Mean change from baseline in # of urgency episodes/day Dar ER 15: -1.27 vs Dar ER 30: -1.63 vs Oxy IR: -1.1 vs Pla: -0.51 (p<0.05 for each compared to placebo) Mean change from baseline in # of micturitions/day Dar ER 15: -1.14 vs Dar ER 30: -1.62 vs Oxy IR: -1.23 vs Pla: -0.85 (p<0.05 for Dar ER 30 vs placebo and Dar ER 30 vs Dar ER 15)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Zinner, 2005	Self report by patient Incidence of dry mouth Dar ER 15: 13.1% vs Dar ER 30: 34.4% vs Oxy IR: 36.1% vs Pla: 4.9% (p<0.05 for Dar ER 15 vs Oxy IR and for Dar ER 30 vs Pla and for Oxy IR vs Dar ER 15 for Oxy IR vs Pla) Incidence of constipation Dar ER 15: 9.8% vs Dar ER 30: 21.3% vs Oxy IR: 8.2% vs Pla: 3.3% (p<0.05 for Dar 30 ER vs Pla and Dar ER 30 vs Oxy IR) Incidence of blurred vision Dar ER 15: 0% vs Dar ER 30: 0% vs Oxy IR: 3.3% vs Pla: 0% (NS) Incidence of dizziness Dar ER 15: 0% vs Dar ER 30: 0% vs Oxy IR: 1.6% vs Pla: 0% (NS)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Zinner, 2005	5 withdrew due to AEs	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Extended Release (ER vs ER)			
Oxybutynin ER vs.Tolterodine ER			
Sussman 2002	Two RCTs (one open-label Tol ER 2mg vs. 4mg, the other blinded Oxy ER 5mg or 10mg) Multicenter USA	Male or female, 18+ yrs, with overactive bladder defined by symptoms of urinary frequency and urgency with or without incontinence. Inclusion/exclusion criteria identical for both protocols.	Pure stress incontinence, urinary retention, gastric retention or uncontrolled narrow-angle glaucoma, significant hepatic or renal dysfunction, symptomatic or recurrent UTI, use of electrostimulation, bladder training, pelvic floor exercise within 1 week, indwelling or intermittent catheterization and any contraindication to antimuscarinic therapy.
Diokno 2003 OPERA	RCT Multicenter USA	Women, aged ≥18, with documented 21-60 urge urinary incontinence episodes per week and avg ≥10 voids per day.	Treatable genitourinary conditions that could cause incontinence, 2 postvoid residual volumes >150 mL, pronounced risk of developing complete urinary retention, clinically important medical problems that could lead to undue risk of anticholinergic effects, hematuria, uncontrolled narrow-angle glaucoma, obstructive uropathy, reduced gastrointestinal motility, and known hypersensitivity to study medications.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Extended Release vs. Extended Release (ER vs ER)			
Oxybutynin ER vs.Tolterodine ER			
Sussman 2002	Tol ER 2mg or 4mg once daily Oxy ER 5mg or 10mg once daily x 8 weeks No dose adjustments allowed	None reported	Patient assessment of symptoms based on 6-point scale (0 = no problems, 6 = severe problems) at baseline and 8 weeks Patient and Physician rated benefit (No, yes - a little, and yes-very much) at 8 weeks
Diokno 2003 OPERA	Oxy ER 10 mg/day vs. Tol ER 4 mg/day x 12 wks	None reported	Diaries at baseline week, and weeks 2, 4, 8, 12. Outcomes: total incontinence episodes, total incontinence episodes, micturition frequency.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Extended Release vs. Extended Release (ER vs ER)				
Oxybutynin ER vs.Tolterodine ER				
Sussman 2002	Number screened/eligible not stated. 1289 enrolled 669 Tol (333 Tol 2mg, 336 Tol 4mg) 620 Oxy (313 Oxy 5mg, 307 Oxy 10mg)	Mean age 62.6 yrs Female 75% Caucasian 84% Black 10% Hispanic 5%	Prevalence of incontinence symptoms: 62% overall (61% Tol, 64% Oxy) Prior Drug Therapy: 19% overall (17% Tol, 21% Oxy) Majority moderate to severe symptoms	89 patients excluded from analysis (reasons/group assigned not reported) 209 withdrew: 48 Tol 2mg (14%) (of these 2 lost to follow-up) 39 Tol 4mg (12%), (of these 4 lost to follow-up) 59 Oxy 5mg (19%) (of these 0 lost to follow-up) 63 Oxy 10mg (21%) (of these 2 lost to follow-up) Analyzed: 313 Tol 2mg, 316 Tol 4mg, 286 Oxy 5mg, 285 Oxy 10mg
Diokno 2003 OPERA	Screened 1485 Eligible NR Enrolled 790 Oxy ER= 391 Tol ER = 399	Mean age=60 100% female Ethnicity: White 85% Black 8% Hispanic 6%	Prior treatment anticholinergic drugs=47%	Total withdrawn: Oxy 52 (13.3%) Tol 42 (10.5%) Lost to followup: Oxy 13 (3.3%) vs. Tol 3 (0.8%) Sample size at baseline, wk 2,4,8,12: Oxy= 382,380,365,346,336,382 Tol = 393,390,383,370,355,393

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Extended Release vs. Extended Release (ER vs ER)	
Oxybutynin ER vs.Tolterodine ER	
Sussman 2002	Patients reporting improvement in symptoms: Tol 2mg 60%, Tol 4mg 70% Oxy 5mg 59%, Oxy 10mg 60% (p<0.01 for all vs Tol 4mg) Degree of change in symptoms was greater in Tol 4mg vs Oxy 10mg (p<0.01) The peak improvement was 1 point for Tol 4mg and 0 points for Oxy 10mg. Subgroup analysis of patients reporting improvement in symptoms who had moderate to severe symptoms at baseline: Tol 4mg 77%, Oxy 10mg 65% (p<0.01) Subgroup analysis of patients reporting improvement in symptoms who were drug naive at baseline: Tol 2mg 60%, Tol 4mg 69% Oxy 5mg 60%, Oxy 10mg 61% (NS) Subgroup analysis of patients reporting improvement in symptoms who were drug experienced at baseline: Tol 2mg 57%, Tol 4mg 75% Oxy 5mg 59%, Oxy 10mg 54% (NS) No difference between groups on patient or physician assessment of benefit - data not presented
Diokno 2003 OPERA	Mean change in urge incontinence episodes: Oxy -26.3 vs. Tol -25.5 (NS) Mean change in total incontinence episodes: Oxy -31.1 vs. Tol -28.6 (NS) Decrease in mean micturition frequency: Oxy 28.4 vs. Tol 25.2 (p=0.003) No incontinence in last week: Oxy 23.0% vs. Tol 16.8% (p=0.03)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Extended Release vs. Extended Release (ER vs ER)	
Oxybutynin ER vs.Tolterodine ER	
Sussman 2002	Dry mouth evaluated on 100 mm Visual Analog Scale(0 - least problem, 100 - most severe) at baseline and 8 weeks Change in dry mouth severity was dose dependent for both drugs. Tol 2mg vs. Tol 4mg p = 0.09, Oxy 5mg vs. Oxy 10mg p=0.05 Change in severity of dry mouth:(100 point VAS) Tol 2mg 2.3 Tol 4mg 6.0 Oxy 5mg 6.3 Oxy 10mg 11.3 (p=0.03 Tol 4mg vs. Oxy 10mg)
Diokno 2003 OPERA	Data collected at each visit or any time reported by participant, rated as mild, moderate, severe. Dry mouth: Oxy 116/391 (29.7%) vs. Tol 89/399 (22.3%) (p=0.02) mild: oxy 87/391 (22.3%) vs Tol 69/399 (17.3%) mod-severe: Oxy 29/391 (7.4%) vs Tol 20/399 (5%) Constipation: Oxy 25/391(6.4%) vs. 31/399 (7.8%) (NS)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Extended Release vs. Extended Release (ER vs ER)		
Oxybutynin ER vs.Tolterodine ER		
Sussman 2002	Only reported for Tol 4mg (19, 6%) and Oxy 10mg 37 (13%).	Report does not make clear why subjects excluded from intention to treat analysis, does not report all withdrawal reasons, does not report adverse event withdrawals for all doses, reports no side effect data other than change in dry mouth. Clinical significance of change in dry mouth not clear.
Diokno 2003 OPERA	All events: Oxy 20/391 (5.1%) vs. Tol 19/399 (4.8%) Due to dry mount: Oxy 7, Tol 4	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	RCT, Multicenter, USA	see Diokno 2003	see Diokno 2003
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	RCT, Multicenter, USA	see Diokno 2003	see Diokno 2003

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	Oxy ER 10mg/day vs. Tol ER 4mg/day x 12 weeks	see Diokno 2003	Data collected at each visit or anytime reported by participant. AE cited as reasons for withdrawal were specifically identified for analysis. AE were coded the FDA "Coding Symbols for Thesaurus of Adverse Reaction Terms" (COSTART V). Focus on AE that COSTART includes under the CNS classification. For additional information see Diokno, 2003
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	Oxy ER 10mg/day vs. Tol ER 4mg/day x 12 weeks	see Diokno 2003	Data collected at each visit or anytime reported by participant. AE cited as reasons for withdrawal were specifically identified for analysis. AE were coded the FDA "Coding Symbols for Thesaurus of Adverse Reaction Terms" (COSTART V). Focus on AE that COSTART includes under the CNS classification. For additional information see Diokno, 2003

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	see Diokno 2003	see Diokno 2003	see Diokno 2003	see Diokno 2003
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	see Diokno 2003	see Diokno 2003	see Diokno 2003 group 1: prior anticholergic treatment, n=373 Oxy ER (180), Tol ER (193) group 2: no prior anticholergic treatment, n=417 Oxy ER (211), Tol ER (206)	see Diokno 2003 group 1: prior anticholergic treatment, n(%) Oxy ER 15(8.3)/3(1.7)/ITT, Tol ER 17 (8.8)/1(0.5)/ITT group 2: no prior anticholergic treatment Oxy ER 37 (17.5)/10(4.7)/ITT, Tol ER 25 (12.1)/2(1.0)/ITT

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	COSTART V CNS AEs including dizziness, insomnia, somnolence, anxiety, hypertonia, nervousness, tremor and confusion (reported in mild, moderate or severe categories). Oxy ER (n=391) vs Tol ER (n=399) (p=NS for all comparisons) Any CNS AE: 9.0% vs 8.3% Dizziness: 3.8% vs 2.5% Somnolence: 1.0% vs 2.3% Insomnia: 1.8% vs 0.8% Depression: 1.3% vs 0.8% Hypertonia: 0.5% vs 1.0%
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	Group 1 VS. Group 2 Mean change in urge incontinence episodes: Oxy -25.4 vs. Tol -24.1 (p=0.306) VS. Oxy -27.2 vs. Tol -26.9 (p=0.663) Mean change in total incontinence episodes: Oxy -28.8 vs. Tol -26.5 (p=0.086) VS. Oxy -33.1 vs. Tol -30.6 (p=0.886) Decrease in mean micturition frequency: Oxy 24.4 vs. Tol 21.8 (p=0.052) VS. Oxy 31.7 vs. Tol 28.5 (p=0.035) No incontinence in last week: Oxy 23.6% vs. Tol 15.1% (p=0.038) VS. Oxy 29.4% vs. Tol 26.4% (p=0.495)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	Incidence and severity of AEs judged possible or probably related to Oxy ER and Tol ER during OPERA study: All comparisons are for Oxy ER (mild, moderate, severe) vs Tol ER (mild, moderate, severe) Dizziness: (1.8% , 0.8%, 0%) vs (1.5%, 0.5% , 0%) Insomnia: (0.8%, 0.5%, 0%) vs (0%, 0%, 0%) Somnolence: (0.5%, 0.3%, 0%) vs (1.5%, 0.5%, 0%) Anxiety: (0.5%, 0.3%, 0%) vs (0%, 0%, 0%) Hypertonia: (0%, 0.3%, 0%) vs (0%, 0%, 0%) Nervousness: (0%, 0.3%, 0%) vs (0%, 0%, 0%) Tremor: (0.3%, 0%, 0%) vs (0.3%, 0%, 0%) Confusion: (0.3%, 0%, 0%) vs (0%, 0%, 0%) Not judged to be related to treatment: Oxy ER: depression, increased libido, or vertigo. Tol ER: abnormal dreams, anxiety, depression, facial paralysis, hypertonia, insomnia, paresthesia, or vertigo.
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	Group 1 (n=180) VS. Group 2 (n=193), all nsd except where p value reported Data collected at each visit or any time reported by participant, rated as mild, moderate, severe. n (%) Dry mouth: any degree: 58 (32.3) vs. 37 (19.2), p=0.004 VS 58 (27.5) vs. 52 (25.2) mild: Oxy 44(24.4) vs Tol29 (15.0) VS Oxy 47 (22.3) vs Tol40 (19.4) mod-severe: Oxy 18 (10.0) vs Tol 8 (4.1) VS Oxy 13 (6.2) vs Tol 12 (5.8) Constipation: Oxy 14 (7.8) vs Tol 10 (5.2) VS Oxy 11 (5.2) vs Tol 21 (10.2) Diarrhea: Oxy 14 (7.8) vs Tol 11 (5.7) VS Oxy 17 (8.1) vs Tol 14 (6.8) Headache: Oxy 8 (4.4) vs Tol 10 (5.2) VS Oxy 14 (6.6) vs Tol 14 (6.8)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	Withdrawals due to CNS AEs: Oxy: 6 (1.5%) Tol: 2 (0.5%)	
Anderson 2006 OPERA post-hoc analysis based on history of prior anticholinergic treatment	Withdrawals due to Aes, Group 1 VS. Group 2: Oxy: 7 (3.9%) vs. Tol: 6 (3.1%) VS Oxy: 13 (6.2%) vs. Tol: 13 (6.3%)	some analysis of non-ITT population that showed significant differences -- not reported here

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	RCT, DB Multicenter	Women >18 years, with urinary urge incontinence (21-60 episodes/week), urinary urgency, and frequency (≥10 voids/day)	Treatable genitourinary conditions that could cause incontinence, 2 postvoid residual volumes >150 mL, sig risk of developing complete urinary retention, clinically sig medical conditions that could lead to undue risk of anticholinergic effects, hematuria, uncontrolled narrow-angle glaucoma, obstructive uropathy, reduced gastrointestinal motility, known hypersensitivity to the study medications
Trospium chloride vs oxybutynin			
Halaska 2003	RCT Multi center Europe	Patients with urge syndrome or urge incontinence	Absolute tachycardia, Closed-angle glaucoma, myasthenia gravis, severe arteriosclerosis of the cerebral vessels, stress incontinence, undue frequency of micturition due to heart failure, renal failure or diuretic therapy, bladder outlet obstruction, acute UTI at the beginning of the trial, hiatus hernia in combination with reflux esophagitis, stenosis in the GI tract, megacolon, colonic ulceration, allergy or intolerance towards atropine, Oxy, trospium or other constituents of trial medications, concurrent medication with anticholinergics, tricyclic or tetracyclic antidepressants, alpha-blockers or beta-sympathomimetics within the last 7 days before starting the trial, urological or gynecological operations within the last 3 months before starting the trial, serious illnesses or conditions which would preclude participation in any clinical trial (malignant neoplasms, alcoholism, drug misuse), pregnancy or lactation, participation in any other study

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	Oxy ER 10mg/day vs. Tol ER 4mg/day x 12 weeks	None	Adverse events data were collected at end of 2, 4, 8, and 12 weeks; investigator assigned severity levels based on observation and patient report
Trospium chloride vs oxybutynin			
Halaska 2003	Average 54 weeks of treatment with either Oxy 5 mg twice daily or Trospium 20 mg twice daily. Multiple appointments for evaluation through the course of the trial	None	Micturition diaries reported at 0, 2, 26, and 52 weeks. Efficacy also reported by doctor and patient as follows: cured, definite improvement, slight improvement, no improvement or deterioration.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	NR/NR/790	Mean age: 60 yrs Range: 18-92 yrs 100% female 84.9% Caucasian	47.2% previously received anticholinergic medication	94 52 in Oxy ER vs 42 in Tol ER
Trospium chloride vs oxybutynin				
Halaska 2003	Screened NR Eligible 358 Enrolled 357	Mean age 53.7 Female 86% Ethnicity NR	Smokers: 13% Previous illnesses: 70% Previous medication: 41% Mean body weight: 71.8 Kg	91 withdrew (Trospium 67, Oxy 24)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	Overall incidence of dry mouth Mild: Oxy ER: 21% vs Tol ER: 17% Moderate: Oxy ER: 5.6% vs Tol ER: 4% Severe: Oxy ER: 1.5% vs Tol ER: 0.5% Discontinued due to dry mouth: Oxy ER: 1.8% vs Tol ER: 1%
Trospium chloride vs oxybutynin	
Halaska 2003	Baseline incontinence episodes Trospium: 1.5; Oxy: 2.1. Treatment in both arms resulted in "the frequency of incontinence episodes diminished by about one episode at each follow-up attendance." Frequency of micturition/day at baseline: Trospium:11.4; Oxy:12.5. Assessed at 2, 26, 52 weeks. Reduction for Trospium 1.2, 2.9, 3.5; Oxy 1.5, 3.4, 4.2. Baseline episodes of urgency: Trospium: 10.2 ;Oxy: 11.0. Reduction for Trospium: 1.6, 3.2, 3.5; Oxy: 1.7, 3.2, 3.6. Subjective appraisal of efficacy after 52 weeks of treatment by physicians 29% Trospium rated as "cured", Oxy 17%. Patient ratings "similar."

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	Investigator assessed AEs at weeks 2, 4, 8, and 12 or when reported by a patient Investigator assigned severity of AEs based on following definitions Mild: event may be noticeable but does not influence daily activities and usually does not need intervention Moderate: Event may be sufficiently troublesome to make the person uncomfortable; it may influence performance of daily activities; and it may need intervention Severe: Event may cause severe discomfort; it usually interferes with daily activities; it usually needs treatment or intervention; and it may cause the person to discontinue the study
Trospium chloride vs oxybutynin	
Halaska 2003	Follow up appointments at 2, 6, 12, 20, 26, 32, 40, 52 weeks to assess safety and tolerability. 20 item questionnaire used to assess tolerability at 26 and 52 weeks. 4 point scale used to measure severity. Subjective tolerability recorded by doctor and patient using very good, good, satisfactory or poor scale. Overall withdrawal 25% Tros, 26.7% Oxy. Adverse events occurred in 64.8% Tros, 76.7% in Oxy. Tros vs. Oxy Dry Mouth: 33% vs 50% Constipation: 7% vs 4% Visual disturbance: 3% vs 6%

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Armstong, 2005 OPERA post-hoc analysis for adverse event, dry mouth	Withdrawals due to any AE: Oxy ER: 20 (5.1%) Tol ER: 19 (4.8%) Withdrawals due to dry mouth: Oxy ER: 7 (1.8%) Tol ER: 4 (1%)	This study focused only on dry mouth AE, not on effectiveness or efficacy of study medications. Was a subanalysis of bigger OPERA study.
Trospium chloride vs oxybutynin		
Halaska 2003	Trospium 16 (6%) Oxy 9 (10%)	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Madersbacher 1995	RCT Multi center Germany	Patients with spinal cord injuries and detrusor hyper-reflexia	Acute urinary tract infection, glaucoma, known allergy to atropine, Oxy or Trospium, tachycardia, renal, hepatic and/or cardiovascular insufficiency, intake of other anticholinergic drugs, body weight over 90 kg, age below 18 years.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Madersbacher 1995	Initial one week washout followed by 2 weeks of treatment with either Oxy 5 mg three times daily or Trospium 20 mg twice daily. To maintain double blind conditions the Trospium group received a placebo at midday	None	Twenty "well being" items were the subject of direct questioning before and at the end of the trial--specifically dry mouth, blurred/double vision, palpitation, constipation, difficulty in swallowing. Severity graded on 4 point scale.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Madersbacher 1995	Screened NR Eligible NR Enrolled 95 Trospium=52 ; Oxy=43 .	Mean age=`32. Female 50% Ethnicity NR	Type of spinal cord injury not specified. Differences in baseline urodynamic measures for maximum bladder capacity and compliance	10/NR/88

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Madersbacher 1995	Not reported. "Severe" dry mouth present in 4% trospium, 23% Oxy. Withdrawal less in trospium (6%) than Oxy (16%). Overall side effect rate comparable. No change in lab parameters.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Madersbacher 1995	Adverse effects assessed via interview focused on "well being" items. Severity grading done--methodology for grading based on a four point scale. Dry mouth: 56% Oxy vs 54% Trospium. "Severe" dry mouth: in 23% Oxy vs 4% Trospium. Withdrawal less in Trospium (6%) than Oxy (16%). Overall side effect rate comparable. No change in lab parameters.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Madersbacher 1995	Trospium 3 (6%) Oxy 7 (16%)	No information on nature of spinal cord injury or duration of injury. No information on other medications patients on during trial.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Transdermal vs. Immediate Release (TD vs. IR)			
Oxybutynin TD vs. Oxybutynin IR			
Davila 2001	RCT Multicenter USA	Men and women, aged ≥18, with history of urge or mixed urinary incontinence, previously diagnosed, with symptomatic improvement during treatment with oral oxybutynin for ≥6 weeks. During 2-wk washout from current treatment, min. 3 incontinent episodes and increase >30%. Diagnosis of detrusor instability based on symptoms and urodynamic study confirming involuntary bladder contractions.	Allergy to oxybutynin, intolerable of transdermal system, pregnancy or lactation, overflow incontinence secondary to underactive or noncontractile detrusor or outlet obstruction, impaired bladder compliance, including tonic increase in pressure greater than 15 cm during filling cystometry, current medical conditions or therapies that could contribute to UI, or medical conditions that could worsen due to oxybutynin.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Transdermal vs. Immediate Release (TD vs. IR)			
Oxybutynin TD vs. Oxybutynin IR			
Davila 2001	Starting dose assigned depending on prior oral oxybutynin dose of </= 10mg, 11-15mg, or >/= 20mg daily: Oxy TD 2.6mg, 3.9mg, or 5.2mg daily (2, 3 or 4 patches per day), patch applied twice weekly Oxy IR 10 mg, 15mg or 22,5mg total daily x 6 wks Dose titrated up if no side effects after 2 wks	NR	3-day diary of daily incontinence episodes, recorded at prestudy, washout, and wks 2,4,6. Questionnaire of anticholinergic symptoms, VAS for efficacy at wks 2,4,6.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Transdermal vs. Immediate Release (TD vs. IR)				
Oxybutynin TD vs. Oxybutynin IR				
Davila 2001	Screened NR Eligible NR Enrolled 76 Oxy TD = 38 Oxy IR = 38	Mean age 63.5 Female 92% Ethnicity: White 95% Black 5%	NR	2/76 (2.6%) withdrawn before 4 wks

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Transdermal vs. Immediate Release (TD vs. IR)	
Oxybutynin TD vs. Oxybutynin IR	
Davila 2001	Oxy TD vs Oxy IR Reduction in mean incontinence episodes at 6 wks: 4.8/7.2 (66.7%) vs. 4.6/7.2 (63.9%)(NS) Zero incontinence: 8/38 (21%) vs.10/38 (26%) VAS score improvement 5.8 vs 6.0 (p<o.0001)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Transdermal vs. Immediate Release (TD vs. IR)	
Oxybutynin TD vs. Oxybutynin IR	
Davila 2001	Invalidated questionnaire to evaluate titration for presence and severity of 10 symptoms assessed at 2, 4 and 6 wks. Oxy TD vs. Oxy IR Dry mouth: 15 (39%) vs. 31 (82%) (p<0.001) Reduction in severity of dry mouth vs prior treatment: 67% vs. 33% Worse dry mouth: 5% vs. 33% Constipation: 8 (21%) vs. 19 (50%) Somnolence 7 (18%) vs. 14 (37%) Blurred vision: 7 (18%) vs. 9 (24%) Impaired urination: 9 (24%) vs. 9 (24%)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Transdermal vs. Immediate Release (TD vs. IR)		
Oxybutynin TD vs. Oxybutynin IR		
Davila 2001	Oxy IR: 1 (dry mouth) Oxy TD: 1 contact dermatitis due to patch	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Transdermal vs. Sustained Release (TD vs.SR)			
Oxybutynin TD vs. Tolterodine SR			
Dmochowski 2003	RCT Multicenter USA	Men and women, aged ≥18, taking current pharmacologic treatment for overactive bladder with beneficial response (by patient response). Post-washout: >/= 4 urge urinary incontinent episodes, with either pure urge or predominant urge, 24 or more voids, and an average urinary void volume of 350ml or less over 3 days.	History of urinary tract surgery in previous 6 months, diagnosis of interstitial cystitis, urethral syndrome, painful bladder syndrome, or overflow urinary incontinence.
Tolterodine vs. Solifenacin			
Chapple et al. 2004	RCT Multicenter International	Patients ≥18 with OAB symptoms (including urgency, urge incontinence, or frequency) for ≥3 months; post-run-in eligibility included an average frequency of ≥8 voids /24 h and 3 episodes of urgency and/or 3 episodes of incontinence during 3-day voiding period.	Patients with clinically significant BOO, a postvoid residual volume of >200ml, stress incontinence, presence of a neurological cause for detrusor muscle overactivity, evidence of UTI or of bladder stones, previous pelvic irradiation, previous or current malignant disease of the pelvic organs, any medical condition contraindicating the use of antimuscaric medication (including narrow-angle glaucoma and urinary or gastric retention), nonpharmalogical OAB treatment including electrostimulation therapy or start of a bladder training program during the 2 wks before or during the study, diabetic neuropathy, use of drugs intended to treat incontinence, use of any drugs with cholinergic or anti-cholinergic side effects, participation in a clinical trial within 30 days prior to study entry, pregnant or nursing women, women intending to become pregnant during the study, and women not using reliable contraceptive methods.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Transdermal vs. Sustained Release (TD vs.SR)			
Oxybutynin TD vs. Tolterodine SR			
Dmochowski 2003	Oxybutynin transdermal (Oxy TD) 3.9 mg/day (applied twice weekly): n=121 Tolterodine sustained release (Tol SR) 4 mg/day: n=123 Placebo: n=117 12 wk treatment period	Maintain any nonpharmacologic incontinence management program.	Diary of urine volume, urge and incontinence episodes; measured at 0, 2, 6, 12 wks. QOL instrument and VAS "periodically."
Tolterodine vs. Solifenacin			
Chapple et al. 2004	Placebo BID; Tolterodine 2mg BID (Tol); Solifenacin 5 mg QD (Sol 5); Solifenacin 10 mg QD (Sol 10)		Patient-reported voiding diary (episodes of urgency and incontinence, times of voiding, volume voided/void, pad use, and episodes of sleep disturbance) at wks 0,4,8, & 12

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Transdermal vs. Sustained Release (TD vs.SR)				
Oxybutynin TD vs. Tolterodine SR				
Dmochowski 2003	Screened NR Eligible NR Enrolled 361	Mean age 63.5 Female 92.8% White 94.5% Black 3.6% Other 1.9%	Prior treatment median duration >1 yr (range 6 wks to 20 years) Oxy 49.6% Tol 47.4%	41 withdrawn 1 lost to followup 361 analyzed
Tolterodine vs. Solifenacin				
Chapple et al. 2004	1281 enrolled; 1081 randomized; 1033 evaluated	Mean age: Placebo: 57.8; Tolterodine (2 mg): 56.9; Solifenacin (5 mg): 58.1; Solifenacin (10mg): 57.2 25% male >98% white	Mean no. of voids/24 h: 12.07; Urge incontinence only: 653/1033; No incontinence: 67/1033; Mixed stress and urge incontinence: 313/1033; Prior drug therapy: 670/1033; Any non-drug therapy: 348/1033	Withdrawn: 36/1077 (3.6%); Lost to fu: 11/1077 (1.0%)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Transdermal vs. Sustained Release (TD vs.SR)	
Oxybutynin TD vs. Tolterodine SR	
Dmochowski 2003	Mean change in incontinence episodes per day at 12 wks: Oxy -2.9, Tol -3.2, Pla -2 (Oxy vs Tol p=0.5878) Mean decrease in urinary frequency per day: Oxy -1.9, Tol -2.2, Pla -1.4 (Oxy vs Tol p=0.2761) Frequency reduction greater for patients with 14+ micturitions/day; reduction NS for <10/day. Avg urinary volume: Oxy +24 mL, Tol +29 mL vs. Pla +5.5 mL (Oxy vs. Tol p=0.7690) Global Assessment of Disease State scores: Oxy vs. Tol p =0.1861 IIQ (QoL scale): -22 vs -23 (NS) Urogenital distress Inventory: -25 vs -28 (NS)
Tolterodine vs. Solifenacin	
Chapple et al. 2004	Change in mean number of urgency episodes/24 h: **Tolterodine:** -38%, p=0.0511 **Solifenacin:** 5mg once daily: -52%, p<0.001 10mg once daily: -55%, p<0.001 **Placebo:** -33%, no p-value reported.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Transdermal vs. Sustained Release (TD vs.SR)	
Oxybutynin TD vs. Tolterodine SR	
Dmochowski 2003	Method of assessment not reported Application site reactions: Oxy 32/121 (25.4%; 5% severe), Tol 7/123 (5.7%), Pla 8/117 (6.9%) Systemic adverse events: Oxy 23/121 (19%), Tol 29/123, Pla 14/117 (12%) Anticholinergic side effects (% only, numbers NR) Dry Mouth Oxy TD 4.1% vs Tol SR 7.3% Constipation Oxy TD 3.3%, Tol SR 5.7%
Tolterodine vs. Solifenacin	
Chapple et al. 2004	Dry mouth: placebo=13 (4.9%),Sol 5mg=39 (14%),Sol 10mg=57 (21.3%), Tol=49 (18.6%); Constipation: placebo=5 (1.9%), Sol 5mg=20 (7.2%), Sol 10mg=21 (7.8%), Tol=7 (2.6%); Blurred vision: Placebo=7 (2.6%), Sol 5mg=10 (3.6%), Sol 10mg=15 (5.6%), Tol=4 (1.5%)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Transdermal vs. Sustained Release (TD vs.SR)		
Oxybutynin TD vs. Tolterodine SR		
Dmochowski 2003	Oxy TD l= 13/121 (10.7%; 12 due to application site reaction, 1 hot flushes). Tol SR = 2/123 (1.6%; 1 fatigue, 1 dizziness).	
Tolterodine vs. Solifenacin		
Chapple et al. 2004	31/1077 (2.9%) for withdrawals due to all adverse events	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Chapple, et al. 2005 STAR (data from uncorrected proof)	RCT, Europe	Men and women aged ≥18y, OAB Symptoms for ≥ 3m, outpatient, demonstrated UI (≥1 episode/24h) and urinary frequency (≥8 micturitions/d) and ≥1 Urgency episodes/24h during 3-day voiding diary period	Stress Incontinence (SI) or Mixed Incontinence where SI was predominant and neurogenic DO
Chapple et al 2007 STAR post-hoc	RCT Europe	Men and women aged ≥18y, OAB Symptoms for ≥ 3m, outpatient, demonstrated UI (≥1 episode/24h) and urinary frequency (≥8 micturitions/d) and ≥1 Urgency episodes/24h during 3-day voiding diary period	Stress Incontinence (SI) or Mixed Incontinence where SI was predominant and neurogenic DO
Darifenacin vs. Oxybutinin			

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Chapple, et al. 2005 STAR (data from uncorrected proof)	Stable dosing phase: (Weeks 0-4) Solifenacin 5mg once/d Tolterodine ER 4mg once/d Flexible dosing phase: (Weeks 5-12) Solifenacin 5mg once/d (Sol 5) Solefenacin 10mg once/d (Sol 10) Tolterodine ER 4mg once/d (Tol 4)	none reported	3-day micturition diary presented at scheduled visits at wks 4, 8 and 12. Symptoms assessed include: micturition frequency (primary endpoint), episodes of urgency, incontinence with and without urgency, nocturia, pad usage/24h, volume voided per micturition. Health related QoL: validated 6-point categorical scale to assess Perception of Bladder Condition.
Chapple et al 2007 STAR post-hoc	Stable dosing phase: (Weeks 0-4) Solifenacin 5mg once/d Tolterodine ER 4mg once/d No dose increase (NDI) phase: (Weeks 5-12) Solifenacin 5mg once/d (Sol 5) Tolterodine ER 4mg once/d (Tol 4)	none reported	3-day micturition diary presented at scheduled visits at wks 4, 8 and 12. Symptoms assessed include: micturition frequency (primary endpoint), episodes of urgency, incontinence with and without urgency, nocturia, pad usage/24h, volume voided per micturition. Health related QoL: validated 6-point categorical scale to assess Perception of Bladder Condition.
Darifenacin vs. Oxybutinin			

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Chapple, et al. 2005 STAR (data from uncorrected proof)	1355 screened/1200 randomized and enrolled / Full analysis set (FAS): 1177	Mean Age: Sol 5 & 10: 56.5y Tol ER: 56.4y Age range: NR Sol: 85.3% female Tol ER: 88.3% female Sol: 99.3% Caucasian 0.7% Other Tol ER: 99.5 Caucasian 0.5% Other	Sol: 70.8% ≤65y; 29.2% >65y; and 6.7% >75y Tol ER: 70.6% ≤65y; 29.4% >65y; and 6.0% >75y	Withdrawals: Sol: 3.5% Tol ER: 3.0%
Chapple et al 2007 STAR post-hoc	1355 screened/1200 randomized and enrolled / Full analysis set (FAS): 1177 post-hoc: Sol 5 NDI:N=297 Tol ER NDI: n=267	Mean Age: Sol 5: 56.5y Tol ER: 56.9y Age range: NR Sol: 87.5% female Tol ER: 87.1% female Sol: 99.3% Caucasian 0.7% Other Tol ER: 99.3 Caucasian 0.7% Other	Sol: 70.0% ≤65y; 30.3% >65y; and 6.7% >75y Tol ER: 70.6% ≤65y; 30.0% >65y; and 7.0% >75y	Withdrawals: Sol: 3.0% Tol ER: 4.2%
Darifenacin vs. Oxybutinin				

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Chapple, et al. 2005 STAR (data from uncorrected proof)	Primary endpoint: micturition frequency Secondary endpoints: episodes of urgency, incontinence with and without urgency, nocturia, pad usage/24h, volume voided per micturition. Health related QoL: validated 6-point categorical scale to assess Perception of Bladder Condition. Sol (5 & 10 combined) vs Tol ER (reductions are endpoint minus baseline numbers) Mean reduction in number of urgency episodes/24h: 2.85 vs 2.42 episodes Mean reduction in number of urge incontinence episodes/24h: 1.42 vs 0.83 episodes Mean reduction in number of incontinence episodes/24h: 1.60 vs 1.11 episodes Mean reduction in number of pads used/ 24h: 1.72 vs 1.19 pads Mean reduction in number of nocturia episodes/night: 0.71 vs 0.63
Chapple et al 2007 STAR post-hoc	Primary endpoint: micturition frequency Secondary endpoints: episodes of urgency, incontinence with and without urgency, nocturia, pad usage/24h, volume voided per micturition. Health related QoL: validated 6-point categorical scale to assess Perception of Bladder Condition. Sol 5 vs Tol ER (from baseline to 4-weeks) Mean reduction in number of urgency episodes/24h: 1.71 vs 1.47 episodes, ns Mean reduction in number of urge incontinence episodes/24h: 1.22 vs 0.91 episodes, ns Mean reduction in number of incontinence episodes/24h: 1.30 vs 0.90 episodes, p=0.0181 Mean reduction in number of pads used/ 24h: 1.21 vs 0.80 pads, p=0.0089 Mean reduction in number of nocturia episodes/night: 0.51 vs 0.44, ns Sol 5 NDI vs Tol ER (from baseline to 12-weeks) Mean reduction in number of urgency episodes/24h: 2.47 vs 2.49 episodes, ns Mean reduction in number of urge incontinence episodes/24h: 1.46 vs 1.03 episodes, ns Mean reduction in number of incontinence episodes/24h: 1.56 vs 1.23 episodes, ns Mean reduction in number of pads used/ 24h: 1.55 vs 1.40 pads, ns Mean reduction in number of nocturia episodes/night: 0.72 vs 0.69, ns
Darifenacin vs. Oxybutinin	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Chapple, et al. 2005 STAR (data from uncorrected proof)	AE were evaluated at each clinic visit in response to general and non-specific questioning by the investigator or volunteered by patient Comparisons: Sol (mild%, moderate%, severe% AEs) vs Tol (mild%, moderate%, severe% AEs) Dry Mouth: (17.5%, 10.8%, 1.7%) vs (14.8%, 7.7%, 1.5%) Constipation: (3.2%, 2.7%, 0.5%) vs (1.3%, 1.0%, 0.2%) Blurred Vision: (0.7, 0%, 0%) vs. (0.7%, 1.0%, 0%)
Chapple et al 2007 STAR post-hoc	AE were evaluated at each clinic visit in response to general and non-specific questioning by the investigator or volunteered by patient Comparisons: Sol NDI (mild%, moderate%, severe% AEs) vs Tol ER(mild%, moderate%, severe% AEs) Dry Mouth: (6.5%, 10.4%, 0.7%) vs (5.0%, 7.0%, 2.1%) Constipation: (2.0%, 1.7%, 0.3%) vs (1.0%, 1.4%, 0.0%) Blurred Vision: (0.3, 0%, 0%) vs. (0.7%, 1.7%, 0%)
Darifenacin vs. Oxybutinin	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Chapple, et al. 2005 STAR (data from uncorrected proof)	Withdrawals due to AEs: Sol: 3.5% Tol ER: 3.0%	Overall withdrawal rates are unclear. Study funded by Yamanouchi Pharmaceutical Co.
Chapple et al 2007 STAR post-hoc	Withdrawals due to AEs: Sol 5 NDI: 1.3% Tol ER: 2.4%	Study funded by Yamanouchi Pharmaceutical Co. Professor Chapple is a consultant and speaker for Astellas Pharma Inc (Yamanouchi, Pfizer, Novartis and Schwarz and has acted as a consultant to UCB
Darifenacin vs. Oxybutinin		

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Chapple & Abrams 2005	RCT, Crossover, UK	Men and women, age 18-75y, with cystometric detrusor overactivity within previous 6m (included idiopathic and neurogenic) with ≥2 associated symptoms (≥7 Urgency episodes/wk and ≥7 micturitions/day, ≥1 incontinence episode/wk requiring pads or change of clothing	Previous bladder surgery for detrusor overactivity (DO), prostatectomy in the last 6m, bladder stones, treatment with diuretic, antimuscarinics, tricyclic antidepressants or digoxin within past 2 wks, stress and mixed incontinence unless DO was principal urodynamic observation and <1 SI episode/week, pregnancy or breast feeding and inadequate contraception, excessive alcohol intake, starting or modifying bladder training program, anticholinergic therapy contraindications.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment
Chapple & Abrams 2005	Three Cohorts: 1) Dar IR 2.5mg three times/d or Oxy IR 2.5mg three times/d 2) Dar ER 15mg once/d or Oxy IR 5mg three times/d 3) Dar ER 30mg once/d or Oxy IR 5mg three times/d each treatment period was for 7 days	none reported	Visual Nearpoint measured at baseline, pre-dose and 2 an 4 hours after the final dose on day 7 of each treatment period using a standard instrument, the RAF nearpoint ruler. Symptoms diary for OAB symptoms and adverse events

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Chapple & Abrams 2005	103 screened/ 65 eligible/ 65 enrolled	Age range: 21-75y 67.7% males 7.7% African-American 92.3% white	93.8% idiopathic DO and 6.2% neurogenic DO	6 withdrawals: Dari ER: 3 Oxy IR: 3 lost to fu: NR

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Chapple & Abrams 2005	urodynamic parameters, salivary flow, heart rate and visual nearpoint Mean max. decrease in salivary flow from baseline to day 7: Cohort 1: Dar 2.5 mg tid: -0.90 ml/min; Oxy 2.5 mg tid: -0.88 ml/min Cohort 2: Dar 15 mg QD: -0.98 ml/min; Oxy 5 mg tid: -1.55 ml/min Cohort 3: Dar 30 mg QD: -1.06 ml/min; Oxy 5 mg tid: -1.30 ml/min

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed
Chapple & Abrams 2005	observed or volunteered AE, serious AEs, and discontinuations, clinical lab tests (haematology, biochemistry, urinalysis and physical examinations) *Cohort 1% (Dar: no. of pts; Oxy: no. of pts) vs. Cohort 2% (D: #; O: #) vs. Cohort 3% (D:#; O:#)* Pts with all AEs: 43% (D:5, O 8) vs 73% (D:16; O;19) vs 98% (D:22; O:24) Pts with treatment-related AEs: 40% (D:4; O:8) vs 68% (D:14; O:19) vs 98% (D:22; O:24) Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2) Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1) Dry mouth: 40% (D: 4; O:8) vs 62.5% (D:13; O:17) vs 94%(D:21; O:23) Constipation: 6.7% (D:1; O:1) vs 29.2% (D:8; O:6) vs 25.5% (D:10; O:2) Dyspepsia: 3.3% (D:1; O:0) vs 16.7% (D:3; O:5) vs 8.5% (D:2; O:2) Headache: 3.3% (D:1; O:0) vs 8.3% (D:1; O:3) vs 10.6% (D:2; O:3) Abnormal vision: 6.7% (D:1; O:1) vs 8.3% (D:1; O:3) vs 12.8% (D:4; O:2) Somnolence: 3.3% (D:0; O:1) vs 4.2% (D:1; O:1) vs 4.3% (D:2; O:1) Asthenia: 3.3% (D:0; O:1) vs 0% vs 6.4% (D:3; O:1) Pharyngitis: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:2; O:1) Dysphagia: 0% vs 8.3%(D: 1; O:3) vs 0% Pruritus: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:3; O:0) Dry eyes: 0% vs 0% vs 6.4% (D:1; O:3) Urinary tract disorder: 0% vs 6.3%(D: 2; O:1) vs 0% Confusion: 0% vs 0% vs 4.3% (D:3; O:0) Epistaxis: 0% vs 0% vs 4.3% (D:1; O:2) Dysuria: 0% vs 0% vs 4.3% (D:1; O:2)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 1. Comparative clinical trials

Author, Year	Withdrawals due to adverse events	Comments
Chapple & Abrams 2005	Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2) Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1)	sponsored by Pfizer

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Immediate Release vs Immediate Release						
Leung 2002	Adequate	Not reported	Some differences, Not statistically significant. Menopausal: 45% Oxy, 66% Tol Coexisting illness: 58.5% Oxy, 50.9% Tol Concomitant drugs: 60% Oxy, 72% Tol	Yes	Yes	Yes
Lee 2002	Adequate	Not reported	Some differences, Previously treated with drug for incontinence: Tol 32%, Oxy 22%; stratification of drugs used Not reported.	Yes	Yes	Yes
Malone-Lee 2000	Adequate	Not reported	Similar	Yes	Yes	Yes
Drutz 1999	Not reported	Not reported	Some differences, mean age and % male higher in Oxy group, Oxy group had more patients with incontinence, and significantly more in Oxy group had prior urinary tract surgery,	Yes	Yes	Yes
Abrams 1998	Not reported	Not reported	Some differences, Not statistically significant. Previously treated with drug for incontinence: 52% Tol, 60% Oxy, 75% Pl Some characteristics Not stratified by group, i.e. concomitant disease or drugs, prior urinary tract surgery.	Yes	Not reported (method of blinding in light of dose adjustments and varying schedules not stated)	Not reported (method of blinding in light of dose adjustments and varying schedules not stated)
Milani 1993	Not reported	Not reported	Not reported	Yes	Yes	Yes

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Immediate Release vs Immediate Release					
Leung 2002	No	Stated ITT, but actual numbers analyzed not reported	No, of those withdrawing a higher proportion of those on Oxy had coexisting disease or concomitant drugs, were slightly older and had higher mean parity.	Withdrawals reported clearly Cross over Not reported Compliance: Oxy 88% Tol 75%	No
Lee 2002	Yes	Yes	Not clear	Yes	18% withdrew from study, 97% of these due to adverse events with higher number in Oxy group.
Malone-Lee 2000	Yes	Yes	Not clear	Attrition reported clearly, crossovers Not reported, adherence measured but Not reported.	No
Drutz 1999	Yes	Only for adverse events	Not clear	Attrition reported clearly, others Not reported	47% of original patients excluded from analysis, 20% withdrew overall, with 12% of original group withdrawing due to adverse events.
Abrams 1998	Yes	Yes	Not clear	Withdrawals due to adverse effects reported clearly Others Not reported	No
Milani 1993	Yes	No	Not clear	Yes	18% drop out rate, higher in Oxy group due to adverse effects

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Immediate Release vs Immediate Release	
Leung 2002	Fair
Lee 2002	Fair (+)
Malone-Lee 2000	Fair
Drutz 1999	Poor
Abrams 1998	Fair
Milani 1993	Poor

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Zeegers 1987	Not reported	Not reported	Not clear	Yes	Yes	Yes

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Zeegers 1987	Yes	No	Not clear	Withdrawals due to adverse effects reported clearly Others Not reported	Yes, high loss to follow-up in Emp group

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Zeegers 1987	Poor

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Halaska 2003	3:1 Trospium: Oxy Methodology not reported	Not reported	Similar demographics. Oxy group had somewhat increased frequency of incontinence, micturitions/day and urgency episodes/day	Yes	Yes	Yes
Madersbacher 1995	Not reported	Not reported	Some differences in gender and baseline urodynamic measures	Yes	Yes	Not reported

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Halaska 2003	Yes	Yes	Not clear	Withdrawals due to adverse effects, poor efficacy, poor compliance reported. No crossovers.	Yes, withdrawal rate 25% overall, similar in both arms
Madersbacher 1995	Yes	No	Not clear	Not clear.	Yes. 11% withdrawal overall Oxy 16% Trospium 6%

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Halaska 2003	Fair
Madersbacher 1995	Fair

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Immediate Release vs Extended Release						
Van Kerrebroeck 2001	Adequate	Not reported	Yes	Yes	Yes	Yes
Appell 2001	Adequate	Not reported	Yes, stratified randomization based on the severity of urge incontinence	Yes	Yes	Yes
Birns 2000	Yes, Block randomization 2pts/block Hospitals 5 pts/block OP Clinic	Not reported	Patient demographics Not given other than mean age: 56 yo	Yes	Yes	Yes
Versi 2000	Not reported	Adequate - central randomization by phone	Stated no significant differences, but not enough data presented to assess	Yes	Yes	Yes
Nillsson 1997	Non-randomized	Not reported	Not reported	Yes	Not reported (stated ER group took placebo in evening)	Not reported (stated ER group took placebo in evening)
Anderson 1999	Not reported	Not reported	Some differences, mean number urge incontinence episodes/wk higher in ER group (NS).	Yes	Yes	Yes
Homma 2003	Yes	NR	Yes	Yes	NR	yes
Swift 2003	Yes	NR	Yes	Yes	NR	Yes

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Immediate Release vs Extended Release					
Van Kerrebroeck 2001	Yes	Yes	Not clear	Yes 95% compliance	12% overall loss to f/u 6% lost due to adverse events: ER 5%, IR 5^, Placebo 6%
Appell 2001	Yes	repeated measures analysis done, but only p-values reported	Not clear	Yes	Overall = 12% 14% Oxy ER, 11% Tol
Birns 2000	Yes	No	Not clear	Yes	1.5% overall
Versi 2000	Yes	Not clear	Not clear	Yes	7% overall 6% ER, 8% IR
Nillsson 1997	Not reported (stated ER group took placebo in evening)	No	Yes	1 patient withdrawn from study by sponsor, adherence Not reported	No
Anderson 1999	Yes	No	Not clear	Yes 98% compliance	12% overall withdrawal 13% ER, 12% IR group
Homma 2003	Yes	Stated ITT. Actual numbers analyzed NR.	Not clear	Attrition yes, crossovers none, adherence yes	Non ADE withdrawals similar between groups, loss to follow up low, but lowest in Oxy grp
Swift 2003	Yes	Yes, carry forward approach	not clear	Attrition yes; adherence 96% took >75% of prescribed medication	No, 12% overall, distributed fairly evenly.

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Immediate Release vs Extended Release	
Van Kerrebroeck 2001	Fair
Appell 2001	Fair
Birns 2000	Fair
Versi 2000	Fair
Nillsson 1997	Poor
Anderson 1999	Fair
Homma 2003	Fair
Swift 2003	Fair

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Radomski 2004	Crossover No randomization	Open label	Crossover. IR Oxy always provided first and only 2 weeks. ER provided 4 weeks	Yes	No	No

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Radomski 2004	No	No for efficacy, yes for adverse events	Not clear. Three withdrawals included in safety analysis.	Yes	3 of 12 withdrew due to adverse events

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Radomski 2004	Poor

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Barkin, 2004	NR	NR	similar	yes	yes, method NR	yes, method NR
Chapple et al, 2005	yes	NR	similar	yes	NR	NR
Chapple & Abrams, 2005	yes	NR	similar	yes	NR	NR
Chapple, Rechberger et al, 2003	NR	NR	some differences, prior drug therapy: placebo 32%, Sol 5mg 34.9%, Sol 10mg 40.1%, Tol 30.8%, types of incontinence: Tol group had more mixed incontinence than all other groups and placebo has the most UI only.	yes	NR	NR
Zinner, 2005	Yes	Yes	Yes (stated but no details reported)	Yes	Yes	Yes

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Barkin, 2004	yes, method NR	no	not clear	withdrawals reported clearly, crossover not reported, Compliance reported in withdrawal reasons: 2 patients in Oxy group, contamination NR	no
Chapple et al, 2005	yes	yes	not clear	withdrawals reported clearly, crossover not reported, Compliance not reported, contamination NR	NR
Chapple & Abrams, 2005	yes	no	not clear	withdrawals reported clearly, crossover reported clearly, Compliance described but not reported, contamination NR	no
Chapple, Rechberger et al, 2003	NR	yes	not clear	withdrawals reported clearly, other NR	no
Zinner, 2005	Yes	NR	Yes	Withdrawals reported, crossover as planned, compliance NR, contamination NR	No

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Barkin, 2004	fair
Chapple et al, 2005	fair
Chapple & Abrams, 2005	fair
Chapple, Rechberger et al, 2003	fair
Zinner, 2005	Fair

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Extended Release vs Extended Release						
Sussman 2002	Not reported Randomization was within drug group - centers were assigned to Tol or Oxy then subjects randomized to dose. Centers blinded to existence of other arm of study.	Not reported	No, some differences: Tol 4mg group had more Caucasians Oxy 10mg group had more patients with prior drug experience, and more men Oxy 5mg group were younger	Yes	Tol arms stated to be open label. Oxy arms Not clear if blinded.	Tol arms stated to be open label. Oxy arms Not clear if blinded.
Diokno 2003	NR	NR	Yes	Yes	Yes	Yes
OPERA						
Armstong, 2005	Yes	Yes	Yes	Yes	Yes	Yes
Transdermal vs. Immediate Release						
Davila 2001	Yes	NR	Yes, except most males (5/6) in Oxy TD group	Yes	NR	NR
Transdermal vs. Extended Release						

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Extended Release vs Extended Release					
Sussman 2002	Tol arms stated to be open label. Oxy arms Not clear if blinded.	Stated to be ITT, to be included patients had to have received at least one dose of study drug AND had a least one post-randomization efficacy assessment. Missing data were imputed by last observation carried forward method.	Not clear	Withdrawals due to adverse effects reported clearly for Tol4mg and Oxy10mg only. Reported loss to follow-up, withdrawal of consent, withdrawal due to lack of efficacy, and due to side effects. Others Not reported	Unable to calculate for Tol 2mg and Oxy 5mg. For Tol 4mg loss to follow-up other than side effects = 6%, for Oxy 10mg = 9%.
Diokno 2003 OPERA	Yes	Yes (using last observation carried forward)	Unclear	Attrition yes Adherence NR	Slightly more loss in Oxy group, including one death. Total loss 104/790 (13.2%)
Armstong, 2005	Yes	NR	Unclear	Attrition yes (12% overall) Crossover NR Adherence NR	No
Transdermal vs. Immediate Release					
Davila 2001	Yes	No, but only 1 drop out from each group	NR		no
Transdermal vs. Extended Release					

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Extended Release vs Extended Release	
Sussman 2002	Fair (-)
Diokno 2003	Fair
OPERA Armstong, 2005	Fair
Transdermal vs. Immediate Release	
Davila 2001	Fair
Transdermal vs. Extended Release	

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Dmochowski 2003	NR	NR	Yes, though more male and black patients in oxy TD group	Yes	NR	Yes

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up
Dmochowski 2003	Yes	Yes	Unclear	Attrition overall 41/361 (11%) Adherence 92%	Unclear, not all withdrawals accounted for

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 2. Internal validity

Author, Year	Score (good/ fair/ poor)
Dmochowski 2003	Fair

Oxy=Oxybutynin, Tol = Tolterodine, Fla = Flavoxate, Emp = Emperonium, IR = Immediate Release, ER = Extended Release, UTI = Urinary Tract Infection

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Study Design Setting	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)
Flavoxate				
Gruneberger 1984	RCT Single Center Germany	39 enrolled, others not reported	Mean age :Fla 48, Cle 53 100% female Ethnicity: not reported	Fla 200mg or Clenbuterol (Cle) 0.01mg three times daily x 6 weeks
Meyhoff 1983	RCT Crossover	20 enrolled, others not reported	Median age: 51 100% female Ethnicity: not reported	Fla 200 mg, Eme 200 mg;or Pl four times daily x 14 days
Bradley 1970	RCT Single Center USA	46 enrolled, others not reported	18/46(39%) male; 28/46(61%) female Age: not reported Ethnicity: not Reported	Fla 200mg or Pro 30 mg four times daily x 7 days
Herbst 1970	RCT Number of centers not stated USA	43 enrolled, others not stated	Age: 75% over 50 20/43(47%) male; 23/43(53%) female Ethnicity: not reported	Fla 200 mg or Pro15 mg four times daily x 7 days
Oxybutynin				

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Other population characteristics (diagnosis, etc)
Flavoxate	
Gruneberger 1984	Neurogenic cause: Fla 9 (47%), Cle 14 (70%) Mixed incontinence: Fla 3 (16%), Cle 3 (15%)
Meyhoff 1983	Comorbid stress incontinence: 10/20(50%); One or more previous operations: 5/20(25%); detrusor instability: 14/20(70%); unable to suppress voluntarily induced detrusor contraction: 5/20(25%)
Bradley 1970	Urinary Tract Infection: Fla 6(25%), Pro 5(23%); Symptoms only: Fla 4(17%), Pro 2(9%); Cystitis alone or mixed: Fla 10(42%), Pro 12(54.5%); Bladder carcinoma alone or mixed: Fla 2(8%), Pro 0; Benign Prostatic hypertrophy: Fla 1(4%), Pro 1(4.5%); Post-Prostatectomy: Fla 0, Pro 1(4.5%); Enuresis: Fla 0, Pro 1(4.5%); Bladder neck obstruction: Fla 1(4%), Pro 0
Herbst 1970	Cystitis/urethrocystitis: 13/43(30%); Symptoms only : 6/43(14%); Post Prostatectomy: 7/43(16%); Urethral calculus: 6/43(14%); Trigonitis/urethrotrigonitis: 5/43(12%); Prostatitis: 4/43(9%)
Oxybutynin	

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Eligibility criteria	Exclusion criteria
Flavoxate		
Gruneberger 1984	Not Reported	Not Reported
Meyhoff 1983	Rapid fill CO2 cystometry revealing detrusor instability as defined according to definitions of the International Continence Society or was considered present if the patient did not have uninhibited detrusor contractions during filling cystometry but was unable to suppress a voluntarily induced detrusor contraction within 50 sec. once it had started; absent or minimal bladder suspension defect, not requiring incontinence surgery; maximum urinary flow rate <15 ml/s; residual urine volume <50 ml following spontaneous voiding; mid-stream urine culture showing <105 colonies/ml	Patients with detrusor sphincter dyssynergia; bladder stone or bladder tumor; neurological disease; glaucoma or severe heart failure; concomitant use of drugs affecting the autonomic nervous system or smooth muscles
Bradley 1970	Not Reported	Not Reported
Herbst 1970	Not Reported	Not Reported
Oxybutynin		

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Number withdrawn/ lost to fu/ analyzed	Method of outcome assessment and timing of assessment
Flavoxate		
Gruneberger 1984	Withdrawals: Fla 5 (25%) due to little or no efficacy and strong side effects, Cle 1 (5%) due to drug interaction	Subjective assessments (not described)
Meyhoff 1983	1 withdrawal due to unspecified disease unrelated to treatment	Patient-reported drug preferences measured at end of trial; Urinary diary (diurnal and nocturnal micturition patterns, total number of voidings, incontinence)
Bradley 1970	Withdrawals: Fla 2(8%); both due to adverse events Pro 2 (9%); 1 dizziness, 1 lost to follow-up	Subjective assessments: rating scale ranging from 'no change' to 'complete recovery'
Herbst 1970	Not Reported	Not Reported
Oxybutynin		

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Outcomes
Flavoxate	
Gruneberger 1984	Patients assessment: Cured/Improved: Fla 11 (58%), Cle 15 (75%)
Meyhoff 1983	Micturations/24h: Fla +1, Eme -0.5, Pl -1 (NS) Incontinence episodes: Fla -1, Eme -1, Pl -2 (NS) Drug preferences: Fla 3 (16%), Eme 4 (21%), Pl 9 (47%) NS
Bradley 1970	"Complete" improvement in: Frequency: Fla 6(29%), Pro 4(38%); Urgency: Fla 7(35), Pro 2(14%) Nocturia: Fla 4(27%), Pro 1(7%);
Herbst 1970	Good to excellent therapeutic response: Fla 50%, Pro 30% (p-value not reported)
Oxybutynin	

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Flavoxate		
Gruneberger 1984	Not clear. Fla: 9 reports of gastric side effects, Cle:4 had trembling and tachycardia, 3 had nervousness	4 withdrew due to gastric complaints, 1 due to severe neurosis, Cle: 1 withdrew due to drug interaction
Meyhoff 1983	Assessment unclear. Total adverse events reported: Fla 34, Eme 26, Pl 16 Dry mouth: Eme 8, Fla 5, Pl 5; Visual disturbances: Eme 2, Fla 3, Pl 1; Nausea/heartburn: Eme 7, Fla 7, Pl 2; Vomiting: Eme 1, Fla 0, Pl 0; Constipation: Eme 3, Fla 0, Pl 0; Dizziness: Eme 4, Fla 1, Pl 1; Headache: Eme 4, Fla 0, Pl 0; Incomplete bladder Emptying: Eme 2, Fla 1, Pl 1; Diarrhea: Eme 2, Fla 3, Pl 1; Depression: Eme 0, Fla 1, Pl 2; Edema: Eme 0, Fla 1, Pl 1; Exanthema: Eme 0, Fla 1, Pl 0; Others: Eme 1, Fla 3, Pl 2	Not Reported
Bradley 1970	Not clear. Fla: Dry mouth 1; Abdominal pain 1; Headache 1 Pro: Dizziness 1; Constipation 1	Fla: 2 withdrew; but not clear due to which adverse events Cle: 1 withdrew due to dizziness
Herbst 1970	Not clear. Dry mouth/throat: Fla 1, Pro 13; Blurred vision: Fla 0, Pro 1; Difficulty in urinating: Fla 0, Pro 1; Drowsiness: Fla 0 Pro 1; Headache: Fla 0 Pro 1 Difficulty in concentrating: Fla 1 Pro 0 Dizziness: Fla 1 Pro 0	Not Reported
Oxybutynin		

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Study Design Setting	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)
Holmes 1989	RCT Crossover Single center London	23 enrolled, others not reported	Age: Oxy 39.6, Pro 44.5 100% female Ethnicity: not reported	Oxy 5 mg or Pro 15 mg three times daily 1 month intervention, 1 week washout, then crossover
Madersbacher 1999	RCT Multicenter Austria	366 enrolled; others not reported	Age: Prov 49.6, Oxy 50.3; Pl 47.6 Prov 9(21%) male, 117(79%) female; Oxy 8(22%) male, 113(78%) female; Pl 4(18%) male, 59(82%) female Ethnicity: not reported	Oxy 2.5 mg or Prov 15 mg three times daily x 4 weeks

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Other population characteristics (diagnosis, etc)
Holmes 1989	Daytime frequency: Oxy 38.6 total voids/3 days, Pro 29.1 total voids/3 days; Nocturia: Oxy 5 total voids/3 nights, Pro 7 total voids/3 nights
Madersbacher 1999	Sensory urge (overall) 196(54%); Motor urge (overall): 78(21%) Years of urge incontinence: Prov 2.4, Oxy 2.4, Pl 2.0 Previous treatment or urge incontinence: Prov 32, Oxy 32, Pl 21

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Eligibility criteria	Exclusion criteria
Holmes 1989	Not Reported	Not Reported
Madersbacher 1999	History of urgency or urge incontinence, a maximum cystometric bladder capacity of < or equal to 300 ml.; age 18 or older; body weight 45 kg. or greater	Detrusor hyperreflexia; postoperative incontinence; infravesical obstruction; a postvoid residual urine of > 15% of the maximal cystometric bladder capacity; acute Urinary Tract infections; angina pectoris; glaucoma; megacolon; clinically relevant cardiac, renal or hepatic dysfunctions; tachy/dysrhythmias; frequency or nocturia due to heart or renal insufficiency; overt cerebral sclerosis

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Number withdrawn/ lost to fu/ analyzed	Method of outcome assessment and timing of assessment
Holmes 1989	Unclear	Daytime frequency: measured in total voids over 3 days; Nocturia: measured by total voids over 3 nights range; Incontinence: rated using linear analogue scale
Madersbacher 1999	Unclear	Bladder diary

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Outcomes
Holmes 1989	Mean change in micturations/24h: Oxy -2.5, Pro -1.2 Mean change in Visual Analog Scale of severity of incontinence symptoms: Oxy -22.2, Pro -17.6
Madersbacher 1999	Mean change in frequency per day: Oxy -2.4, Prov -1.9, Pl -1

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Holmes 1989	Unclear. Dry mouth: Oxy 29.8, Pro 18.4; Constipation: Oxy 10.1, Pro 9.3; Blurred vision: Oxy 12.1, Pro 16.2	Withdrawals: 3
Madersbacher 1999	Total incidence: Prov 64%, Oxy 72%, Pl 42% Frequency of severe dry mouth: Oxy>Prov (p 0.0093) Visual disturbance: Prov 27%, Oxy 18%, Pl 14% Nausea: Prov 4.1%, Oxy 9.9%, Pl 8.3% Vomiting: Prov 2.1%, Oxy 1.4%, Pl 2.8%	Withdrawals: Pro 13%, Oxy 11%, Pl 9.7

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Study Design Setting	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)
Hycoscyamine				
Serels 1998	Unclear Cross-over Single Center USA	34 enrolled; Others not reported	Mean age: 62 yrs Range: 28-91 100% female Ethnicity: NR	Hyoscyamine 0.375 mg bid; Doxazosin 2 mg QHS; Hyo + Dox (combination) Pts got each therapy for a month, unless they were unwilling to cross-over

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Other population characteristics (diagnosis, etc)
Hycoscyamine	
Serels 1998	NR

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Eligibility criteria	Exclusion criteria
Hycoscyamine		
Serels 1998	NR	NR

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Number withdrawn/ lost to fu/ analyzed	Method of outcome assessment and timing of assessment
Hycoscyamine		
Serels 1998	NR	NR

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Outcomes
Hycoscyamine	
Serels 1998	Improvement on AUA symptom score: Hyo = 68%; Dox = 68%; Combination= 77% Mean improvement in American Urological Assoc.(AUA) symptom score over baseline (p value: baseline vs endpoint score): Hyo: 34% (p<0.001) Dox: 30% (p=0.002) combination: 48% (p=0.004) Increased Voiding Pressure: % (n) Hyo: 53%(20), Dox: 66% (15), Combin: 72% (8) Decreased Compliance: Hyo: 53% (9), Dox: 61% (8), Combin: 100%(3)

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 3. Anticholinergic overactive bladder syndrome drugs compared with other drugs

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Hycoscyamine		
Serels 1998	*Percentages are in order: Hyo, Dox, combination* Moderate -to-severe side effects: 19 (61%), 8 (47%), 8 (61%) These percentages are estimated from a graph: Dry mouth: 70 %, 20%, 58% Fatigue: 33%, 31%, 8% Dizziness: 25%, 20%, 23% Headaches: 22%, 8%, 8% Constipation: 26%, 11%, 8% Diarrhea: 10%, 8%, 0% Vaginal dryness: 3%, 0%, 0% Night sweats: 3%, 0%, 0% Leg edema: 0%, 3%, 8%	Not Reported

Oxy = Oxybutynin, Fla = Flavoxate, Cle = Clenbuterol, Prov = Propiverine, Pro = Propantheline, Pl = Placebo, RCT = Random Controlled Trial, NS = Not significant

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Study Design Setting	Number screened/ eligible/enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)
Goode 2002	RCT Single site USA	486 screened, 197 randomized/105 analyzed	Mean age 67	Oxy 2.5mg or Pl 3X daily, increasing by 2.5mg once daily to max 5mg 3X daily Beh: visit 1 = biofeedback to isolate pelvic muscles and teach exercises, visit 2 = teach patients to adapt to urge sensations, if not 50%+ improvement, bladder-sphincter biofeedback with patient contracting pelvic muscles against increasing volumes of fluid, visit 4 = review, encouragement and fine-tune Duration of study: 8 wks
Burgio 2001	RCT Single site USA	468 screened/ 197enrolled	Age Range: 55 to 91 yrs Mean age 68yrs 97% White 3% African American	Oxy 2.5mg or Pl once daily to 5mg three times daily Biofeedback 4 sessions
Burgio 1998	RCT Single site USA	468 screened/197 enrolled	Mean age 68yrs 100% female Ethnicity not reported	Oxy 2.5mg once daily to 5mg three times daily Biofeedback 4 sessions
Burgio 2000 (extension of Burgio 1998)	Modified crossover following the RCT reported in Goode 2002	128 screened/35 enrolled	Mean age 69.3 Female 100% Ethnicity 100% white	Oxy as described in Burgio 1998 added to behavioral therapy patients for 8 weeks. Behavioral therapy as described in Burgio 1998 added to Oxy patients

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Other population characteristics (diagnosis, etc)	Eligibility criteria	Exclusion criteria
Goode 2002	48% mixed type incontinence Severity of urinary incontinence: 54% severe, 20% mild Previous drugs 28%	Age >=55 yrs, ambulatory, urge incontinence >/= 2x/wk for at least 3 months, urodynamic evidence of bladder dysfunction.	Continual leakage, postvoid residual > 200ml, uterine prolapse past the introitus, narrow-angle glaucoma, unstable angina, decompensated congestive heart failure, history of malignant arrhythmias or impaired mental status.
Burgio 2001	See Goode 2002	See Goode 2002	See Goode 2002
Burgio 1998	Type of Urinary Incontinence: Urge only(%)=49.2 Beh, 49.3 Oxy, 47.7 Pl; Mixed stress and urge(%)=50.8 Beh, 50.7 Oxy, 52.3 Pl; Severity: Mild(<5 accidents per week)=18.5 Beh, 17.9 Oxy, 18.5 Pl; Moderate(5-10 accidents per week)=29.2 Beh, 29.9 Oxy, 27.7 Pl; Severe(>10 accidents per week)=52.3 Beh, 52.2 Oxy, 43.8 Pl Duration of symptoms (years): 9.4 Beh, 9.8 Oxy, 12.7 Pl	Patients aged >= 55 yrs; ambulatory; predominant pattern of urge incontinence of at least a 3 month history; demonstrate at least 2 urge incontinence accidents per week on the baseline bladder diary (number of urge accidents to exceed number of stress accidents); urodynamic evidence of bladder dysfunction (detrusor instability during filling or provocation or maximal cystometric capacity of < or equal to 350 ml.)	Patients with continual leakage; postvoid residual urine volume more than 200 ml; uterine prolapse past the introitus; narrow-angle glaucoma; unstable angina; decompensated congestive heart failure; history of malignant arrhythmias; impaired mental status-Mini Mental Status Evaluation <20)
Burgio 2000 (extension of Burgio 1998)	Ambulatory, community dwelling with urge incontinence	Patients completing the Burgio 1998 RCT in OXY or behavioral therapy treatment arms offered the alternative treatment in combination with the previous for additional 8 weeks. See Burgio 1998 for initial eligibility	See Burgio 1998

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Number withdrawn/ lost to follow-up/ analyzed	Method of Outcome Assessment and Timing of Assessment	Outcomes
Goode 2002	92 excluded from analysis: 28 did not complete treatment, 64 did not undergo post-treatment cystometry	Bladder diary	Reduction in Voiding frequency/24h: Oxy -2.1 Beh -1.8 Pl -0.3 Reduction in frequency of accidents Oxy 78.3% Beh 82.3% Pl 51.5%
Burgio 2001	42 withdrawn (either did not complete both psychological exams (14), or reasons not reported) 155 analyzed	Hopkins Symptom Checklist at baseline and at 8 weeks. Results in 9 subscales and a Global Severity Index, 50 on any scale is normal, 63+ is "extreme enough to be a case"	Change in Global Severity Index: Oxy 2.1, Beh 3.4, Pl 1.0 (p = 0.26)
Burgio 1998	24 withdrew/0 lost to f/u/190 analyzed	Bladder diaries, patient satisfaction and overall evaluation of perceived improvement questionnaires (2 wks post-treatment),	Change in incontinence episodes: Oxy 10.2/wk Beh 13/wk (p = 0.04 vs. Oxy) Pl 7/wk (p = 0.009 vs. Oxy) In subgroup of women (n=131) with nocturia Mean reduction in nocturia from baseline: Oxy: 0.3 voids/night (p=0.007 vs Pl) Beh: 0.5 voids/night ((p<0.001 vs Pl; p=0.02 vs Oxy) Pl: 0.0 voids/night
Burgio 2000 (extension of Burgio 1998)	1 withdrawal from OXY/0 lost to FU/34 analyzed	See Burgio 1998	Reported percent reduction in incontinence. Behavioral to combined therapy 57.5% to 88.5% Oxy to combined therapy 72.7% to 84.3%

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
Goode 2002	Not reported	Not reported	Not enough data presented to fully evaluate results. This study includes all the same authors as the Burgio 2000 and Burgio 2001 studies, screened and initially enrolled exactly the same number. The number analyzed differs.
Burgio 2001	See above	See above	This is a subgroup analysis from the Burgio study, of those completing psychological analysis.
Burgio 1998	Unclear how assessed or when. Dry mouth Oxy 97%, Beh 35%, Pl 55% Inability to void Oxy 22%, Beh 6%, Pl 3% Constipation Oxy 39%, Beh 22%, Pl 37% Blurred vision Oxy 15%, Beh 10%, Pl 10% Confusion Oxy 8%, Beh 6%, Pl 11%	Not reported	
Burgio 2000 (extension of Burgio 1998)	Not reported	Not reported	This is a subgroup analysis of patients agreeable to combined therapy post Burgio 1998 trial.

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Study Design Setting	Number screened/ eligible/enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)
Soomro 2001	Randomized Crossover, open label Single site UK	43 enrolled, others not reported	Mean age 50yrs70% female Ethnicity not reported	Oxy 2.5mg twice daily, titrated to 5mg three times daily by day 7. Electrical Nerve Stimulation (ENS): 2 self-adhesive pads applied bilaterally over perianal region. Patients controlled amplitude to produce a tickling sensation, at 20Hz frequency and pulse of 0.2 millisecond on continuous mode. Patients instructed to use up to 6 hrs daily. 6 weeks duration on each arm, with 2 wk washout between arms.
Colombo 1995	RCT Single site USA	81 screened, others not reported	Age: Oxy=48, Beh=49 100 percent female Ethnicity not reported	Oxy 5 mg three times daily or bladder training x 6 weeks

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Other population characteristics (diagnosis, etc)	Eligibility criteria	Exclusion criteria
Soomro 2001	Mean functional capacity 154	Patients with a history of frequency, urgency and urge incontinence who had not been previously treated at the department, including some who had previously received treatment from a general practitioner at least 6 months prior to study enrollment.	Not Reported
Colombo 1995	Detrusor instability: Oxy=14, Beh=13; Low-compliance bladder: Oxy=9, Beh=8; Sensory bladder: Oxy=15, Beh=16	Patients showing detrusor instability, low-compliance bladder and sensory bladder	Stable bladder at cystometry; neurologic disease; detrusor hyperreflexia; age greater than 65 years; coexisting genuine stress urinary incontinence; genital prolapse; postvoid residual volume greater than 50 ml; previous gynecological or urogynecological operation; prior use of any drug for the treatment of urinary urge incontinence; urethral diverticula; fistulas; urinary tract neoplasia; bacterial or interstitial cystitis; bladder stones; and previous pelvic radiotherapy

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Number withdrawn/ lost to follow-up/ analyzed	Method of Outcome Assessment and Timing of Assessment	Outcomes
Soomro 2001	Not Reported	Voiding diary, Bristol urinary symptom questionnaire and Quality of Life questionnaire	Reduction in voiding frequency/24h: Oxy -2, ENS: -2 Symptoms by Bristol urinary symptom questionnaire : significant changes in score in both groups on frequency, and dissatisfaction with spending rest of life with current symptoms compared to baseline No difference on leaking or hesitancy compared to baseline Oxy only had significant change in score for incomplete emptying compared to baseline SF-36: No significant differences compared to baseline Patients finding treatment effective: Oxy 10, ENS 4
Colombo 1995	6 withdrawn: Oxy=4 due to anticholinergic adverse events; Beh=2 consent withdrawals	Clinical cure: total disappearance of urge incontinence and did not require protective pads or further therapies	Clinical cure: Detrusor instability group: Oxy=93%, Beh=62% Low-compliance bladder group Oxy=67%, Beh=75% Sensory bladder group: Oxy=60%, Beh=81%

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 4. Anticholinergic overactive bladder syndrome drugs compared with non-drug therapy

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
Soomro 2001	Post-treatment side effects questionnaire (at 6 wks) Dry mouth Oxy 87%, ENS 6% Blurred vision Oxy 53%, ENS 6% Dry skin Oxy 30%, ENS 28% Skin irritation Oxy NA, ENS 11% Difficulty using machine ENS 13%	Not reported	
Colombo 1995	Unclear. Oxy: Dry mouth=15; constipation=6; Nausea=5; Dizziness=2; Decrease in visual acuity=1; Tachycardia=1; Beh = none reported	Oxy = 4(3 due to dry mouth; 1 due to glaucoma) Beh = none reported	

Oxy = Oxybutynin, Beh = Behavior, Pl = Placebo, ENS = Electrical Nerve Stimulation

Evidence Table 5. New overactive bladder syndrome drugs compared with placebo

Author Year	Dose	Mean Change in Number of Micturitions/24h		Mean Change in Number of Incontinence Episodes/24h	
		OAB drug (n)	*Placebo* (n)	*OAB drug* (n)	*Placebo* (n)
Rentzhog 1998	TOL 2mg BID	↓20% (not given)	Not reported	↓46% (not given)	Not reported
Jacquetin 2001	TOL 2mg BID	↓1.4 (103)	↓1.2 (51)	↓1.3 (79)	↓0.4 (39)
Malone-Lee 2001	TOL 2mg BID	↓0.7 (73)	0 (42)	↓0.7 (51)	0 (33)
Van Kerrebroeck 1998*	TOL 2mg BID	↓0.1 (17)	↓0.1 (16)	↓2.4 (17)	↓1.9 (16)
Millard 1999	TOL 2mg BID	↓2.3 (129)	↓1.4 (64)	↓1.7 (117)	↓1.3 (55)
Chancellor 2000	TOL 2mg BID	↓1.7 (514)	↓1.2 (507)	↓1.5 (514)	↓1.0 (507)
Zinner 2002	TOL 4mg QD <65y/o	↓2 (292)	↓1.4 (284)	↓1.7 (292)	↓1.1 (284)
	TOL 4mg QD +65y/o	↓1.4 (214)	↓0.9 (223)	↓1.6 (214)	↓0.9 (223)
Chapple 2004	TOL 2 mg BID	↓1.9 (263)	↓1.2 (267)	↓1.1 (263)	↓0.8 (267)
Chapelle 2004	TOL 2 mg BID	↓1.8 (37)	↓1.0 (36)	↓0.4 (37)	↓0.3 (36)
Kelleher 2002	TOL ER 4 mg/day	NR	NR	↓2.2 (507)	↓1.3 (508)
Khullar 2004	TOL ER 4mg/day	↓1.2 (569)	↓0.9 (285)	↓1.5 (569)	↓1.1 (285)
Landis 2004	TOL ER 4 mg/day	↓1.9 (492)	↓0.4 (494)	↓1.3 (492)	↓0.7 (494)
Szonyi, 1995	OXY 2.5mg BID	Daytime frequency lower with Oxy (P = 0.0025)		Not reported	Not reported
Chapple 1990	Flavoxate 200mg TID	Difference in mean change = -0.292 P = 0.95		Not reported	Not reported
Zinner 2004	TROS 20 mg BID	↓2.4 (256)	↓1.3 (256)	↓2.3 (256)	↓1.9 (256)
Alloussi 1999	TROS 20 mg BID	Efficacy assessment done by investigator favored trospium		NR	NR

Author Year	Dose	Mean Change in Number of Micturitions/24h		Mean Change in Number of Incontinence Episodes/24h	
		OAB drug (n)	*Placebo* (n)	*OAB drug* (n)	*Placebo* (n)
Cardozo 2000	TROS 20 mg BID	Efficacy assessment done by investigator favored trospium		NR	NR
Dmochowksi 2002	OXY TD 1.3 mg/day 2.6 mg/day 3.9 mg/day applied twice/week	↓1.8 (130) ↓1.7 (133) ↓2.3 (125) (*P*=0.0457)	↓1.7 (132)	↓2.1 (NS) ↓2.0 (NS) ↓2.7 (*P*=0.0165)	↓2.1
Cardozo 2004	SOL 5 mg 10 mg	↓2.4 (286) ↓2.8 (290)	↓1.6 (281)	↓1.6 (173) ↓1.6 (165)	↓1.3 (153)
Cardozo 2005	DAR 30 mg QD	↓0.8 (35) *P*=NS	↓0.3 (36)	NR	NR
Haab 2004	DAR A: 3.75mg QD B:7.5 mg QD C: 15 mg QD	A: ↓1.7 (49), *P*=NR B: ↓1.6 (219) C: ↓1.7 (106) (*P*<0.001 for both B & C vs placebo)	↓0.8 (152)	A: ↓1.2 (49) B: ↓1.3 (219) C: ↓1.5 (106)	↓1.1 (152)
Muskat 1996	SCP TD Changed every 3 days (4 patches total)	Diurnal frequency: ↓7.5 (10) *P*<0.05	Diurnal frequency: ↓0.7 (10)	NR	NR
Steers 2005	DAR A: 7.5 mg B: 7.5 for 2 wks then 15 mg for 12 wks	A: ↓2.0 (104) B: ↓1.9 (157) (*P*≤ 0.001 for both combined vs. placebo)	↓1.0 (123)	A: ↓1.1 (104) B: ↓1.2 (156)	↓0.3 (123)
Chapple 2007	DAR 7.5 mg/day for 2 wks Optional titration to 15 mg/day for rest of the 12 wk period	Median -3.0(266) (*P*=0.006)	Median -2.2 (133)	Median -2.0 (266) (*P*=0.328)	Median -1.86 (133)
Staskin 2007	TROS 60 mg/day for 12 wks	-2.81 (292) (*P*<0.001)	-1.99 (300)	-2.48 (292) (*P*=0.0022)	-1.93 (300)
Dmochowski 2008	TROS 60 mg/day for 12 weeks	-2.5 (267) (*P*≤0.001)	-1.8 (276)	-2.4 (267) (*P*<0.001)	-1.6 (276)
Zinner 2006	DAR 15 mg/day for 12 wks	Median -2.20 (212) (*P*=0.176)	-1.80 (220)	-1.8 (212) (*P*=0.035)	-1.4 (220)

Author Year	Dose	Mean Change in Number of Micturitions/24h		Mean Change in Number of Incontinence Episodes/24h	
		OAB drug (n)	*Placebo* (n)	*OAB drug* (n)	*Placebo* (n)
Hill 2006	DAR CR A: 7.5mg/day, B: 15/day C: 30mg/day for 12 wks	Median A: -1.7((107) B: -1.9(106) C: -2.2(114) *P* value vs placebo A: *P*=0.066, B: *P*=0.033, C: *P*<0.001	-1.1(108)	Median A: -1.2(107) B: -1.5(106) C: -1.6(114) *P* value vs placebo: A: *P*=0.007, B:*P*<0.001, C: *P*<0.001	Median -0.8(108)
Rudy 2006	TROS 20mg BID for 12 wks	-2.67 (323) (*P*<0.0001)	-1.76 (325)	-1.86(323) (*P*<0.0001)	-1.29 (325)
Rudy, Cline, 2006	TROS 20mg BID for 12 wks	NR	NR	NR	NR
Rackley 2006	TOL ER 4mg/day for 12 wks	NR -15%(429)	NR -9%(421)	NR	NR
Kaplan, 2006	TOL ER 4mg/day for 12 wks	NR -10.8% (371)	NR -7.9% (374)	NR	NR
Kelleher, 2006	SOL A: 5mg/day B: 10mg/day For 12 wks	A: MUI -2.5 (159) A: UUI -2.2 (352) B: MUI -2.6 (452) B: UUI -2.8 (652) *P* value vs placebo all groups: *P*<0.001	MUI -1.4 (430) UUI -1.4 (644)	A: MUI -1.6 (113), *P*<0.05 A: UUI -2.4 (198), *P*<0.001 B: MUI -1.9 (373) , *P*<0.001 B: UUI -1.7 (398) , *P*<0.001 *P* value vs. placebo	MUI -1.3 (365) UUI -0.9 (415)
Nitti, 2006	TOL ER 4mg/day for 12 wks	NR	NR	NR	NR
Roehrborn, 2006	TOL ER 4mg/day for 12 wks	NR -12% (77) *P*=0.22	NR -4% (86)	-11.9 (77) *P*<0.05	-5.9 (86)
Dmochowski, 2007	TOL ER 4mg/day for 12 wks Time of day A:24:00-06:00 B:06:00-12:00 C:12:00-06:00 D:06:00-24:00 E: 24h	A:-0.22 (507), *P*<0.05 B: -0.57 (507), *P*<0.001 C: -0.55 (507), *P*<0.001 D: -.043 (507), *P*<0.002 E: -1.8 (507), *P*<0.001	A: -0.17 (507) B: -0.35 (507) C: -0.39 (507) D: -0.30 (507) E: -1.2 (507)	NR	NR

Author Year	Dose	Mean Change in Number of Micturitions/24h		Mean Change in Number of Incontinence Episodes/24h	
		OAB drug (n)	*Placebo* (n)	*OAB drug* (n)	*Placebo* (n)
Wein, 2007	TOL ER 4mg/day for 12 wks	NR	NR	NR	NR

All weekly rates were divided by 7 and reported as daily rates
Abbreviations: TROS = trospium chloride; OXY = oxybutynin; DAR = darifenacin; TOL = Tolterodine tartrate; SOL = solifenacin; SCP = scopolamine; IR = immediate release; ER = extended release; TD = transdermal;
*****Study of patients with detrusor hyperreflexia

Evidence Table 6. Quality assessment of placebo-controlled trials

Author, Year	Internal validity Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Zinner, 2006	Yes	NR	Yes	Yes	"Double-blind" methods NR	Yes
Staskin, 2007	Yes	Yes	Yes	Yes	Yes	Yes
Hill, 2006	Yes	Yes	Yes	Yes	Yes	Yes
Dmochowski, 2008	Yes	Yes	Yes	Yes	"Double-blind" methods NR	Yes
Chapple, 2007	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of placebo-controlled trials

Author, Year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Attrition: differential/high	Intention-to-treat (ITT) analysis	Quality Rating	Funding
Zinner, 2006	Yes	Attrition yes (15% overall) Crossover NR Protocol violations were reported	No	Yes	Fair	Novartis Pharma AG
Staskin, 2007	Yes	Attrition yes (11.7%) Crossover NR Protocol violations were reported	No	Unclear, NR, but analysis done on all pts, including those who withdrew	Good	Esprit Pharma and Indevus Pharmaceuticals
Hill, 2006	Yes	Attrition yes (11.4% overall) Crossover NR Adherence Yes (>80% in 99% of pts) Contamination NR	No	Unclear, NR, but analysis done on all pts, including those who withdrew	Good	Pfizer, Inc
Dmochowski, 2008	Yes	Attrition for AEs reported, but not for other reasons Crossover NR Adherence Yes (78.3% consumed >75% of study meds) Contamination NR	Unclear	Unclear, NR, but analysis done on all pts, including those who withdrew	Fair	Esprit Pharma and Indevus Pharmaceuticals
Chapple, 2007	Yes	Attrition yes (9.5% overall) Crossover NR Adherence yes (≥89% of pats taking ≥80% of study meds) Protocol violations were reported	No	Yes	Good	Novartis Pharma

Evidence Table 6. Quality assessment of placebo-controlled trials

Rudy, 2006	Not reported	Not reported	Yes	Yes	Yes	Yes
Rackley, 2006	Not reported	Not reported	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of placebo-controlled trials

Rudy, 2006	Yes	Attrition-Yes, Crossover-No, Adherence-NR, Contamination-NR	No/No Non completers: Trospium-7.3% Placebo-4.6%	Yes, LOCF	Fair	Indevus Pharmaceuticals Inc
Rackley, 2006	Yes	Attrition-Yes, Crossover-No, Adherence-NR, Contamination-NR	Yes (14% overall), No	Yes	Fair	

Evidence Table 7. Assessment of abstracts for publication bias

Author Year	Interventions (Drug, dose, sample size)	Micturitions mean change *(time period)*	Urge incontinence episodes mean change *(time period)*
Head-to-head			
Van Kerrebroeck 1997	A: Tolterodine 2 mg BID *(n=120)* B: Oxybutynin 5 mg TID *(n=120)*	A: -2.1 B: -2.7 *(unclear)*	A: -1.7 B: -2.1 *(unclear)*
Lee 2001	A: Tolterodine 2 mg BID (n=112) B: Oxybutynin 5 mg BID (n=116)	A: -2.6 B: -1.8 (24 hours)	A: -2.2 B: -1.4 (24 hours)
Schmidt 1998	A: Oxybutynin-XL 15 mg/day *(n=33)* B: Oxybutynin-IR 15 mg TID *(n=32)* C: Placebo *(n=15)*	Not reported	Mean percent reduction *(weekly)* A: 92% B: 72% C: 45%
Sand 2001	A: Oxybutynin-XL 10 mg/day *(n=nr)* B: Tolterodine 4 mg BID *(n=nr)* *(total n=382)*	Not reported	Not reported
Junemann 2000	A: Trospium Chloride 20 mg BID *(n=57)* B: Tolterodine 2 mg BID *(n=63)* C: Placebo *(n=60)*	A: -3.4 B: -2.6 C: -1.9 *(24 hours)*	Not reported
Zinner 2004	A: Oral darifenacin CR 15 mg QD (*n=58)* B: Oxybutynin 5 mg TID (*n=58)* C: Placebo (*n=58)*	NR	NR
Placebo-controlled			
Garely 2001	A: Tolterodine 4 mg OD *(n=507)* B: Placebo *(n=508)*	Median % decrease A: 17% B: 11%	Median % decrease A: 71% B: 33%
Millard 1997	A: Placebo B: Tolterodine 1 mg BID C: Tolterodine 2 mg BID *(n=unclear)*	A: -1.4 B: -2.3 C: -2.2 *(unclear)*	A: -1.3 B: -1.7 C: -1.8 *(unclear)*
Jonas 1997	A: Tolterodine 1 mg BID *(n=99)* B: Tolterodine 2 mg BID *(n=99)* C: Placebo *(n=44)*	A: -0.6 B: -1.4 C: -1.7 *(24 hours)*	A: -1.5 B: -1.1 C: -1.6 *(24 hours)*

**Data not provided*

Evidence Table 7. Assessment of abstracts for publication bias

Author Year	Interventions (Drug, dose, sample size)	Micturitions mean change *(time period)*	Urge incontinence episodes mean change *(time period)*
Moore 1997	A: Tolterodine 1 mg BID B: Tolterodine 2 mg BID C: Placebo (*Total n=306*)	A: -1.7 B: 1.8 C: not reported *(24 hours)*	Not reported
Whishaw 1997	A: Tolterodine 1 mg BID *(n=unclear)* B: Tolterodine 2 mg BID *(n=unclear)* C: Placebo *(n=unclear)* *(Total n=316)*	A>C* B>C* *(24 hours)*	A=B=C *(24 hours)*
Van Kerrebroeck 2000	A: Tolterodine 4 mg/day *(n=507)* B: Placebo *(n=508)*	Percent change A: -17% B: -11%	Percent change A: -53% B: -30%
Placebo-controlled, cont.			
Hill 2004	A: Darifenacin CR 7.5 mg QD (*n=108)* B: Darifenacin CR 15 mg QD (*n=107)* C: Darifenacin CR 30 mg QD (*n=115)* D: Placebo (*n=109)*	NR	Median % Change A: -9.8 B: -10.9 D: -6.6 (*weekly)*
Rudy 2004	A: Trospium chloride 20 mg BID (*n=329)* B: Placebo (*n=329)*	A: -2.67 B: -1.76	A: -65.9 B: -43.6
Moore 1997	Same as Millard, 1997		
Comparative Observational Studies			
Boccuzzi 2002	Oxybutynin IR Tolterodine IR	12 months	Oxy 83% Tol 76%
Taira 2002	Tol, Oxy, Oxy XL, Hyoscyamine, Flavoxate, imipramine, propantheline		

**Data not provided*

Evidence Table 7. Assessment of abstracts for publication bias

Author Year	Interventions (Drug, dose, sample size)	Micturitions mean change *(time period)*	Urge incontinence episodes mean change *(time period)*
Juzba 2001	Oxybutynin Tolterodine (formulations not stated)	3 months	Cox regression the risk of discontinuation was statistically significantly lower in Tol users, who were 43% less likely to discontinue

**Data not provided*

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Tolterodine (Tol)				
Siami 2002	Multicenter USA	Open label, uncontrolled 12 weeks	Men and women age 18+ with diagnosis of overactive bladder with symptoms of urinary frequency (8+ micturitions/24h), urgency (strong and sudden desire to urinate), with or without urge incontinence	Pure or predominantly stress incontinence, indwelling or intermittent catheter, symptomatic or recurrent UTI, hepatic or renal dysfunction, program of electrostimulation, bladder training or pelvic floor exercises within 4 weeks.
Michel 2002	Multicenter Germany	Open label, uncontrolled, cohort 12 weeks	Tol prescription	None specified
Appell 2001	Multicenter (multinational)	Open label 9 month study	Patients completing 12 week RCT enrolled after 1-week washout period.	None specified

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Tolterodine (Tol)			
Siami 2002	Tol 4mg ER once daily	Number screened not reported. 1147 enrolled 1138 analyzed (9 took no drug) 735 drug naïve 403 previously treated (not with Tol)	Age range 18-91 Mean age drug naive 60yr Mean age prior treatment 62.5yrs Drug naïve;70% female, Prior Treatment; 79% female Drug naïve; 87% white, Prior treatment; 90% white
Michel 2002	Tol - varying doses. Mean dose 2mg twice daily	2250 enrolled	Mean age 61 yrs 77% female
Appell 2001	Tol 2mg twice daily	939 eligible/854 enrolled	Age Range 19-89 Mean 60yrs 76% female

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events
Tolterodine (Tol)			
Siami 2002	Spontaneously reported and elicited during visits (1, 4 and 12 wks). Investigator classified adverse events as mild (does not interfere with patient's usual function), moderate (interferes to some extent), or severe (interferes significantly).	Dry mouth was the most common adverse event reported, at 16%. Of these events 8% were severe, 20% moderate, and 72% were mild. No other adverse events were reported in greater than 6% of patients.	90 (8%)
Michel 2002	Spontaneously reported and elicited during visits (6 and 12 wks). Patients asked to rate tolerability at 12 wks (very good, good, moderate, poor)	127 events were reported by 93 patients (4.1%). Dry mouth was the most common (2%). Tolerability ratings: very good 39% good 56% moderate 4% poor 0.9% Logistic regression showed no association between tolerability rating and age, gender and baseline symptoms, but did show improved tolerability related to higher dose (4mg)	61
Appell 2001	Spontaneously reported adverse events, withdrawals, and dose reductions (by patient as needed). Adverse events classified as mild, moderate, severe. Severe Adverse events were assessed for relationship to Tol. Blood chemistry/hematology. Patients seen at 3 and 9 months.	76% of patients reported adverse events. Dry Mouth 28% (2% of all patients had severe dry mouth) UTI 12% Constipation 7% Headache 7% Abdominal pain 6% 13% reduced dosage 3 serious adverse events were judged possibly or probably related to Tol (constipation, abdominal pain, and tachycardia) 3 cases of urinary retention (0.4%)	73 (9%), of these 12 due to dry mouth (1%)

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Comments
Tolterodine (Tol)	
Siami 2002	Short-term
Michel 2002	Realistic setting, but unclear if tolerability assessment is made by physician or patient
Appell 2001	

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Abrams 2001	Multicenter (multinational)	Open label 12 months study	Patients completing 4wk RCT enrolled after 4-week washout period.	None specified
Kreder 2002	Multicenter (multinational)	Open label 12 month study	Patients completing 12 wk RCT enrolled	None specified
Abrams, 2001	Multicenter, Europe	Open label, uncontrolled, 12 months	male and female patients, age >18 (≥65y in one 4-week study), urodynamically proven overactive bladder and symptoms of urinary frequency (average (≥8 micturitions/24h), urgency, an/or urge incontinence (average(≥ 1 incontinence episode/24h).	clinically significant stress incontinence, hepatic or renal disease, recurrent or symptomatic UTI, conditions contraindicating antimuscarinic therapy, clinically significant voiding difficulty with risk of urinary retention, treatment with or initiation during the study of, any antimuscarinic drug or any drug for bladder control problems or bladder training, within 14d prior to the baseline visit.
Michel, 2005	Multicenter, Germany	Open label, uncontrolled, 9 months	none	none

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Abrams 2001	Tol 2mg twice daily	895 eligible/714 enrolled	Age range 18-92 Mean age 60yrs 69% female
Kreder 2002	Tol ER 4mg once daily (no dose adjustments allowed)	1337 eligible/1077 enrolled	Age range 20-93 Mean age 60 yrs 82% female
Abrams, 2001	Tol 2mg twice daily with optional reduction to 1mg twice daily	screened NR/895 eligible after completion of 4-week RCT studies/714 enrolled	mean age 59.7y, 68.5% women, ethnicity NR
Michel, 2005	Tol 4mg once daily	screened NR/ eligible not applicable/ 3824 enrolled	overall mean age 64.8y. 75.8% female. mean age/gender incontinent patients, 66.3y/ 81.7% female and continent patients, 61.4y/ 62.6% and Ethnicity not reported

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events
Abrams 2001	Spontaneously reported adverse events, withdrawals, and dose reductions (by patient as needed). Adverse events classified as mild, moderate, severe. Severe Adverse events were assessed for relationship to Tol. Blood chemistry/hematology. Patients seen at 6 and 12 months.	77% reported an adverse event. Dry mouth 289 (41%) (27% mild, 3% severe) UTI 10% Headache 6% Abdominal pain 6% 5 serious adverse events were considered related to Tol (hernia, dyspepsia, pulmonary edema, and acute urinary retention) 167 (23% reduced dosage).	105 (15%)
Kreder 2002	Spontaneously reported adverse events, withdrawals, and dose reductions (by patient as needed). Adverse events classified as mild, moderate, severe. Severe adverse events were assessed for relationship to Tol. Blood chemistry/hematology. Patients assessed by phone at 1 month, and seen at 3, 6, 9 and 12 months, and again by phone 1 week after end of study.	Dry mouth 139 (12.9%) UTI 44 (4.1%) URI 43 (4%) 4 serious adverse events considered possibly related to Tol ER: urinary retention (2), aggravated MS (1), 'medication error' (1)	107 (10%) Most common reason: dry mouth 19 (18%)
Abrams, 2001	spontaneously reported AE, withdrawals and dosage reductions and at 6 month assessment visit. AE were classified as mild (easily tolerated), moderate (sufficient discomfort for interference with normal daily activities) or severe (incapacitating in terms of work and normal daily activities)	41% dry mouth (27% mild, 10% moderate and 35 severe) Other AE: autonomic nervous system disorders, general body disorders, gastrointestinal disorders and urinary disorders.	105 patients (15%)
Michel, 2005	Physician observed and reported at baseline, 1, 3, 6, and 9 months	overall AE: 13%, dry mouth: 7.8%	2.8% due to lack of tolerability

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Comments
Abrams 2001	
Kreder 2002	
Abrams, 2001	62% of patients completed 12months' treatment with tol
Michel, 2005	post-marketing surveillance of Tol ER sponsored by Pharmacia (now Pfizer)

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Takei, 2005	extension of Homma, 2003, a comparative controlled RCT	open label, uncontrolled, 12 months		
Oxybutynin (Oxy)				
Gleason 1999	Multicenter USA	Open label 12 week study	Men and women with idiopathic urge incontinence or mixed incontinence with clinically significant urge component, with at least 6 urge incontinence episodes weekly.	Uncontrolled medical condition, post void residual volume >100ml or significant beruria or pyuria.
Salvatore, 2004	Kings College Hospital London, UK	open label, random allocation to starting dose (not described), open ended continuation, follow-up after 2y	women with videourodynamic diagnosis of DO or low bladder compliance	NR
Oxybutynin (Oxy) vs. Tolterodine (Tol)				
Lawrence 2000	Pharmacy Benefit Management Database USA	Pharmacy Claims Data for April - December 1998	New prescription for Tol or Oxy	Terminated coverage with plan, received more than 30 day supply, incomplete data

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Takei, 2005	Tol 4mg once daily	188 out of 293 continued open label	mean age 63.6y, 65.4% female, all Japanese
Oxybutynin (Oxy)			
Gleason 1999	Oxy ER 5 to 30mg/day	Number screened not reported. 256 enrolled	38.9% >65 yrs 91% female 92% white
Salvatore, 2004	Oxy IR 2.5mg twice daily or Oxy IR 5mg nightly. These doses were to be self adjusted by the patients to a level where side effects were considered acceptable. The maximum recommended dose was 5mg tid.	screened NR/ eligible NR/ 96 enrolled	mean age 57.5y (range 32-80y), all female, no ethnicity reported
Oxybutynin (Oxy) vs. Tolterodine (Tol)			
Lawrence 2000	Tol or Oxy (IR)	1531 eligible/1020 analyzed	Median age Tol 73 (range 18-93), Oxy 70 (range 18-95) % female: Tol 68%, Oxy 97%

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events
Takei, 2005	safety was assessed at 4, 12, 24, 36 and 52 weeks of the continuation study and at post-treatment follow-up. AE were recorded at each visit. Clinical lab assessment (serum chem, hematology and urinalysis) at 12, 24, and 52 weeks. ECG at baseline, and 12 and 52 weeks or upon withdrawal	total incidence of dry mouth 33.5%, mild in all but one case. Nasopharyngitis (26.6%) considered unrelated to treatment.	19 patients withdrew due to AE
Oxybutynin (Oxy)			
Gleason 1999	Reports of adverse events were solicited at visits at weeks 1, 4, 8 and 12.	Dry mouth 59% (36% mild, 23% moderate to severe) 2 serious adverse events possibly related to Oxy were related to pre-existing gastric reflux disease.	20 (8%) Most commonly nausea, dry mouth and somnolence, urinary retention, and increased post-void residual
Salvatore, 2004	phone or postal questionnaire at 2y after baseline. Questionnaire intended to assess efficacy, acceptability and compliance of two regimens. Not clear if questionnaire was administered prior to treatment.	34.8% complained of side effects. No serious AE reported.	43.2% of women who ceased treatment cited AE as reason for termination.
Oxybutynin (Oxy) vs. Tolterodine (Tol)			
Lawrence 2000	Determined discontinuation of medication by gap in refill data, assessed time to discontinuation.	Continuing therapy for 6 months: Tol 164 (32%), Oxy 111 (22%) (p<0.001) Difference remains significant after controlling for age and co-payment amount. Patients discontinued Oxy significantly earlier (mean 45 days) than Tol (mean 59 days) (p<0.001). Never refilling prescription: Oxy 68% Tol 55%	

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Comments
Takei, 2005	
Oxybutynin (Oxy)	
Gleason 1999	
Salvatore, 2004	68.75% responded to questionnaire
Oxybutynin (Oxy) vs. Tolterodine (Tol)	
Lawrence 2000	

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Solifenacin (Sol)				
Haab, 2005	extension of Cardozo, 2004 a placebo controlled trial	open label, uncontrolled, 40 weeks	in addition to criteria for original study: informed consent and completion of treatment in the previous double-blind studies within </= 14d prior to entry into extension study.	clinically significant outflow obstruction, postvoid residual urine≥ 200mL, persistent or recurrent urinary tract infection, bladder stones, chronic interstitial cystitis, previous pelvic radiation or previous or current malignant disease of the pelvic organs and any medical condition contraindicating use of anticholinergic medication. Women of childbearing potential, pregnant or nursing or intended to become pregnant during study or unreliable contraception method.
Darifenacin (Dar)				
Haab, 2006	extension of Steers, 2005 and Haab, 2004, both PCTs	open label, non-comparative, 2 years	in addition to criteria for original study: completion of one of the two feeder trials without no major protocol violation	same as feeder studies

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Solifenacin (Sol)			
Haab, 2005	Sol 5mg once daily and Sol 10mg once daily with dose adjustments available at weeks 16, 28 and 40.	Screened and eligible NR/ 1633 enrolled in safety analysis	mean age 56.4y with a range of 18-82y, 78% women, 98.1% white, 0.5% black, 0.8% Asian, 0.6% other
Darifenacin (Dar)			
Haab, 2006	Dar 7.5 once daily or Dar 15mg once daily all started with 7.5 mg and were allowed to make dose adjustments after two weeks as needed	719/716/716	mean age 57.3y 85.15 female NR

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events
Solifenacin (Sol)			
Haab, 2005	safety was assessed at 4, 16, 28, 40 and 52 weeks of the extension study. At each visit patients were assessed: vital signs, physical examination, serum chem, hematology and urinalysis, 3-day diary, and QoL questionnaire. ECG and bladder ultrasound were performed week 28 and end of study.	total incidence of dry mouth 21%, with 10% of the lower dose group and 17% of the higher dose group. About 10% reported constipation and 7% reported blurred vision. The majority (> 50%) of the episodes of dry mouth, constipation and blurred vision were mild in severity.	4.7% withdrew due to AE
Darifenacin (Dar)			
Haab, 2006	safety was assessed at 0 and 2weeks and then 3,6,9,12,18,21,24 months adverse events were spontaneously reported by patients or observed by investigators patients also completed a questionnaire on bowel habits at end of feeder study and at 6, 12 and 24 months	treatment related AEs: total=343 (47.9%), serious AEs = 1, dry mouth=166 (23.3%), constipation=142 (19.8%), UTI=8 (1.1%), Dyspepsia=37 (5.2%), headache=14 (2%)	64 (8.9%) withdrew due to AE, 46 (6.4%) withdrew due to treatment-related AE

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Overactive bladder syndrome observational studies: Adverse events

Author, Year	Comments
Solifenacin (Sol)	
Haab, 2005	81% of enrolled patients completed 40 weeks of open label treatment
Darifenacin (Dar)	
Haab, 2006	

Evidence Table 9. Quality assessment of observational study

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?*	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?
Haab, 2006	yes	yes	yes	yes	yes	yes

Evidence Table 9. Quality assessment of observational study

Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment	Comments
yes	yes	good	

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs. Tolterodine (Tol)		
Leung 2002 Hong Kong	Tol 2mg twice daily Oxy 5mg twice daily	106 enrolled
Lee 2002 South Korea	Tol 2mg twice daily Oxy 5mg twice daily	228 enrolled (Tol 112, Oxy 116)
Malone-Lee 2000 UK and Ireland	Tol 2mg twice daily Oxy 5mg twice daily x 8 weeks Dose reduction allowed in Oxy group	482 screened 379 randomized 378 analyzed (1 received no drugs) Tol 190, Oxy 188

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs. Tolterodine (Tol)			
Leung 2002 Hong Kong	Xerostomia Questionnaire at 4 and 10 weeks, independent reporting of other side effects. Significant deterioration on all measures of dryness except denture fit, for both drugs. NS between groups. Side effects reported: Oxy 49% Tol 60% (NS) Reported to be mostly abdominal aches, general malaise and urinary retention	Unclear. States that most withdrawals not due to side effects, but that patients withdrawing while on Oxy were more likely to have co-existing illnesses (p<0.012).	Fair Compliance measured. Oxy 87.5% (11 to 99.3) Tol 75% (8.9 to 98.8) (NS)
Lee 2002 South Korea	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, and relationship to study drug. 227 patients assessed Tol: 62 patients reported 101 adverse events Oxy: 94 patients reported 154 adverse events (p = 0.001) Dry mouth: Tol 39 (35%) 72 (63%) (p<0.001) Severe dry mouth: Tol 1 (1%), Oxy 6 (5%) Micturation disorder: Tol 10 (9%), Oxy 16 (14%) Dyspepsia/abdominal pain: Tol 14 (13%), 12 (10%) Headache: Tol 4 (4%), Oxy 6 (5%)	Overall 29 (13%) Tol 11 (6 dry mouth, 55%) Oxy 18 (16 dry mouth, 88%)	Fair
Malone-Lee 2000 UK and Ireland	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity. Special attention to reporting of dry mouth. No description of scale for assessment of intensity or seriousness. At least one adverse event: 69% Tol, 81% Oxy Severe intensity: 13% Tol, 28% Oxy Serious and considered drug-related: 3 patients (1.6%) Tol, 0 Oxy Dry Mouth: overall 37% Tol, 61% Oxy (p<0.0001) Severe: 4% Tol, 15% Oxy (NS)	Overall 50 (13%) 22 (12%) Tol, 28 (15%) Oxy Due to dry mouth: 3% Tol, 7% Oxy	Fair Dose reductions requested by 6% Tol, 25% Oxy (p<0.0001)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Abrams 1998 UK, Ireland and Sweden	Tol 2mg twice daily Oxy 5mg three times daily Placebo three times daily Subjects >/= 65 yrs in UK and Ireland could start the dose of Oxy at 2.5mg and increase to 5mg during first 2 weeks Dose reduction allowed	293 enrolled (118 Tol, 118 Oxy, 57 Pl)
Drutz 1999 USA/Canada	Tol 2mg twice daily Oxy 5mg three times daily Placebo three times daily Dose reduction allowed	277 enrolled (Tol 109, Oxy 112, Placebo 56)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Abrams 1998 UK, Ireland and Sweden	All adverse events were recorded and categorized by intensity (mild, moderate, severe). The likelihood of relationship to study drug was evaluated for serious adverse events and patient withdrawn if deemed medically necessary or patient wished withdrawal. At least one adverse event reported: 89% Tol, 97% Oxy, 81% Pl (Tol vs. Oxy p = 0.023) Dry mouth: 50% Tol, 86% Oxy, 21% Pl (Tol vs. Oxy p<0.001) More patients reported dry mouth to be severe on Oxy than on Tol or Pl (numbers not given) 1 serious adverse event (syncope) was considered related to Tol	Overall: 10% Tol 8%, Oxy 17%, Pl 2% Due to dry mouth: Tol 0.8%, Oxy 13%, Pl 3.5%	Fair Dose reductions requested by 8% Tol, 32% Oxy, 2% Pl (Tol vs. Oxy p<0.001)
Drutz 1999 USA/Canada	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, at visits at 2, 4, 8 and 12 wks ITT analysis: % reporting adverse events: Tol 78%, Oxy 90, placebo 75 (p = 0.013 Tol vs Oxy) Dry mouth: Tol 30%, Oxy 69%, placebo 15% (p <0.001 Tol vs Oxy) Moderate to severe dry mouth: Tol 9%, Oxy 44%, placebo 7% Other adverse events reported: headache: Tol 15%, Oxy 10% dizziness: Oxy 11% (others not reported) cardiovascular events: Tol 7%, Oxy 8% Dose reduction: Tol 7%, Oxy 23%, placebo 4% (p<0.001 Tol vs Oxy)	Overall 12% Tol 7 (6%), Oxy 23 (21%), placebo 4 (7%) (p = 0.002 Tol vs Oxy)	Poor Only Allowed dose reductions in protocol, but then excluded these from analysis. Incomplete reporting of adverse events. 46 excluded from analysis due to protocol violations, but which groups assigned not reported.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs Flavoxate (Fla)		
Milani 1993 Italy	Fla 400mg or Oxy 5 mg three times daily, then crossover	50 enrolled
Zeegers 1987 Netherlands, Austria	Randomized to either: Fla 200mg or Emp 200mg or Pl three times daily x 3 weeks each or Oxy 5mg or Emp 200mg or Pl three times daily x 3 weeks each Order of drugs also randomized.	Stated to be consecutive patients 60 enrolled (30 in Fla/Emp/Pl, 30 in Oxy/Emp/Pl)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs Flavoxate (Fla)			
Milani 1993 Italy	Adverse events were elicited at 4 wks, and rated as serious or nonserious and according to intensity. By ITT: Fla 11/50 (22%), Oxy 42/50 (84%), plus 5 patients withdrawn due to adverse events. Dry mouth: Fla 2%, Oxy 78% Abdominal or stomach pain: Fla 24%%, Oxy 36%	5 (10%) not clear when these occurred.	Poor
Zeegers 1987 Netherlands, Austria	Combined in score 15% Pl, 26% Emp, 8% Fla, 17% Oxy	Overall 20% 2 Pl, 8 Emp, 0 Fla, 2 Oxy	Poor

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Immediate Release vs Immediate Release (IR vs IR)		
Trospium chloride IR vs Oxybutynin IR		
Halaska 2003	Average 54 weeks of treatment with either Oxy 5 mg twice daily or Trospium 20 mg twice daily. Multiple appointments for evaluation through the course of the trial	Screened NR Eligible 358 Enrolled 357
Maderspacher 1995	Initial one week washout followed by 2 weeks of treatment with either Oxy 5 mg three times daily or Trospium 20 mg twice daily. To maintain double blind conditions the Trospium group received a placebo at midday	Screened NR Eligible NR Enrolled 95 52 Trospium, 43 Oxy.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Immediate Release vs Immediate Release (IR vs IR)			
Trospium chloride IR vs Oxybutynin IR			
Halaska 2003	All adverse events: Trospium 68%, Oxy 77% All adverse events possibly/probably connected with treatment: Trospium 48%, Oxy 59%, p=0.02. All gastrointestinal adverse events possibly/probably connected with treatment: Trospium 39%, Oxy 51%, p=0.02. Dryness of mouth: Trospium 33%, Oxy 50%, p<0.01. "Time to event" reported as significant in favor of Trospium (p<0.01). Withdrawal due to adverse events classified as having at least a possible association: Trospium 3.7%, Oxy 6.7% Withdrawal due to adverse events classified as having no association: Trospium 0.7%, Oxy 0%. Withdrawal due to other serious adverse events: Trospium 1.5%,Oxy 3.3% Tolerability assessed by subjective appraisal of physicians at 26 & 52 wks:Trospium rated very good by 49% (26 wks) and 63% (52 wks); Oxy rated at 36%(26 wks) and 42%(52 wks). Appraisal by patients reported as "almost identical."	91 withdrew: Trospium 67 (25%), Oxy 24 (26.7%)	Fair. Long FU. Significant number of withdrawals for multiple reasons.
Maderspacher 1995	Analysis of tolerance carried out on all 95 subjects. Twenty "well being" items asked directly by investigator before and at end of trial. Severity grading assessed using 4 point scale. Overall rate of side effects reported as "almost comparable" in both groups. Dry mouth: Trospium 54%, Oxy 56% Severe dry mouth: Trospium 4%, Oxy 23%	10 withdrawals Trospium 3 (6%) Oxy 7 (16%)	Fair. All patients spinal cord injured. Type and level of injury not specified. Concurrent medications not noted.

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Oxybutynin ER v Oxybutynin IR		
Versi 2000 USA	Oxy ER 5-20mg once daily or Oxy IR 5-20mg/d - schedule not reported	screened 417 eligible/enrolled 226
Birns 2000 UK	Oxy ER 10mg once daily or Oxy 5mg twice daily	162 screened 130 randomized
Anderson 1999 USA	ER Oxy 5-30mg once daily or IR Oxy 5mg once to four times daily. . dose reductions allowed for adverse effects	158 screened 105 enrolled 93 analyzed

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Oxybutynin ER v Oxybutynin IR			
Versi 2000 USA	Reports of adverse effects recorded at each pt visit Dry mouth: ER 48%, IR 59% Kaplan Meier analysis moderate or severe dry mouth reports indicates a significant difference (p = 0.007) in favor of ER	Overall: 10 (8%) ER: 3 (3%) IR: 7 (6%)	Fair Mean duration of treatment/follow-up not stated. Only dry mouth reported in detail.
Birns 2000 UK	Assessed during visits every two weeks 78 pts reported adverse events (60%) (ER 55%, IR 67%) Dry mouth: ER 23%, IR 17% Dizziness ER 2%, IR 9% Vision abnormality ER 7%, IR 5% Cough ER 3%, IR 5% Headache ER 0, IR 5%	1 (considered unlikely due to study drug)	Fair Mixed types of incontinence Study included a run-in phase to establish tolerability, patients with adverse events excluded during run-in
Anderson 1999 USA	Spontaneously reported and anti-cholinergic effects assessed at each study visit Dry mouth: ER 68%, IR 87% (p = 0.04) Moderate to severe dry mouth: ER 25%, IR 46% (p = 0.03) Somnolence: ER 38%, IR 40% Blurred vision: ER 28%, IR 17% Constipation: ER 30%, IR 31% Dizziness ER 28%, IR 38%	2 (4%) in each group due to anticholinergic adverse events	Fair Previously all pts had responded to IR oxy Very high incidence of adverse events - may reflect the aggressive dose titration Duration of study (mean) not reported, very little data on final dose in either group

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Nillsson 1997 Finland	Oxy ER 10mg once daily Oxy 5mg twice daily crossover	17 enrolled
Radomski 2004	Oxy IR twice daily at dose at discretion of investigator for first two weeks (if on Oxy IR prior same dose continued 3 patients, if deemed obese 5 mg twice daily otherwise 2.5 mg twice daily), followed by two week washout, followed by Oxy CR 15 mg once daily for four weeks	# screened not reported. 12 included for safety analysis. 9 included for efficacy analysis (completed 8 week study)
Barkin 2004	Oxy IR 5mg tid, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks Oxy ER 15mg tid, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks	125 enrolled (Oxy IR 60, Oxy ER 65)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Nillsson 1997 Finland	Patients reported on a questionnaire throughout study, classified as mild, moderate, severe 14/16 on ER, 5/17 on IR reported at least one adverse event Dry mouth: ER 69%, IR 82% Headache ER 44%, 41% Dyspepsia ER 31%, IR 12% fatigue ER 13%, 24% Blurred vision 25%, IR 12% % Severe: ER 17%, IR 14% reported that these were NS, but unclear what data being compared.	None reported	Poor Very high numbers of subjects reporting adverse events
Radomski 2004	Adverse events collected during scheduled visits and entered in diary. Dry mouth: ER vs IR (mild, moderate, severe): 25%,25%,8% vs 58%,8%,8%. Constipation: ER 8%, IR 8% Back Pain: ER 8%, IR 8% Pain-unspecified: ER 42%, IR 17% Increased salivation: ER 17%,IR 8% Asthenia: ER 8%, IR 17% Peripheral edema: ER 8%, IR 8%	2 withdrawals in OXY IR phase. 1 withdrawal in Oxy ER phase. Events reported: severe stomach pain, mild peripheral edema, severe vision distortion	Poor All subjects exposed to Oxy IR first, exposed to longer duration of ER. Study open label
Barkin 2004	<u>Oxy ER vs Oxy IR (%)</u> Dry mouth: overall: 68% vs 72%; moderate or severe: 38% vs 45% Pharyngitis (dry throat): 35% vs 40% Dry skin: 17% vs 12% Diarrhea: 14% vs 5% Headache: 12 % vs 22% Uriniary tract infection: 12 % vs 18% Dizziness: 11% vs 18% Dyspepsia: 11% vs 17% Rhinitis: 11% vs 15% Abdominal pain: 9% vs 10% Asthenia: 18% vs 15% Constipation: 8% vs 10% Taste perversion: 8% vs 12% Cough increased: 6% vs 13% Dysphagia: 6% vs 13% Dry eyes: 3% vs 15% Nausea: 5% vs 17%	Oxy IR: 12 (20%) Oxy ER: 11 (17%)	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Tolterodine ER vs Tolterodine IR		
Van Kerrebroeck 2001 Multinational	Tol ER 4mg once daily or Tol IR 2mg or Placebo twice daily	1529 enrolled Tol ER: 507 Tol IR: 514 placebo: 508
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Tol ER 4 mg (n=417) once daily vs. Tol IR 2 mg twice daily (n=408) vs. Pla (n=410) for 12 wks.	1235 enrolled Tol ER: 417 Tol IR: 408 placebo: 410
Extended Release vs.Immediate Release (ER vs IR)		
Oxybutynin ER v Tolterodine IR		
Appell 2001 USA	ER Oxy 10mg once daily Tol 2mg twice daily	378 enrolled (Oxy ER 185, Tol 193) 332 completed (Oxy ER 160, Tol 172)

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Tolterodine ER vs Tolterodine IR			
Van Kerrebroeck 2001 Multinational	Spontaneously reported events were categorized and causation assigned dry mouth further categorized Dry mouth: ER 23%, IR 30%, Placebo 8% Constipation: ER 6%, IR 7%, Placebo 4% Headache: ER 6%, IR 4%, Placebo 5%	Overall 88 (5.7%) ER: 27 (5.3%) IR: 28 (5.5%) placebo 33 (6.5%)	Fair Dry mouth classified as mild/moderate/severe but data only reported for ER
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Reporting details NR. Tol ER vs. Tol IR vs. Pla: Dry mouth: 105/415 (25.3%) vs. 127/407 (31.2%) vs. 33/410 (8.0%) Dry skin: 2 (0.5%) vs. 5 (1.2%) vs.1 (0.2%) Dizziness: 7 (1.7%) vs. 7 (1.7%) vs. 4 (1.0%) Somnolence: 12 (2.9%) vs. 11 (2.7%) vs. 8 (2.0%) Abnormal vision: 5 (1.2%) vs. 4 (1.0%) vs. 2 (0.5%) Constipation: 27 (6.5%) vs. 27 (6.6%) vs. 14 (3.4%)	Tol ER 22/417 (5%) vs. Tol IR 20/408 (5%) vs. Pla 26/410 (6%)	Fair Dry mouth classified as mild/moderate/severe Reporting details NR Patients excluded from AE assessment (Tol ER=2; Tol IR=1)
Extended Release vs.Immediate Release (ER vs IR)			
Oxybutynin ER v Tolterodine IR			
Appell 2001 USA	Patient reported dry mouth occurred in equal proportion in each group both groups had similar rates of dry mouth and other adverse effects	Overall 7.7% Oxy ER 14 Tol 15	Fair

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Tolterodine ER vs. Oxybutynin IR		
Homma 2003	Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks	Enrolled = 608 Tol ER = 240 Oxy IR = 246 Pla = 122
Extended Release vs.Immediate Release (ER vs IR)		
Solifenacin IR vs. Tolterodine ER		
Chapple 2005 STAR trial	Flexible dosing, Weeks 0-4: Sol 5mg qd Tol ER 4mg qd Stable-dose phase,Weeks 5-12: Sol 5mg qd (Sol 5) Sol 10mg qd (Sol 10) Tol ER 4mg qd (Tol 4)	Full analysis set (FAS): 1177

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Tolterodine ER vs. Oxybutynin IR			
Homma 2003	Dry mouth: Tol 0.4% vs. Oxy 9.4% All events: Tol 5.0% vs. Oxy 17.1% p<0.001 Serious event, possibly drug related: 1 Oxy cardiac failure. No deaths and no clinically significant changes in lab or ECG values.	Compliance >75% of medication: Tol 98% vs. Oxy 93%	Fair Adverse events undefined; ascertainment techniques NR
Extended Release vs.Immediate Release (ER vs IR)			
Solifenacin IR vs. Tolterodine ER			
Chapple 2005 STAR trial	AE evaluted at each clinic visit in response to questioning by the investigator or volunteered by patient Comparisons: Sol (mild%, moderate%, severe% AEs) vs Tol (mild%, moderate%, severe% AEs) Dry Mouth: (17.5%, 10.8%, 1.7%) vs (14.8%, 7.7%, 1.5%) Constipation: (3.2%, 2.7%, 0.5%) vs (1.3%, 1.0%, 0.2%) Blurred Vision: (0.7, 0%, 0%) vs. (0.7%, 1.0%, 0%)	Withdrawals due to AEs: Sol: 3.5% Tol ER: 3.0%	

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Darifenacin IR and Darifenacin ER vs. Oxybutynin IR		
Chapple and Abrams 2005	1) Dar IR 2.5mg tid or Oxy IR 2.5mg tid 2) Dar ER 15mg qd or Oxy IR 5mg tid 3) Dar ER 30mg qd or Oxy IR 5mg tid each treatment period was 7 days	65 enrolled
Diokno 2003 OPERA	Oxy ER 10 mg/day vs. Tol ER 4 mg/day x 12 wks	Enrolled 790 Oxy ER= 391 Tol ER = 399

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Darifenacin IR and Darifenacin ER vs. Oxybutynin IR			
Chapple and Abrams 2005	*Cohort 1% (Dar: # of pts; Oxy: # of pts) vs. Cohort 2% (D: #; O: #) vs. Cohort 3% (D:#; O:#)* All AEs: 43% (D:5, O 8) vs 73% (D:16; O;19) vs 98% (D:22; O:24) Treatment-related AEs: 40% (D:4; O:8) vs 68% (D:14; O:19) vs 98% (D:22; O:24) Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2) Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1) Dry mouth: 40% (D: 4; O:8) vs 62.5% (D:13; O:17) vs 94%(D:21; O:23) Constipation: 6.7% (D:1; O:1) vs 29.2% (D:8; O:6) vs 25.5% (D:10; O:2) Dyspepsia: 3.3% (D:1; O:0) vs 16.7% (D:3; O:5) vs 8.5% (D:2; O:2) Headache: 3.3% (D:1; O:0) vs 8.3% (D:1; O:3) vs 10.6% (D:2; O:3) Abnormal vision: 6.7% (D:1; O:1) vs 8.3% (D:1; O:3) vs 12.8% (D:4; O:2) Somnolence: 3.3% (D:0; O:1) vs 4.2% (D:1; O:1) vs 4.3% (D:2; O:1) Asthenia: 3.3% (D:0; O:1) vs 0% vs 6.4% (D:3; O:1) Pharyngitis: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:2; O:1) Dysphagia: 0% vs 8.3%(D: 1; O:3) vs 0% Pruritus: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:3; O:0) Dry eyes: 0% vs 0% vs 6.4% (D:1; O:3) Urinary tract disorder: 0% vs 6.3%(D: 2; O:1) vs 0% Confusion: 0% vs 0% vs 4.3% (D:3; O:0) Epistaxis: 0% vs 0% vs 4.3% (D:1; O:2) Dysuria: 0% vs 0% vs 4.3% (D:1; O:2)	Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2) Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1)	
Diokno 2003 OPERA	Dry mouth: Oxy 116/391 (29.7%) vs. Tol 89/399 (22.3%) (p=0.02) mild: oxy 87/391 (22.3%) vs Tol 69/399 (17.3%) mod-severe: Oxy 29/391 (7.4%) vs Tol 20/399 (5%) Constipation: Oxy 25/391(6.4%) vs. 31/399 (7.8%) (NS)	All events: Oxy 20/391 (5.1%) vs. Tol 19/399 (4.8%) Due to dry mount: Oxy 7, Tol 4	Fair Data collected at each visit or any time reported by participant, rated as mild, moderate, severe by investigator

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Transdermal vs. Immediate Release (TD vs. IR)		
Oxybutynin TD vs. Oxybutynin IR		
Davila 2001	Starting dose assigned depending on prior oral oxybutynin dose of </= 10mg, 11-15mg, or >/= 20mg daily: Oxy TD 2.6mg, 3.9mg, or 5.2mg daily (2, 3 or 4 patches per day), patch applied twice weekly Oxy IR 10 mg, 15mg or 22,5mg total daily x 6 weeks Dose titrated up if no side effects after 2 weeks	Enrolled 76 Oxy TD = 38 Oxy IR = 38
Dmochowski 2003	Oxybutynin transdermal (Oxy TD) 3.9 mg/day (applied twice weekly) Tolterodine sustained release (Tol SR) 4 mg/day Placebo 12 wk treatment period	Enrolled 361 Oxy TD: 121 Tol SR: 123 Placebo: 117

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 10. Short-term comparative studies: Adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Transdermal vs. Immediate Release (TD vs. IR)			
Oxybutynin TD vs. Oxybutynin IR			
Davila 2001	Oxy TD vs. Oxy IR Dry mouth: 15 (39%) vs. 31 (82%) (p<0.001) Reduction in severity of dry mouth vs prior treatment: 67% vs. 33% Worse dry mouth: 5% vs. 33% Constipation: 8 (21%) vs. 19 (50%) Somnolence 7 (18%) vs. 14 (37%) Blurred vision: 7 (18%) vs. 9 (24%) Impaired urination: 9 (24%) vs. 9 (24%)	Oxy IR: 1 (dry mouth) Oxy TD: 1 contact dermatitis due to patch	Fair Unvalidated questionnaire to evaluate titration for presence and severity of 10 symptoms assessed at 2, 4 and 6 wks.
Dmochowski 2003	Application site reactions: Oxy 32/121 (25.4%; 5% severe), Tol 7/123 (5.7%), Pla 8/117 (6.9%) Systemic adverse events: Oxy 23/121 (19%), Tol 29/123, Pla 14/117 (12%) Anticholinergic side effects (% only, numbers NR) Dry Mouth Oxy TD 4.1% vs Tol SR 7.3% Constipation Oxy TD 3.3%, Tol SR 5.7%	Oxy TD l= 13/121 (10.7%; 12 due to application site reaction, 1 hot flushes). Tol SR = 2/123 (1.6%; 1 fatigue, 1 dizziness).	Fair Method of assessment not reported

* Pad test = patient fills bladder to 300ml, then performs a series of maneuvers, i.e. coughing 5 times. Change in pad weight at end of test is recorded. RCT = Random Controlled Trial, UTI = Urinary Tract Infection, NS = No statistical difference

Evidence Table 11. Clinically significant drug interactions [1]

	Flavoxate Hydrochloride	Oxybutynin Chloride	Tolterodine Tartrate	Darifenacin	Solifenacin Succinate	Trospium Chloride
Drugs affecting hepatic enzymes (CYP 450) Inhibitors of CYP2D6, CYP3A4	Not reported	Not reported	**No significant interaction. No action required.**[2]	**No dose adjustment needed for CYP2D6 and moderate CYP3A4 inhibitor.** Dosage should not exceed 7.5 mg when co-administered with potent CYP3A4 inhibitor.[6]	**Further studies needed.**[5]	Not reported
Fluoxetine	Not reported	Not reported	**No dose adjustment required**. May increase concentration of tolterodine by four fold.[2]	Not reported	Not reported	Not reported
Diuretics	Not reported	Not reported	**No significant interactions.**[1]	Not reported	Not reported	Not reported
Oral Contraceptives	Not reported	Not reported	**No significant interactions. No action required.**[2]	Not reported	Not reported	Not reported
Anticoagulants	Not reported	Not reported	**No significant interactions.**[2]	Not reported	Not reported	Not reported
Alcohol	Not reported	**Monitor**. Increased sedation with CNS depression.[2]	Not reported	Not reported	Not reported	Not reported
Antihistamines	Not reported	**Monitor**. Increased anticholinergic effects.[2]	Not reported	Not reported	Not reported	Not reported
Macrolide antibiotics	Not reported	**Information not available.**[2]	Not reported	Not reported	Not reported	Not reported

Evidence Table 11. Clinically significant drug interactions [1]

	Flavoxate Hydrochloride	Oxybutynin Chloride	Tolterodine Tartrate	Darifenacin	Solifenacin Succinate	Trospium Chloride
Azole antifungal agents	Not reported	**No significant interaction**. Serum concentrations of oxybutynin increased three fold when coadministered with itraconazole. Half-life was unaffected and the interaction is of only minor significance.[3]	**Dose adjustment required**. May inhibit metabolism of tolterodine. Doses of >1mg twice daily should be avoided.[2]	Not reported	**Monitor.** Co-administration with a single 10 mg solifenacin dose increased solifenacin's concentration by 40%. Half-life increased by 55% and AUC increased by 100%.[5]	Not reported

1 AHFS Drug Information, ASHP, 2002.
2 Drug Information Handbook 7th Ed. Lexi-Comp, 1999-2000.
3 Benedetti et al. Drug Metabolism Reviews, 1999.
4 Epocrates Version 6.02, 2003.
5 Drug Facts and Comparisons, Wolters Kluwer Company. 2004.
6 Drugs@FDA, 2005.