

Drug Class Review

Agents for Overactive Bladder

Final Update 4 Report

March 2009



The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. 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.

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

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator
Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director
Oregon Health & Science University

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The medical literature relating to the topic is scanned periodically (see <http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm> for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report based on the information contained in the scan. Please see timeline on the DERP website for details on the date of its release. Prior versions of this report can be accessed at the [DERP website](#).

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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 solifenacina 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 solifenacina 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 |

^aNot 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 question(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.

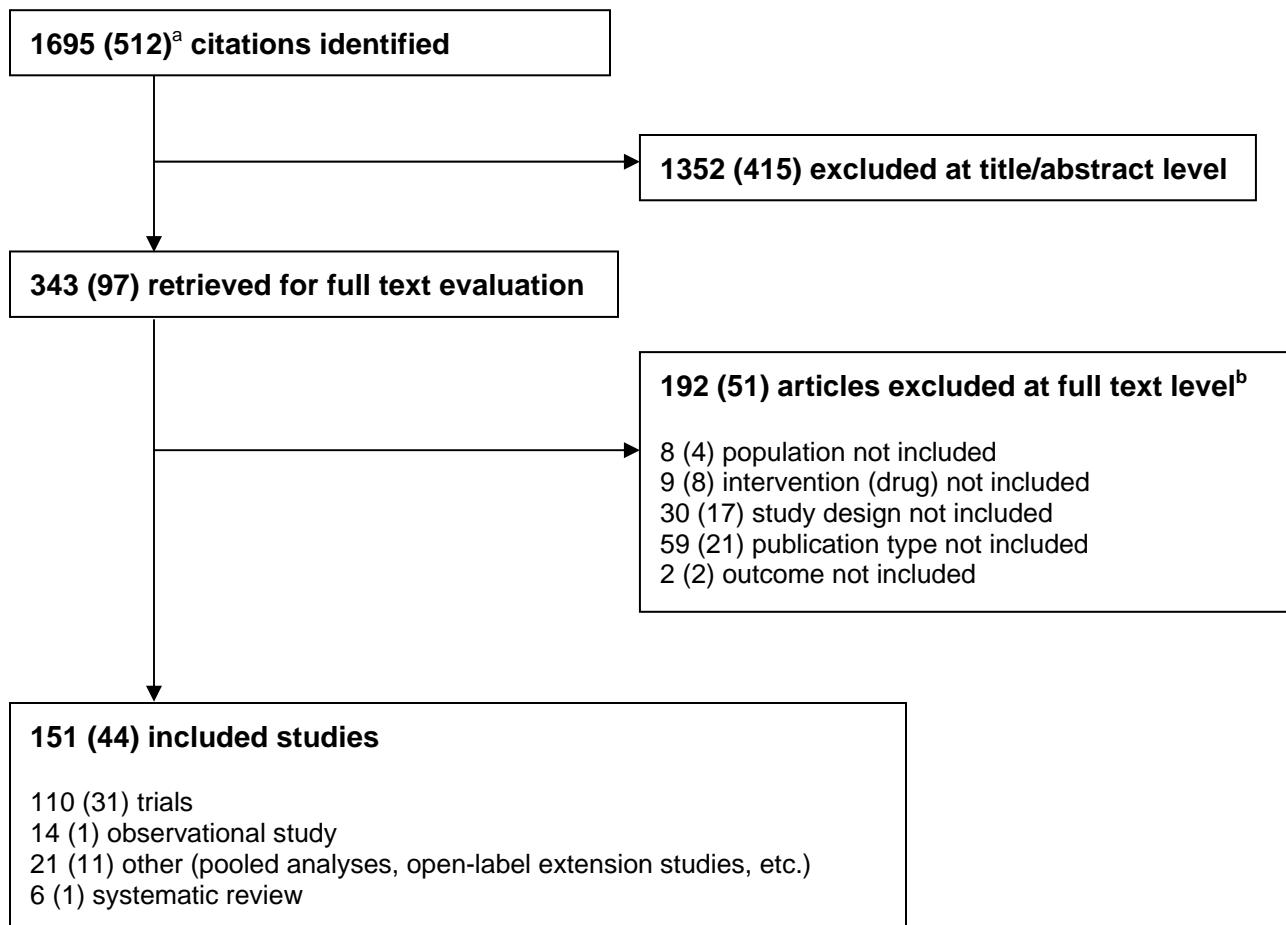
Each version of the report has been posted in draft form to the Drug Effectiveness Review Project website for public comment. Key stakeholders were notified of these postings. For Update 4 we received comments from 3 stakeholders (Novartis, Pfizer, and Orth-McNeil Janssen). The comments received and 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.
- Solifenacina (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 solifenacain.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, solifenacain, and/or darifenacain.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 review¹⁶ 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 study⁵⁰ 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 trial³¹ 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 study³⁸ 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 trial³¹ 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 OPERA³¹ 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 oxybutynin⁴⁴ 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 reviews¹⁵⁻¹⁸ 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 flavoxate⁶⁸ 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 solifenacin 10 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-release⁹⁰ 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 daily⁴⁶ 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 trial²⁸ 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 solifenacina (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 solifenacina 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 solifenacina 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 solifenacina 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 solifenacina (-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 darifenacina (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, darifenacina, solifenacina, or flavoxate. We found 1 head-to-head study³⁴ 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 study¹¹¹ 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 long-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 study¹¹⁵ 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 study¹¹⁹ 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 placebo⁶⁶ or a placebo-controlled trial⁵⁰ 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 mg¹²⁰ 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 study¹²⁴ 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 study³⁸ 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 study⁴⁷ showed a small difference and the second²² 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 solifenacain (5 mg or 10 mg) with tolterodine extended-release (4 mg). Data from the solifenacain 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 solifenacain, 24% for tolterodine; $P<0.05$), constipation (6.4% for solifenacain, 2.5% for tolterodine; $P=0.009$), and blurred vision (0.7% for solifenacain, 1.7% for tolterodine; NS).²⁸ Withdrawals due to adverse events did not differ significantly between groups (3.5% of patients receiving solifenacain, 3.0% for tolterodine). A subanalysis of the STAR trial compared only the 5 mg dose of solifenacain (the “no dose increase” subgroup) with tolterodine extended-release over 12 weeks.¹⁰⁶ Solifenacain 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 solifenacain 5 mg, solifenacain 10 mg, and tolterodine immediate-release 4 mg to placebo reported incidence of dry mouth as follows: 14% of the solifenacain 5 mg group, 21.3% of the solifenacain 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 solifenacain 10 mg, 7.2% for solifenacain 5 mg, 2.6% for tolterodine, and 1.9% for placebo. The comparisons of tolterodine with each solifenacain dose were statistically significant and favored tolterodine ($P<0.05$ for both). Similarly, blurred vision was reported by 5.6% of solifenacain 10 mg patients, 3.6% of solifenacain 5 mg patients, 1.5% of tolterodine patients, and 2.6% of placebo patients. The comparison of tolterodine and solifenacain 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 solifenacain 10 mg (2.6%), solifenacain 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 solifenacain.¹⁶ This review found that tolterodine extended-release had significantly lower all-cause withdrawals compared with placebo and no significant difference for solifenacain 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 solifenacina (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 solifenacina,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 study²³ 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 solifenacina (the “no-dose-increase” subgroup) con tolterodine extended-release found that over 12 weeks both groups had a comparable incidence of withdrawal due to adverse events (1.3% solifenacina compared with 2.8% tolterodine).¹⁰⁶

One placebo-controlled trial⁵⁰ reported an apparently lower rate of withdrawal due to adverse events among patients receiving tolterodine immediate-release (1.9%) than those receiving either solifenacina 10 mg (2.6%) or solifenacina 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 that 16% 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 trial⁸² 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 trials¹²⁹ 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 Korea³⁶ 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 solifenacain, 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-uurological 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 study³⁸ 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 | <p>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.</p> <p>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.</p> <p>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.</p> |

^aQuality 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.

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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 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 internal 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 (heart 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 combining 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 oxybutynin/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 ascenders 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. <i>International Urology & Nephrology</i> . 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. <i>Neurology & Urodynamics</i> . 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. <i>European Urology</i> . 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]. <i>JAMA</i> . 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. <i>BJU International</i> . 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. <i>Journal of Korean Medical Science</i> . 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. <i>Urology</i> . 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. <i>BJU International</i> . Aug 2006;98(2):377-380. | 6 |