Drug Class Review
on
Agents for Overactive Bladder

Final Report Update 3 Evidence Tables

December 2005

Original Report Date: February 2003
Update 1 Report Date: January 2004
Update 2 Report Date: May 2005

A literature scan of this topic is done periodically

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

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report. Please see timeline on the DERP website for details on the date of its release.

TABLE OF CONTENTS

Appendices

INTRODUCTION

Overactive bladder syndrome (OAB) is defined by the International Continence Society (ICS) as a medical condition referring to the urinary symptoms of frequency and urgency, with or without urge incontinence, when appearing in the absence of local pathological factors.[1] Nocturia is also commonly present.[2] 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.[3] 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. Urge urinary incontinence is the complaint of involuntary leakage accompanied by or immediately preceded by urgency.[4, 5]

While urge incontinence is not inevitable its incidence does increase with age.[6] It has been estimated that overactive bladder affects 20% of community dwelling senior citizens and around 50% of the institutionalized elderly.[3, 6] 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 first requires a clear diagnosis of the type of incontinence associated with OAB. If multiple forms are present it is important to determine which form is dominant. Non-pharmacologic treatment consists of behavioral training (prompted voiding, bladder training, pelvic muscle rehabilitation), transcutaneous electrical nerve stimulation (TENS), catheterization and use of absorbent pads.[7] Pharmacological treatment for OAB includes darifenacin, flavoxate hydrochloride, hyoscyamine, oxybutynin chloride, tolterodine tartrate, trospium chloride, scopolamine transdermal, and solifenacin succinate. Flavoxate hydrochloride acts as a direct spasmolytic on smooth muscle and maintains anticholinergic as well as local analgesic properties.[3, 8] Oxybutynin chloride has direct antispasmodic action on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle.[3, 8, 9] Tolterodine tartrate acts as a competitive muscarinic receptor antagonist.[3, 8, 10] Trospium chloride is a quaternary ammonium derivative with predominantly muscarinic action.[11] Darifenacin and solifenacin are competitive muscarinic receptor antagonists.[12, 13]

Anticholinergic agents have been included in a number of expert based or guideline reviews of high risk drugs for the elderly particularly two reviews by Beers et al.[14, 15] While these are not systematic reviews they identify drugs with significant potential for adverse effects in the elderly. These reviews do not provide comparative information.

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 (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs,

and outcome measures of interest to both clinicians and patients. The scope of the current review was approved in May 2005. Two drugs, solifenacin, and darifenacin were approved for use in the US for OAB after September 2004. The participating organizations approved the following key questions to guide this review:

1. For adult patients with urinary urge incontinence/overactive bladder, do anticholinergic OAB drugs differ in effectiveness?
    a. In head to head trials of anticholinergic drugs what is the comparative efficacy?
    b. What is the comparative efficacy of anticholinergic OAB drugs across active and placebo controlled trials?

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

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

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Library (2nd Quarter, 2005), MEDLINE (1966-July Week 3 2005), EMBASE (1980-July Week 3 2005), and reference lists of review articles. In electronic searches, we used broad searches, only combining terms for drug names with terms for relevant research designs (see Appendix A for complete search strategy). We have attempted to identify additional studies through searches of reference lists of included studies and reviews, the FDA web site, as well as searching dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

Two reviewers independently assessed studies for inclusion, with disagreements resolved through consensus. We included English-language reports of randomized controlled trials, involving adults with symptoms of urge incontinence, overactive bladder or irritable bladder. Interventions included one of the eight OAB drugs (flavoxate, oxybutynin, tolterodine, trospium, darifenacin, hyoscyamine sulfate, scopolamine or solifenacin) compared with another anticholinergic OAB drug, another OAB drug (i.e., an anticholinergic drug not on the US market), non-drug therapy (i.e., bladder training) or placebo. For adverse effects, we also included observational studies of at least 6 weeks' duration. Outcomes were mean change in number of incontinence episodes per 24 hours, mean change in number of micturitions per 24 hours, mean change in number of pads used per 24 hours, and subjective patient or physician assessments of symptoms (i.e., the severity of problems caused by bladder symptoms, extent of

perceived urgency, global evaluation of treatment symptoms, quality of life, and adverse effects, including drug interactions).

To evaluate effectiveness or efficacy we included only controlled clinical trials. The validity of controlled trials depends on how they are designed. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing efficacy.[16-18] Clinical trials that are not randomized or blinded, and those that have other methodological flaws, are less reliable, but are also discussed in our report.

Trials that evaluated one anticholinergic OAB drug against another provided direct evidence of comparative effectiveness and adverse event rates. In theory, trials that compare these drugs to other drugs used to treat OAB or placebos can also provide evidence about efficacy. However, the efficacy of the drugs in different trials can be difficult to interpret because of significant differences in key characteristics of the patient populations. Comparability of results across trials (direct comparisons or indirect comparisons) is difficult due to differing outcomes and different methods with which outcomes are assessed. Such assessments across trials should be done with caution.

To evaluate adverse event rates, we included clinical trials and observational cohort studies. Clinical trials are often not designed to assess adverse events, and may select low-risk patients (in order to minimize dropout rates) or utilize inadequate methodology for assessing adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time, utilize higher quality methodologies for assessing adverse events, or examine larger sample sizes.

Data Abstraction

The following data was 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 available and the trial did not report high overall loss to follow-up.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[17, 18] We rated the internal validity of each trial based on 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 in one or more categories were rated poor quality; trials which met all criteria, were rated good quality; the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target

population in whom the intervention was to be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the funder.

Appendix B also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the 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 six or more of the seven predefined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Data Synthesis

In addition to overall discussion of the study findings, meta-analyses were conducted where possible. Forest plots of the standardized effect size for efficacy measures or the risk difference for 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 the drugs in mean change in number of micturitions or incontinence episodes per day or per week. Differences in adverse event rates and withdrawals due to adverse events are expressed as the "percent risk difference." This is the difference between the proportions healed in two groups of patients at a given time-point (e.g., at 4 weeks, 80% in group A and 75% in group B is a 5% risk difference). As a measure of the variance around these estimates, the 95% confidence interval (CI) is also reported. 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.

RESULTS

Overview

Our searches identified 796 citations: 143 from the Cochrane Library, 214 from MEDLINE, 353 from EMBASE, 19 from Pre-Medline, 21 from reference lists, and 47 from pharmaceutical company submissions. We included 71 randomized controlled trials, and 30 other types of publications. Thirty-four studies were excluded for the reasons detailed in Figure 1. An additional 30 citations provided information for background, methodology, and drug interactions. We excluded 13 reports published in abstract form only, but used these to assess potential publication bias. Figure 1 summarizes the flow of study inclusions.

The searches for the third update were conducted in July 2005, resulting in 391 new citations with the two new drugs added. Forty-five papers were reviewed, and ultimately 15 new studies were included (6 head-to-head trials, 7 placebo-controlled trials, 2 drug vs nondrug trials). We also included 5 observational studies and two systematic reviews. We excluded 3

reports published in abstract form only, and included these in our assessment of potential publication bias.

We did not find any effectiveness trials of OAB drugs. The included trials are efficacy trials, primarily of short duration and assessing outcome measures related to efficacy. Most of the randomized trials had fair internal validity, but their applicability to community practice was difficult to determine. These 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 drug, but some studies compared doses at the higher end of the range for one drug to the lower end of the range for another. Of those studies that stated the funding source, all were funded by the pharmaceutical industry, and industry employees often served as co-authors.

Systematic Reviews

A good quality systematic review focused on comparing the effects of different anticholinergic drugs for OAB using randomized controlled trials that compared one anticholinergic drug to another or two different doses of the same drug.[19] This review was originally conducted in 2003 and recently updated. This review concurs with our findings that there is no evidence to show a statistically significant difference in efficacy between oxybutynin and tolterodine. However, the evidence indicates there may be fewer withdrawals due to adverse events and lower risk of dry mouth with tolterodine. The authors also conclude that although there is not sufficient evidence to claim differences in efficacy or withdrawals due to adverse events for the extended versus the immediate-release forms of the oxybutynin and/or tolterodine, evidence did demonstrate less risk of dry mouth with the extended release drugs. In addition, this review found similar efficacy for the 1 mg, 2 mg and 4 mg doses of tolterodine and greater incidence of dry mouth with the 2 mg and 4 mg doses.

The recent fair quality systematic review evaluated differences in tolerability, safety and efficacy between these OAB agents: oxybutynin, tolterodine, trospium, darifenacin and solifenacin.[20] This review found that solifenacin had greater efficacy for some clinical outcomes when compared to tolterodine based on one short-term trial. The authors determined that oxybutynin ER caused a greater number of patients to return to continence and a greater mean reduction in incontinence episodes than tolterodine ER, which was also based on one study. In contrast, we concluded, as did the original study[21] mentioned above, that there is no significant difference in mean reduction of incontinence episodes between oxybutynin ER and tolterodine ER. It appears that this 2005 review found clinical significance of this difference using a per protocol analysis to calculate relative risk values. This review also found that tolterodine ER had significant reductions of all-cause withdrawals compared to placebo, with non-significant results for solifenacin and darifenacin and oxybutynin IR had a greater risk of withdrawing from treatment compared with placebo. Regarding adverse event profiles, this review reported mixed results. For instance, the authors found that compared to placebo, oxybutynin IR (based on a single study) and tolterodine IR and ER showed the most favorable adverse event profile. However, the active control trials showed that oxybutynin IR had high rates of moderate to severe dry mouth. It should be noted that this fair quality review excluded observational studies that often contain long-term data, which can be relevant for evaluation of safety and tolerability.

Another fair quality systematic review used almost exclusively placebo-controlled trials to evaluate effectiveness of anticholinergic drugs for OAB and included trials published before

January 2002. The review concluded that the statistically significant differences between anticholinergic drugs and placebo were small.[22]

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

1a. In head to head trials of anticholinergic OAB drugs what is the comparative efficacy?

We found 24 head-to-head trials of oxybutynin, tolterodine, trospium, flavoxate, solifenacin, and/or darifenacin. All included studies are summarized in Evidence Table 1. Study quality assessments are presented in Evidence Table 2.

No good quality study was found. The only two flavoxate studies[23, 24], one study comparing oxybutynin IR and tolterodine IR[25] and two studies comparing oxybutynin immediate and extended release[26], were assessed as poor quality, and all others were fair quality. The poor quality studies suffered from lack of details on randomization, allocation concealment and baseline characteristics or lack of randomization and differences in potentially important baseline characteristics. Ten studies used an intention to treat analysis overall, three studies used an intention to treat analysis for adverse events but not 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 exclusively or predominantly urge incontinence. One trial involving trospium and oxybutynin only included patients with a spinal cord injury.[27] 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. One study included only female patients[28], and another analyzed the female subgroup of a larger trial.[29] Eight of 16 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 six fair quality studies comparing an immediate release formulation of one anticholinergic OAB drug to another.[28, 30, 31, 32] Four of these studies compared oxybutynin to tolterodine and were all sponsored by Pharmacia (the makers of tolterodine). Tolterodine was dosed at 2mg twice daily in all studies, while oxybutynin was dosed at 5mg twice daily in two studies[28, 32] and 5mg three times daily in two.[31, 33] Two compared immediate release formulations of oxybutynin to trospium. One trial was sponsored by a company that makes trospium, the other did not report sponsorship. The study durations ranged from 2 to 54 weeks.

We found six fair quality studies comparing an extended release formulation of an anticholinergic urinary incontinence drug to an immediate release formulation.[34-39] Four studies compared oxybutynin ER to oxybutynin IR,[36-38, 40] one tolterodine ER to tolterodine IR,[34] one study oxybutynin ER to tolterodine IR,[41] and one tolterodine ER to oxybutynin IR. Oxybutynin doses ranged from 5mg to 30mg a day, while tolterodine was dosed at 4mg a day.

Of the four studies comparing oxybutynin ER to oxybutynin IR, one was 6 weeks in duration, and compared 10mg per day of oxybutynin either ER once daily or 5mg IR twice daily ER to IR. Patients getting the ER formulation received a single daily 10mg dose; patients on the IR formulation got 2 daily 5mg doses.[36] The other three studies[37, 38, 40] used a dose titration up to the threshold of either intolerable side effects (in which case the dose was reduced by 5mg per day) or maximum efficacy. In the latter case, the "optimal" dose was then maintained for 7 days. Total, mean or range duration of trial actually experienced were not reported. In one study the "optimal" dose was maintained for 4 weeks and the efficacy analysis was performed with an "efficacy" population defined as patients, who completed ≥ 2 weeks in the stable-dose phase and did not have major protocol violations.[40] All four studies were funded by or had authors from the companies who make the extended release formulations involved.

We found only one study comparing tolterodine ER 4mg once daily to tolterodine 2mg twice daily (a placebo arm was also included) for 12 weeks.[34] This was the largest study included, with over 500 patients per treatment, and used an intention to treat analysis. In a subgroup analysis of women only from this study, 1235 women were included.

One study of tolterodine ER compared to oxybutynin IR in 600 Asian patients (Japanese or Korean) was found. Doses compared were 4mg tolterodine and 9mg oxybutynin daily. The manufacturer of tolterodine ER provided funding, and the formulation of oxybutynin IR used does not appear to be available in the US.

One study compared oxybutynin ER to tolterodine IR.[41] This study compared oxybutynin 10mg once daily and tolterodine 2mg twice daily for 12 weeks. The funding was provided by the manufacturer of the extended release form of oxybutynin (Alza) and one of the authors was employed by this company.

Two studies comparing extended release formulations of oxybutynin and tolterodine to each other were found.[21, 42] The OPERA trial enrolled 790 women to take either tolterodine ER 4mg or oxybutynin ER 10mg daily for 12 weeks.[21] The manufacturer of oxybutynin ER provided the funding for this study. In the second study (the ACET trial), oxybutynin was dosed at 5 to 10mg once daily and tolterodine at 2 to 4mg once daily.[42] Funding of this study was not reported. The study design was unusual and problematic, in that it consisted of two separate trials. One trial randomized patients to one of two doses of tolterodine in an open label (unblended) fashion. The other randomized patients to one of two doses of oxybutynin. Other than the two 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 could not be considered a purely randomized trial. They state that centers were assigned based on 1) geographic location, and 2) prescribing patterns for both drugs with an effort to produce balance.

The transdermal (TD) form of oxybutynin (which received FDA approval in late February 2003) was studied compared to oxybutynin IR and tolterodine ER in separate studies.[43, 44] The study of oxybutynin TD versus oral IR allowed dose titration, from 1.3 to 5.2mg per day via patch, or 5 to 15 mg per day orally.[43] The other study randomized patients to 3.9mg/day TD or 4mg/day tolterodine ER. The manufacturer of the TD system funded both studies.

Two studies comparing trospium chloride to oxybutynin IR were found. The first trial conducted in multiple German centers compared trospium 20mg twice daily (plus a mid day placebo dose) to oxybutynin IR 5 mg three times daily. All the subjects in this trial had spinal cord injuries. No included outcomes were reported. The trial is discussed in the section on subpopulations (Key Question 3).[27] The second trial was conducted in multiple European

centers comparing trospium 20 mg twice daily to oxybutynin IR 5 mg twice daily. One author of this study was from a pharmaceutical company that manufactures trospium in Europe. Data was collected over an average of 54 weeks at multiple intervals.[45]

One fair quality systematic review[20] reported efficacy differences between antimuscarinics (oxybutynin, tolterodine, trospium, darifenacin and solifenacin) using clinical outcomes. This review concluded that solifenacin resulted in significantly greater reductions in urgency episodes and micturition frequency when compared to tolterodine IR. The original study[46] compared the active medications to placebo in the primary analysis, and conducted only "exploratory" analyses of tolterodine versus solifenacin. The systematic review concluded that oxybutynin ER caused a significantly greater mean reduction in incontinence episodes and a significant increase in the number of patients who returned to continence when compared to tolterodine ER. This change in incontinence episodes was not reported as a significant difference in original OPERA trial[21] and the authors of the systematic review appear to have used a per protocol analysis to calculate relative risk values, resulting in a significant difference. The proportion returned to continence was not an outcome measure included to assess efficacy in this systematic review.

Two studies compared solifenacin to tolterodine (one tolterodine IR and the other tolterodine ER). The first, a fair-quality study, compared solifenacin 5mg , solifenacin 10mg, tolterodine IR 2mg twice daily, and placebo.[46] This study was not powered to show treatment differences between the active treatment arms. Thus, the authors did not do a statistical analysis of the drugs compared to one another, but they did statistical analyses of each drug compared to placebo.

The second study, the STAR trial[47] was designed as a "non-inferiority trial" with respect to its primary outcome (mean number of micturitions/24 hours), such that claims of superiority are not intended to be drawn from this data. In this trial, Chapple et al.[47] compared tolterodine ER 4mg to a "flexible" dose of solifenacin (5mg or 10mg) over a total of 12 weeks. Patients were randomized to either tolterodine 4 mg ER or solifenacin 5mg for the first four weeks. Then, at week 4, patients were allowed to increase their dose if they were not satisfied with treatment efficacy. The resulting dose was maintained for the remaining eight weeks of the study. The investigators stated that using flexible dosing allowed the trial to mirror clinical practice as closely as possible. One problematic aspect of this trial in its efficacy and safety analysis should be noted: data for both doses of solifenacin are combined in the analyses of outcome results. Thus, it is not possible to determine which dose of solifenacin provided greater efficacy or if the different doses caused a difference in rates of adverse events. Because the authors did not do a statistical analysis of the adverse events between solifenacin and tolterodine, we did a statistical analysis of the adverse events rates of the STAR trial ourselves, using the StatsDirect program.

Incontinence episodes and micturitions per 24 hours

Immediate release vs Immediate release

The objective measures in these studies were mean change in numbers of incontinence episodes per day or micturitions per day. Four studies examined oxybutynin versus tolterodine immediate release formulations. One study by Leung[28] 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 three 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 –1.4 to –1.8. The difference in standardized effect sizes of the mean change (from baseline to end of study) reported in these studies is plotted in Figures 2 and 3. One study examined trospium versus oxybutynin IR formulations. Significant differences were not found for micturition frequency, incontinence episodes or urgency episodes.[45] No significant differences were found between the drugs, by intention to treat analysis, in any study.

Immediate release vs Extended release

Two studies[37, 38] using a dose titration of oxybutynin ER or IR to adverse effects or efficacy reported no significant difference between groups in the mean change in incontinence episodes per week (rather than per day), but not enough data was reported to allow graphing. Converted to mean change in incontinence episodes per day, the mean change in the ER groups was –3.2 and –2.2, and in the IR groups was –2.9 and –2.2 in the Anderson and Versi studies, respectively. Time period from baseline to assessment was not reported. Neither study used an intention to treat analysis. The withdrawal rate for extended release and immediate release groups was 13% (ER) and 12% (IR)[38] and 6% (ER) and 8% (IR).[37] Alza, manufacturer of the oxybutynin ER formulation, funded both studies.

A study of 10mg oxybutynin ER once daily or 5mg oxybutynin IR twice daily[36] used an ER formulation used in this study is not available in the US and different outcome measures than the other studies: the proportion with day and nighttime *continence*, day/night micturition, and day/night incontinence episodes. For these reasons, we did not evaluate this study further here.

An additional study comparing titrated "optimal" doses of 10-30mg oxybutynin ER once daily (increasing in 5mg increments) or 5mg oxybutynin IR twice daily (also maximum of 30mg/day) 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.[40] Baseline reductions in incontinence episodes/24h were 2.0 and 2.4 for the controlled release and immediate release forms respectively. Similarly, reductions in micturitions/24h at the end of treatment were 1.8 and 2.4 for ER and IR forms respectively. These differences were not statistically significant. This was a study of a controlled-release product newly introduced into the Canadian market by Purdue Pharma and is currently not available in the U.S.

In the OPERA study of tolterodine ER 4mg once daily versus tolterodine 2mg twice daily,[34] no significant differences were found in mean change (absolute) in micturitions or incontinence episodes per week (see Figure 4). Converted to per day, the mean change in incontinence episodes was –1.6 (ER) and –1.5 (IR) and mean change in number of micturitions per day was –3.5 (ER) and –3.3 (IR). 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% ER, 60% IR, 33% placebo. The authors state that they present this outcome because the data were positively skewed, and that they believe the relative change is more relevant than the absolute change. Few other studies report data in this way. This outcome measure and the fact that the data were skewed limit comparability of these results to those in other trials. Overall withdrawal was 12%, with similar rates in the two drug treatment groups. A subgroup analysis of only women in this study found similar results, and is discussed under Question 3.[29]

Oxybutynin ER was compared to tolterodine IR in one study.[35] Based on an analysis of covariance, adjusting for baseline and severity of symptoms, oxybutynin ER was significantly more effective at reducing the number of incontinence episodes per week (p = 0.03), and number of micturitions per week (p = 0.02). This analysis was not intention to treat; the proportions of patients excluded from the analysis are 14% in the oxybutynin ER group and 11% in the tolterodine group. Therefore, due to dropouts, the analysis presented may not reflect actual reductions in efficacy. Insufficient data were presented to calculate the mean change in incontinence or micturitions based on intention to treat for this review.

Tolterodine ER was compared to oxybutynin IR in Japan and Korea.[39] No significant differences were found in percent change in median incontinence episodes, pad use, or micturitions per day. The median percent change in incontinence episodes was 78.6% for tolterodine, and 76.5% for oxybutynin. The absolute change is not reported, and again the data were reported to be skewed. The changes in voids per day were –2.1 and –2.0 for tolterodine and oxybutynin, respectively. There was no change in pad use, however.

A study of solifenacin 5mg or 10mg once daily and tolterodine IR 2mg twice daily demonstrated that both doses of solifenacin and tolterodine produced significantly lower mean number of micturitions when compared with placebo.[46] Solifenacin at both doses, but not tolterodine, resulted in statistically significant improvements in urge and overall incontinence episodes per 24 hours, and episodes of urgency. "Exploratory" analyses of solifenacin versus tolterodine resulted in significant differences favoring solifenacin at both doses in reducing the episodes of urgency, and solifenacin 10mg was superior to tolterodine in reducing micturitions per 24 hours.

The STAR trial, which was designed as a "non-inferiority" trial for its primary outcome,[47] examined the difference between a "flexible" dose of solifenacin (5mg or 10mg) and tolterodine ER 4 mg (all once daily), which revealed significantly higher rates of efficacy in decreasing urgency episodes, incontinence, urge incontinence and pad usage for the solifenacin patients.[47] However, the study did not demonstrate statistically significant between-treatment differences in the primary endpoint, micturitions/24h, nor in nocturia episodes. Thus, the finding of no between-treatment statistically significant difference for the primary outcome qualifies as evidence that solifenacin was "non-inferior" compared to tolterodine ER in reference to this primary endpoint. Based on the flexible-dose study design of this trial, both doses of solifenacin were combined and analyzed as one group for outcomes data and rates of adverse events.

The trials of solifenacin are reported here because although the dosing is once daily, this is based on elimination pharmacokinetics, not an extended release formulation.

Extended release vs Extended release

The OPERA trial[21] randomized 790 patients to 10mg daily of oxybutynin ER or 4mg daily of tolterodine ER for 12 weeks. 47% of patients had prior anticholinergic drug therapy for urge incontinence. There was no difference between the groups in the mean change in urge incontinence episodes (-26.3 vs –25.5 per week, oxybutynin vs tolterodine) which was the primary outcome measure. There were also no differences found based on mean change in total incontinence episodes. Differences were found in the proportion of patients with no incontinence (23% vs 17%; p = 0.03) and the mean change in micturitions per week (28.4% vs 25.2%, p=0.003) at week 12, in favor of oxybutynin ER. 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 two extended release formulations did not report these outcomes.[42]

Transdermal vs Immediate release

A six-week study comparing oxybutynin TD to oxybutynin IR 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).[43] Dose was then titrated to effect or side effects over the 6-week study period. 76 patients were enrolled. No significant differences were found in this small study in the percent change in mean incontinence episodes (66.7% vs. 63.9%) or the number with zero incontinence episodes in week 6 (21% vs.26%).

Transdermal vs Extended release

A study of 361 patients randomized to oxybutynin TD 3.9mg per day or 4mg tolterodine ER per day or placebo.[44] All patients had to have 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 based on mean change in incontinence episodes per day at 12 weeks (oxybutynin TD -2.9, tolterodine ER -3.2 p=0.5878) or mean decrease in urinary frequency per day (oxybutynin TD -1.9, tolterodine ER -2.2, p=0.2761).

Symptoms and Overall Assessment of Benefit

Immediate release vs Immediate release

All four studies involving oxybutynin IR vs tolterodine IR reported some measure of success based on subjective patient assessments. Two studies[30, 31] used a six-point scale of symptom severity (0 = no problems, 6 = severe problems). The proportion of patients improving by one point or more on this scale was reported in both studies. In the study comparing tolterodine 2mg twice daily to oxybutynin 5mg twice daily for 8 weeks,[30] 45% reported improvement on tolterodine and 41% on oxybutynin. In the study comparing tolterodine 2mg twice daily to oxybutynin 5mg three times daily,[31] 50% on tolterodine and 49% on oxybutynin reported improvement at 12 weeks. These findings were not statistically significant.

We also reviewed a study of tolterodine IR versus oxybutynin IR involving Chinese women. [28] Two visual analog scales (VAS) were used: one assessed overall severity of symptoms (0 = no effect, 10 = maximum severity); the other assessed changes 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) than the tolterodine group. The patient perception of 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 2mg twice daily versus oxybutynin 5mg twice daily, patients were asked if they felt that the study drug had benefited them (yes/no) and if yes, was it little or much benefit.[32] 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, oxybutynin IR in 17% of cases. Patients were reported as providing "practically identical figures."[45]

Immediate release vs Extended release

One study of oxybutynin IR vs tolterodine ER in Japanese and Korean women assessed subjective outcome measures.[39] Patients were asked to assess their perception of bladder condition (on a 6-point scale), urinary urgency (on a 3-point scale), and overall treatment benefit (on a 3-point scale) and quality of life (measured by KHQ), at baseline and 12 weeks. There was no difference between the groups based on the change in the patients' perception of bladder condition (improved; tolterodine ER 72% vs. oxybutynin IR 73%; the deterioration rate for both treatments was 5% and for placebo, 8%). The patients' assessment of urinary urgency was also similar between the groups (improved ability to hold urine tolterodine ER 49% vs. oxybutynin IR 57%). The treatment benefit was rated as "much" by 42% on tolterodine ER vs. 53% on oxybutynin. Although the treatments showed a difference in quality of life compared to placebo, no significant differences between treatments were found on any domain in the quality of life assessment.

The STAR trial[47], which compared the difference between a "flexible" dose of solifenacin (5mg or 10mg) and tolterodine ER 4 mg, reported the patient Perception of Bladder Condition (PBC) of those patients receiving solifenacin to be significantly improved compared tolterodine ER-treated patients.[47] The PBC is a validated 6-point categorical scale used by patients to assess their perception of bladder condition in terms of the severity problems it has caused them; a decrease in the score represents an improvement in the perception of bladder condition. The change in score from baseline was –1.51 for solifenacin and –1.33 for tolterodine. While this difference was statistically significant (p=0.006), the difference represents only a 3% change on the 6-point scale, and the clinical significance is not known.

Extended release vs Extended release

The OPERA study of tolterodine ER and oxybutynin ER did not measure these outcomes.

The other study of extended release formulations of tolterodine and oxybutynin[42] assessed patient symptoms at baseline and 8 weeks using the six-point scale described above. Again, a change of one 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 (as no, yes – a little, or yes- very much). The proportion reporting improvement on the six-point scale was 60% on tolterodine 2mg, 70% on tolterodine 4mg, 59% on oxybutynin 5mg, and 60% on oxybutynin 10mg. Significantly more patients were improved on tolterodine 4mg a day compared to all

other groups ($p < 0.01$). An analysis of the degree of change comparing tolterodine 4mg and oxybutynin 10mg indicated that patients reported greater improvement on tolterodine ($p<0.01$). However, this finding appears to be weighted 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 4mg (77% "improved") than those on oxybutynin 10mg (65% "improved"). The authors report that there were no statistically significant differences in response between the treatment arms in subgroups of patients who were drug naïve or drug experienced at enrollment, however the proportion with improvement on tolterodine 4mg was 75% and on oxybutynin 10mg 54%. By chi square analysis, this difference is statistically significant ($p = 0.02$). No differences among the four 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, with centers being chosen by the investigators and assigned to either tolterodine or oxybutynin. Enrolled patients were then randomized to one of two doses of the assigned drug. Differences between the groups were present at baseline, including race (higher proportion White in tolterodine groups), age (younger in oxybutynin groups), and proportion of patients who had previously received anticholinergic drug therapy for OAB (higher proportion in oxybutynin groups). These differences are not accounted for in the analysis. Considering these differences, the finding of a significant difference in proportion of patients with prior drug therapy experience who improved with tolterodine 4mg compared to oxybutynin 10mg may actually reflect confounding or selection bias. Without a reporting of which drug the patients had received (and presumably failed) prior to enrollment, it is not possible to rule out an important effect on these findings. Although the authors state that an intention to treat analysis was performed using last observation carried forward, they also state that patients had to have been assessed in at least one post-randomization visit to be included in the analysis. The protocol only mentions two visits, randomization and assessment at eight weeks, so patients lost to follow-up would be excluded, and in fact 89 patients were withdrawn.

Transdermal vs immediate release

A small, 6-week study of oxybutynin TD compared to oxybutynin IR assessed the patient 's perception of the overall treatment efficacy using a visual analog scale at baseline and 6 weeks.[43] No difference was found between the groups, with a change in score of 5.8 for the oxybutynin TD group, and 6.0 for the oxybutynin IR group.

Transdermal vs extended release

A study of 361 patients assigned to oxybutynin TD 3.9mg per day or tolterodine ER 4mg per day used the Incontinence Impact Questionnaire, and the Urogenital Distress Inventory to measure quality of life and a visual analog scale to measure treatment efficacy "periodically during the trial".[44] It is not clear when these were measured, other than at baseline. There was no significant difference in the global assessment of disease state scores, or the two quality of life instruments used.

1b. In trials of anticholinergic OAB drugs compared to non-drug therapy, other drug therapy, or placebo what is their comparative efficacy?

We found six trials of one of the three anticholinergic incontinence drugs compared to another drug not currently used or not on the market in the U.S. (Evidence Table 3).[48-53] Two used oxybutynin[52, 53] and four used flavoxate.[48-51] The mean change in micturitions per day in the two oxybutynin studies were –2.5 and –2.4, within the range of change seen in the head-to-head trials. The flavoxate studies used 200mg three or four times a day. Two studies were for only 7 days, one for 14 days and one for 6 weeks. The ability to compare the results of these studies to results found with oxybutynin or tolterodine is extremely limited, as only one study (20 patients, 14 day duration) used outcome measures similar to the head-to-head trials.[48] This study enrolled women, mean age 51 years, with cystometry-proven detrusor instability in a randomized crossover study of flavoxate, emepronium or placebo. The mean change in number of micturitions per day for flavoxate was +1 (emepronium -0.5, placebo –1). The mean change in the number of incontinence episodes per day was –1 for flavoxate (emepronium -1, placebo –2). This is also the only study that met fair quality criteria; all others were poor primarily because of lack of important details such as eligibility and exclusion criteria.

We found five studies comparing oxybutynin to non-drug therapy (bladder training, electrostimulation therapy)[54-58] These trials are summarized in Evidence Table 4. Four of these appear to be reporting different outcomes from the same trial and will be treated as one study.[54, 56, 58] Two studies reported the mean change in number of micturitions per day (oxybutynin IR –2, and –2.1) or mean change in incontinence episodes per week (oxybutynin IR –10.2).[54-56] These data are within the range reported in the head-to-head trials. The other studies report outcomes such as proportion with clinical cure (IR 73%) or change on Global Severity Index (IR 2.1), which were not used by other studies of oxybutynin, tolterodine or flavoxate. These studies include an extension phase of a trial that reports the results of combination therapy (IR and behavioral therapy) following the completion of the original randomized trial comparing oxybutynin IR and behavioral therapy.[59]

We found 24 placebo-controlled trials (one is an unpublished study that was provided by the manufacturer)[46, 60-81] and three systematic reviews[19, 20, 82] of OAB drugs. Only one of the systematic reviews did not present enough data to assess individual drugs; it assessed the effectiveness of any anticholinergic OAB drug compared to placebo.[82] Nine of the trials that met inclusion criteria assessed tolterodine compared to placebo.[62-68] The results for these trials on mean change in number of micturitions or incontinence episodes per day are presented in Evidence Table 5. The range of mean change in micturations/24h for tolterodine 4mg daily is -0.1 to -2.3, while the placebo rates range from 0 to 1.4. In the head-to-head trials, the range of mean change in micturations/24h for tolterodine 4mg/day was –1.7 to –3.5. The range of mean change in incontinence episodes/24h is -0.7 to -1.7 and placebo ranges from 0 to -1.9. In the head-to-head trials, the range of mean change in incontinence episodes/24h for tolterodine was –1.3 to –2.2. The findings of the placebo-controlled trials show a lower reduction in micturitions and incontinence episodes than the head-to-head trials, but are consistent with each other.

Two additional studies were found comparing tolterodine ER to placebo. Change in micturition frequency and incontinence episodes were consistent with previous tolterodine ER versus placebo trials and with results of comparative trials involving tolterodine ER.[77, 78]

Only one study each was found comparing oral oxybutynin[61] and flavoxate[60] to placebo. Other studies did not meet the inclusion criteria. The oxybutynin study used a dose of 2.5mg twice daily, and compared median change in daytime incontinence and frequency. Actual data were not reported, but the analysis showed oxybutynin to be better than placebo at reducing daytime frequency ($p = 0.0025$), but not incontinence. The flavoxate study compared 200mg flavoxate three times daily to placebo. The difference between flavoxate and placebo in the mean change in number of micturitions per day was not statistically significant (-0.292, $p = 0.95$).

Transdermal oxybutynin delivered at doses of 1.3, 2.6, and 3.9mg per day was compared to placebo for 12 weeks.[76] Less than half of those enrolled in a 4 week screening process were randomized in this study, and there was a 14% drop-out rate during the trial. The mean change in incontinence episodes per day was –2.7 with 3.9mg TD, vs –2.1 with placebo ($p < 0.05$). The other doses were not significantly different from placebo on primary the outcome measure. The degree of change see in both groups is larger than seen in other placebo-controlled trials, or head-to-head trials.

Three trospium vs. placebo trials were found.[74, 75, 79] Only one, a 12 week trial, reported change in micturitions per day, -2.4 for trospium, -1.3 for placebo and change in incontinence episodes, -2.3 for trospium and -1.9 for placebo.[79] In a head to head trial similar results for reduction in micturitions per day were found for trospium at 26 weeks, -2.9.[45]

A very small placebo-controlled trial evaluating scopolamine transdermal patch in 20 women diagnosed with detrusor instability showed greater improvements in diurnal frequency, nocturia, urgency, and urge incontinence with scopolamine than placebo.[72] It is important to note that this trial was limited to two weeks of treatment only.

One study comparing solifenacin 5mg and 10mg to placebo to assess efficacy and also safety and tolerability demonstrated statistically significant greater reductions in micturitions per 24 hours, number of incontinence episodes, and episodes of urgency in both doses of solifenacin compared to placebo.[70] This study also showed that approximately 50% of patients from both dosage groups who had at least one incontinence episode at baseline returned to continence by the end of the study. Nocturia reduction was only seen in the 10mg dose.

Three trials comparing darifenacin to placebo were found in the article searches,[69, 71, 73], and one trial was identified by the manufacturer. The first study with darifenacin 30mg[69] examined warning time as defined by the time from the first sensation of urgency to voluntary micturition or incontinence, which was increased under active treatment compared to placebo. Darifenacin 30mg is twice the currently FDA approved maximum daily dose of 15mg per day. Authors note that the 30mg dose used in this trial was chosen during the investigation phase and was assumed to be clinically effective at the time of study design. Secondary efficacy endpoints included clinical monitoring urgency severity, subjective urgency severity recorded at home, and home diary number of urgency episodes. This study was very short with a two-week treatment period, and reported the outcome data as median changes, not mean changes.

The second trial involved a dose titration of 7.5mg to 15mg darifenacin (when requested and tolerated) compared to placebo.[73] This study reported a median change of number micturitions/24h and change in incontinence episodes/week for darifenacin and placebo at 12 weeks of –18.9% vs. –10% and –67.3% vs. –42.9%, respectively. An additional darifenacin trial showed similar results at three different doses, 3.75mg, 7mg and 15mg and also reports improvements in terms of medians.[71] The median percent change from baseline of micturition frequency/24h was –13.8%, -16.3%, -15.3% and –8.0% for 3.75mg, 7.5mg, 15mg and placebo

respectively and the median percent change from baseline of number of incontinence episodes per week was –58.8%, -67.7%, -72.8% and –55.9% for 3.75mg, 7.5mg, 15mg and placebo respectively.

The final study identified was submitted by the manufacturer.[83] This study included darifenacin 15 and 30 mg, tolterodine IR 2 mg twice daily, and placebo arms. A total of 680 patients were enrolled. Only results from the darifenacin and placebo arms were reported. The primary outcome was number of micturitions per week, but median change in micturitions per day is also reported. The median percent changes were -19.1% for darifenacin 15mg, -19.7% for darifenacin 30mg, and -3.2% for placebo. The difference compared to placebo was significant only for the darifenacin 30mg comparison ($p = 0.047$), but not the darifenacin 15mg comparison ($p = 0.075$). The fact that all four of these studies used medians to report results instead of means makes it impossible to make indirect comparisons of efficacy and safety for darifenacin.

Quality of life

Quality of life in patients with urge incontinence has been shown to be significantly lower than among the general US population.[84-86] However, the 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 Kings Health Questionnaire, and the Incontinence Quality of Life Index (IQoLI), a tool developed for women with urge incontinence.

Assessments of the effect on quality of life of treatment with tolterodine compared to oxybutynin have been done based on two head-to-head trials,[41, 87] with one open-label extension study of tolterodine.[35] Quality of life of tolterodine IR and ER versus placebo was assessed in one randomized trial and one open label extension study.[80, 88-90] All of these studies included assessments of patients who completed the study. One also attempted to assess changes in those who withdrew from the trial,[87] but the numbers of subjects in each arm were not sufficient to allow a comparative analysis. Three studies used the Kings Health Questionnaire as the urinary incontinence-specific quality of life tool.[80, 87-90]

A 12-week study comparing oxybutynin IR and ER measured quality of life with two validated questionnaires, the Incontinence Impact Questionnaire and the Urogenital Distress Inventory.[40] Although investigators mentioned the significant improvement in the 2 disease-specific quality of life scales with both treatments, there are no precise results reported.

A clinical trial comparing tolterodine IR, ER and placebo also assessed quality of life during the trial and during an open-label extension period. To date, the quality of life results comparing tolterodine IR to placebo and tolterodine ER to placebo have been published but not the comparison of tolterodine IR to ER.[80, 88-90] The tolterodine versus placebo 12-week trial showed a statistically significant improvement in the tolterodine group versus placebo. Differences in mean change on individual domain scores ranged from –0.2 to –8.36. These results were maintained, and improved after 3 months and 12 months open-label treatment.[89] The comparison of tolterodine ER to placebo also found improvements that favored tolterodine on six of ten domains on the KHQ.[80] 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.[90] Comparing results of the KHQ reported for the IR and ER forms (in two publications), no overall difference is apparent, with differences on individual domains ranging from –1.88 to +1.68.[80, 88]

The head-to-head comparison of tolterodine and oxybutynin found significant improvements among patients 60 years old and above on the Kings Health Questionnaire at 10 weeks compared to baseline. Importantly, however, no difference was found between the drugs. The degree of change seen from baseline to 10 weeks in this study were lower than reported in the 12-week placebo controlled trial, with the mean change in the drug groups comparable to the mean change in the placebo group.

A subanalysis of only the Japanese patients in a 12-week head-to-head comparison of tolterodine ER to oxybutynin IR[39] , described above, examined the results of the Kings Health Questionnaire for this specific population.[91] Results showed that both medications improved quality of life in Japanese OAB patients, though the results of the drugs were only statistically significant compared to placebo but were not compared to one another.

Another 12-week study comparing tolterodine and oxybutynin used the SF-36 and the IQoLI [92] Again, 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. Based on the experimental IQoLI (assessing women only), all groups improved significantly over 12 weeks, but no significant differences were seen between the groups.

A systematic review of antimuscarinic drugs for OAB included global and disease-specific quality of life assessments reported in placebo-controlled trials only.[20] The review found significant differences in QoL when comparing tolterodine IR and ER, trospium, solifenacin, and oxybutynin TD to placebo. However, due to limited analyses of direct comparisons, no significant differences were found between drugs. A separate publication with details of antimuscarinic effects on QoL was not available at the time of the current review (see Reference 42 of the systematic review mentioned)

Abstracts: Assessment of Publication Bias

In addition to the fully-published reports of head-to-head trials cited above, we found six head-to-head studies that were published in abstract format only, at the time of writing (see Evidence Table 6).[93-98] Two of these may be interim analyses of included studies, and do not present enough data to compare to published studies.[94, 95] Three studies appears to be independent of the included studies.[93, 96] One study compared tolterodine 2mg twice daily to oxybutynin 5mg three times daily for 12 weeks. The mean change in number of micturations/24h was –2.1 for tolterodine and –2.7 for oxybutynin. The mean change in number of incontinence episodes/24h was –1.7 for tolterodine and –2.1 for oxybutynin. There was no significant difference between groups on either measure or on patients' perception of bladder condition using a 6-point scale. These numbers are within the ranges reported in the head-to-head trials, and do not indicate a publication bias based on effect size. Another study compared tolterodine IR 2mg twice daily to oxybutynin IR 5mg twice daily and found the mean change in micturitions per day to be greater with tolterodine (-2.6) compared to oxybutynin (-1.8); as well as the mean change in incontinence episodes (tolterodine -2.2, oxybutynin -1.4). These numbers are comparable to those found in other studies when the lower dose of oxybutynin is taken into account.

One study compared tolterodine to trospium and placebo. Trospium resulted in a -3.4 decrease per day in micturition frequency compared to -2.6 for tolterodine and -1.9 for placebo. Sufficient details were not available in the abstract to evaluate the study.[97]

Eight placebo-controlled trials published in abstract form were also found[99-106]. The results are comparable to results of fully published articles and are summarized in Evidence Table 6.

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

Long-Term Studies

There are no long-term head-to-head studies designed to assess adverse events of tolterodine, darifenacin, solifenacin, or flavoxate. We found one head to head study[45] comparing adverse events in trospium and oxybutynin over an average of 54 weeks. This study compared trospium at 20 mg twice daily to oxybutynin IR at 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.

We found three study of prescription claims data that evaluated the discontinuation rate of new prescriptions for tolterodine or oxybutynin (see Evidence Table 7).[107] One study evaluated the proportion of patients discontinuing treatment (not refilling prescription) in a 6-month period in 1998. Thirty-two percent of patients 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 co-payment). The mean time to discontinuation was 45 days for oxybutynin and 59 days for tolterodine; 68% on oxybutynin never refilled the original prescription, compared to 55% on tolterodine. 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 ER, or oxybutynin ER or IR.[108] Inpatients were included. The researchers identified 33,067 patient records for the study, with 50% taking tolterodine ER, and 25 and 26% taking tolterodine ER and IR, respectively. Compliance (based on prescription refills) was not found to be different between tolterodine ER and oxybutynin ER, but oxybutynin IR is stated to be lower (no statistical analysis presented). Persistence rates were low overall, but highest for tolterodine ER (mean 139 days) compared to oxybutynin ER (mean 115 days) or oxybutynin IR (mean 60 days). Statistical analyses of these differences were not conducted. The difference was statistically significant at months 1, 2, 3 and 12 ($p< 0.001$) for the comparison of tolterodine ER to either formulation of oxybutynin. Differences at other months are presumed to be nonsignificant (data not reported).

The third study used a Medicaid claims database, excluding those eligible for Medicare or in institutions.[109] The researchers identified 1637 patient records for the study. In this study, only 11% were taking tolterodine ER, 13% oxybutynin ER, and 76% oxybutynin IR. Notably, 30% of oxybutynin IR users were under 18 years old. In this study, only 32% on oxybutynin IR, and 44% on either tolterodine or oxybutynin ER continued to take the drugs after 30 days ($p<0.001$). The 1-year persistence rates were 9%, 6% and 5% for tolterodine ER, oxybutynin ER, and oxybutynin IR, respectively ($p=0.086$). In a Cox-regression model adjusting for age, sex and race, persistence was not difference between oxybutynin IR and tolterodine ER. In this

analysis, oxybutynin ER had a higher risk of nonpersistence after 30 days on drug that tolterodine ER (no difference in the first 30 days). An analysis of risk for "nonpossession" (similar to compliance measures based on days supply provided) indicated no differences between the drugs. Similarly an analysis of switching from the index drug showed "little difference", with 6% switching drug.

We found five open label studies of tolterodine, one 12-week uncontrolled study[110] and four 9 to 12 month extension studies following RCTs.[35, 111-113] Overall adverse event reporting was high (see Evidence Table 7). Dry mouth was the most common adverse event reported, ranging from 13 to 41% of patients. In the short-term study, 8% of these were classified as severe; while in longer-term studies 2-3% reported severe dry mouth. Other adverse events reported included urinary tract infection, headache, and abdominal pain. The longer studies reported 3 to 5 adverse events rated as serious and classified 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 of these studies[35, 113] reported that dry mouth accounted for only 1-2% of patients withdrawing overall.

An uncontrolled 12-month open-label extension of 4 randomized placebo-controlled trials for tolterodine IR evaluated a total of 714 patients.[112] Total number of withdrawals due to adverse events was 105 (15%) with dry mouth reported by 41% of the patients. Dose reduction was offered for those patients with tolerability problems. In a 12-month open-label extension of the previously cited head-to-head comparison of tolterodine ER to oxybutynin IR study, patients were offered tolterodine ER 4mg. The most frequent adverse event in this extension was dry mouth, reported by 33.5% of patients during the 12 months, which is lower than levels (36.8%) found in the 12-week original study. There was a 1% withdrawal rate due to adverse events over the 1ong-term study. It is not clear if the patients in either of these 2 studies overlap patients in previously reported studies (above) that also combine data from patients followed after participating in RCTs.

In addition to these open label prospective studies, we reviewed two uncontrolled studies identifying patients by new tolterodine prescriptions.[114, 115] One study evaluated adverse events and tolerability over 12 weeks.[114] Only 4% of patients reported any adverse event, with dry mouth being the most common (2%). The other study[115] identified all new prescriptions for tolterodine in the UK in a six month period, and asked the prescribing general practitioner to retrospectively complete a standard form assessing adverse events at 3 and 9 months. Overall, the physicians reported 3634 events; 13% of these were classified as an "adverse drug reaction (ADR)". Dry mouth was the most common, accounting for 2.9% of all events and 0.5% of all ADRs. Dry mouth was followed by unspecified adverse events, headache or migraine, and UTI. 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 the non-drug protocol, did not meet our criteria for efficacy, but did report adverse events data.[116] 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 along with increased back and leg pain.

An open label 12-week study of oxybutynin reported 59% of patients with dry mouth, 23% moderate to severe.[117] Similar to the open-label tolterodine studies, withdrawals due to adverse events were 8% overall, 1.6% due to dry mouth.

Solifenacin safety and tolerability was studied in a long-term, 40-week open-label extension study[118] that included patients who had completed one of two different trials: one was a placebo-controlled 12-week trial by Cardozo and colleagues[70] that compared solifenacin 5mg and 10mg to placebo, and the second trial[46] compared solifenacin 5 mg, solifenacin 10mg, tolterodine 2 mg IR twice daily, and placebo. In the 40-week 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%, blurred vision.

Open-label extension studies are only generalizable to the patient populations included in the trials and to those 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.[119, 120] In addition, one extension study of darifenacin was identified by the manufacturer, but data provided were not adequate for quality assessment of the study.

Short-Term Trials

Adverse events reported in short-term head-to-head trials are summarized in Evidence Table 8. 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. Comparisons of the rates of adverse events and dry mouth are presented in Figures 5 and 6. The risk of dry mouth was 28% lower with tolterodine IR than oxybutynin IR (pooled risk difference -0.28, 95% CI -0.34, -0.21). Two of these studies[32, 33] reported the incidence of severe dry mouth with tolterodine and oxybutynin, 1% vs 5% (NS), and 4% vs 15% ($p = 0.01$). The other study reported that more patients on oxybutynin than those on tolterodine reported severe dry mouth, but numbers were not reported. One additional study[28]assessed dry mouth using a xerostomia questionnaire. They found a significant deterioration on all measures of the scale (except denture fit) for both drugs, with no difference between them.

One short-term trial of trospium versus oxybutynin IR found a higher incidence of severe dry mouth in oxybutynin IR, 23% vs. 4% though overall adverse events were comparable.[27] Overall incidence of adverse events was high.

The three studies comparing oxybutynin IR and oxybutynin ER showed differing results, with the two studies using an extended release formulation made by ALZA reporting lower incidence of dry mouth and adverse events with the ER than IR formulation.[37, 38] These studies also reported a higher incidence of severe dry mouth with the IR formulation, especially as doses increase. Both studies showed a larger difference in moderate to severe dry moth at the 10 and 15 mg levels than at 5 mg per day levels, but at 20 mg/day dose one study[37] showed a small difference, and the other[38] showed a much larger difference. This second study also allowed 25 and 30 mg/day doses of the ER formulation, which resulted in higher proportions of patients with moderate to severe dry mouth than the lower doses, but similar to each other. The study using an extended release formulation made by a Finnish company reported higher rates of dry mouth, but lower rates of overall adverse events in the ER group[36] However, this version of extended release oxybutynin is not currently available in the US. The one study comparing tolterodine ER to IR reported no difference in overall adverse event rates, but a slightly lower rate of dry mouth (risk difference -7% 95% CI -12, -1.6) with the ER form. An additional study comparing oxybutynin IR and oxybutynin ER showed slightly higher withdrawal rates due to adverse events for the immediate release form (20% vs. 17%) and similar numbers of reported dry mouth, however

these differences were not statistically significant.[40] Most other adverse events were reported in greater numbers for the oxybutynin IR, but again differences were not statistically significant.

The study of tolterodine ER vs oxybutynin IR found significantly fewer patients reporting dry mouth with tolterodine ER (33.5%) compared to oxybutynin IR 53.7%, p<0.001.[39] Overall adverse events were not reported in a way that could be directly compared.

The study of oxybutynin ER versus tolterodine IR found no difference in overall reports of adverse events, and a non-significant reduction in the proportion with dry mouth.

In the better quality study of the two ER formulations, dry mouth was the most common adverse event noted, and was significantly more frequent in the oxybutynin ER group than the tolterodine ER group (29.7% vs. tolterodine 22.3%, p=0.02).[21] While not reaching statistical significance, the number of patients with mild or moderate to severe dry mouth were greater in the oxybutynin group.

The other study comparing the ER formulations of tolterodine and oxybutynin used a visual analog scale to assess change in severity.[42] The authors reported a dose-dependent change for both drugs, but a statistically significant increase only for oxybutynin 10mg once daily compared to tolterodine 4mg once daily (p = 0.03). Other adverse events reported include headache, abdominal pain, constipation, micturition disorders, UTIs, dizziness, somnolence, and vision disturbances. The rate of occurrence of these varied from study to study, and the overall rates of adverse events varied from study to study, reflecting differences in approach to identifying and classifying adverse events.

A small study of oxybutynin TD versus IR found a much higher rate of dry mouth in the IR group (39% vs 82%, p<0.001).[43] The rate of dry mouth reported with the IR form in this study was the highest incidence reported in any study. Based on an unvalidated questionnaire, the severity of dry mouth appeared worse in the IR group, but few rated these side effects "intolerable". All patients had been taking oxybutynin IR prior to enrolment, and 67% on TD reported a reduction in dry mouth, compared to 33% on IR. However, overall adverse event rates were not reported. This was a short, 6-week study.

A 12-week study of oxybutynin TD versus tolterodine ER found fewer systemic adverse events among patients in the oxybutynin TD group, including dry mouth, but these did not reach statistical significance.[44] Application site reactions were reported in 26% of the oxybutynin TD group and 5.7% in the tolterodine-placebo patch group.

In a comparison of varying doses of darifenacin ER and IR and oxybutynin IR, visual nearpoint (a measure of the anticholinergic effect on vision) was not statistically different between the drugs.[121]

The STAR trial, which was designed as a non-inferiority trial for its primary outcome measure, compared solifenacin (5mg or 10mg) and tolterodine ER 4mg, reported adverse events data as both solifenacin dosage groups combined compared to the tolterodine group. Because the authors did not do a statistical analysis comparing the rates of the adverse events, we conducted our own statistical analysis. The adverse events that were most commonly reported for both groups were dry mouth (30% for solifenacin, 24% for tolterodine, p<0.05), constipation (6.4% for solifenacin, 2.5% for tolterodine, p = 0.009), and blurred vision (0.7% for solifenacin, 1.7% for tolterodine, NS).[47] Withdrawals due to adverse events were not significant between groups and were 3.5% for patients receiving solifenacin compared to 3.0% for those receiving tolterodine .

In a trial by Chapple et al.[46] the comparisons of solifenacin 5mg, solifenacin 10mg, and tolterodine IR to placebo the rates of patients reporting dry mouth were as follows: 14% of the

solifenacin 5 mg group, 21.3% of the solifenacin 10mg group, 18.6% of the tolterodine group, and 4.9% of the placebo group.[46] These differences were not statistically significant by chi square analysis. The reports of constipation were 7.8% for solifenacin 10mg , 7.2% for solifenacin 5mg , 2.6% for tolterodine 4mg, and 1.9% for placebo. The comparisons of tolterodine versus either solifenacin dose are statistically significant, favoring tolterodine ($p < 0.05$ for both). Similarly, blurred vision was reported by 5.6% of solifenacin 10mg patients, 3.6% of solifenacin 5mg patients 1.5% of tolterodine 4mg patients, and 2.6% of the placebo patients. The comparison of tolterodine and solifenacin 10mg is statistically significant by chi square analysis ($p = 0.0115$) The percentages of withdrawals due to adverse events were lowest for patients receiving tolterodine (1.9%) followed by solifenacin 10mg (2.6%), solifenacin 5mg (3.2%) and lastly by the placebo patients (3.7%), however none of these differences were statistically significant by chi square analysis.5.

One fair quality systematic review reported adverse event differences between antimuscarinics using only data from short term randomized controlled trials.[20]The review concludes that oxybutynin IR (based on one study), tolterodine IR and ER have the most favorable adverse event profiles in placebo-controlled trials. However, the authors also find that oxybutynin IR has the highest rate of adverse events in active control trials. Oxybutynin IR was found to have a greater rate of dry mouth compared with oxybutynin ER, oxybutynin TD, and tolterodine ER and IR in the meta-analysis. Further, they report that there is evidence to show that oxybutynin TD has lower rates of dry mouth and in one study, greater rates of withdrawal due to adverse events (skin reactions at application site) when compared with tolterodine ER.

CNS Adverse Events

A subanalysis of CNS adverse events in the OPERA trial (tolterodine ER vs oxybutynin IR) showed a similar low incidence of these specific adverse events in both drugs.[122] Withdrawals due to CNS adverse events were 0.15% and 0.005% for oxybutynin IR and tolterodine ER respectively (no significant difference). No other studies of comparative CNS adverse events were found.

Withdrawal Due to Adverse Events

Withdrawals due to adverse events may be a more reliable measure of the importance of adverse events to the patients involved. And of course a large number of withdrawals also reflect negatively on the overall effectiveness of a drug. In 3- to 12-month open-label extension studies of tolterodine (ER or IR) the rate of withdrawal due to adverse events ranged from 8 to 15%, with higher rates for the longer studies. Observational studies reported much lower rates of withdrawal due to adverse events (3-5%) reflecting a less sensitive measure of reasons for withdrawal. The one three-month open-label extension study of oxybutynin ER reported a rate of 8%. A 54 week trial comparing oxybutynin IR to trospium reported overall withdrawal rates of 25% for trospium and 26.7% for oxybutynin IR with all adverse event related withdrawals at 5.9% for trospium and 10% for oxybutynin IR.[45] Withdrawals related to adverse events felt associated with the drugs were higher for oxybutynin, 6.7% vs 3.7%.

Three 12-month extensions of randomized controlled trials looking at tolterodine IR 2mg twice daily, tolterodine ER 4mg, and solifenacin 5mg or 10mg once daily reported withdrawal rates due to adverse events of 15%,[112] 10.1%,[123] and 4.7%,[118]respectively. The extension study

of tolterodine ER,[123] with a withdrawal rate of 10%, included somewhat older patients (mean 64 years), while the other 2 studies[112, 118] included patients of similar age (mean 56 to 60 years). In the study of solifenacin,[118] with the lowest rate of withdrawal, 22% of participants were male, compared to rates of 34.6% and 32.5% in the tolterodine ER and IR studies, respectively.

In short-term head- to-head trials, the rate of withdrawal due to adverse events for tolterodine IR ranged from 5 to 15%, for oxybutynin IR from 4 to 17%, and in one short term trospium trial 6%.[27] The rates for tolterodine ER ranged from 5 to 6%, for oxybutynin ER 3 to 14%, and for transdermal oxybutynin 3% to 11%. Within-study comparisons are presented in Figure 7. Six of seven studies comparing tolterodine to oxybutynin in any formulation found a lower rate of withdrawal with tolterodine, and reached statistical significance in four.[31, 39, 42, 44]

An additional 9-week study comparing oxybutynin IR and oxybutynin ER showed slightly higher withdrawal rates due to adverse events for the immediate release form (20% vs. 17%).

The single short-term trospium trial reported 16% withdrawal from oxybutynin IR vs 6% withdrawal for trospium.[27] One study[35] found no difference between tolterodine IR and oxybutynin ER, but the reporting of withdrawals due to adverse events also included those withdrawn due to intercurrent illnesses and therefore may not be accurate. In one study, withdrawals due to adverse events were lower in the tolterodine ER group (5.0% vs. oxybutynin IR 17.1% $p<0.001$) as were withdrawals due to dry mouth (tolterodine ER 0.4% vs. oxybutynin IR 9.4%). [39] Three studies[34, 37, 38] comparing IR to ER forms of the same drug (tolterodine or oxybutynin) found no significant difference in the rate of withdrawals based on the formulation used.

The OPERA trial (tolterodine ER versus oxybutynin IR) subanalysis of CNS adverse events showed withdrawals due to CNS adverse events were 0.15% and 0.005% for oxybutynin IR and tolterodine ER respectively (not significantly different).[122]

In a fair quality study of tolterodine ER and oxybutynin ER[21]overall withdrawal from the study due to adverse events did not differ between the groups (5.1% vs 4.8%), although the number withdrawing due to dry mouth was higher in the oxybutynin ER group (7 vs 4 in the tolterodine ER group). In addition, the number lost to follow up was noticeably higher in the oxybutynin ER group than the tolterodine ER group (13 vs 3).

A study of oxybutynin TD versus tolterodine ER found a significantly higher rate of withdrawal in the oxybutynin TD group (11% vs 1.7%), mostly due to application site-reactions.[44] A small study of oxybutynin TD versus oxybutynin IR found no difference in withdrawal rates, with only one withdrawal per group in the 6-week study.

A fair quality systematic review found that tolterodine ER was associated with significantly fewer all-cause withdrawals compared with placebo.[20] This review also reported significant differences in the active control comparisons, which favored oxybutynin ER, tolterodine IR and tolterodine ER when compared to oxybutynin IR.

A very short-duration trial of darifenacin versus oxybutynin reported 3 treatment-related withdrawals due to adverse events overall.[121] The study, designed as a crossover, only included a total of 65 participants divided into three cohorts and not all members of each cohort participated in all of the measurements.

The STAR trial comparing the difference between solifenacin (5mg or 10mg) and tolterodine ER 4 mg reported withdrawals due to adverse events for patients receiving tolterodine (3.0%) versus solifenacin (3.5%).[47] This difference was not found to be statistically significant in our statistical analysis of the adverse events of this study.

Chapple et al[46] reported lower withdrawals due to adverse events for patients receiving tolterodine IR (1.9%) compared to those receiving solifenacin 10mg (2.6%) or solifenacin 5mg (3.2%). In this study, the withdrawal rate due to adverse events was the highest for patients taking the placebo (3.7%). These differences are not statistically significant.

Drug Interactions

Clinically significant drug interactions are rare with the anticholinergic urinary incontinence drugs (see Evidence Table 9). Concomitant use of any of the four drugs with another drug with anticholinergic properties may increase the frequency or severity of anticholinergic side effects (dry mouth, constipation, etc.). In addition, these drugs may decrease gastric motility thereby altering absorption of some medications that are absorbed in the GI tract. However, these effects apply to all three drugs. Based on a study of healthy subjects, ketoconazole may inhibit the metabolism of tolterodine, resulting in clinically significant increases in serum levels of the latter drug.[124] Dose reduction of tolterodine (to 2mg per day) is recommended. The clinical importance of this finding for patients with UI, and its relevance to other azole antifungal drugs is not clear. While the serum levels of oxybutynin are also increased, the half-life is not and dose reduction is not recommended.

Abstracts: Assessment of Publication Bias

Three additional comparative observational studies were found in abstract format only. These studies assessed the medication discontinuation rates for oxybutynin and tolterodine based on prescription refill data. One study[125] compared oxybutynin IR vs tolterodine IR discontinuation at 12 months, and found similar results to the included study. The discontinuation rate was higher for oxybutynin than tolterodine, but again overall the rates were high for both (76% for tolterodine, 83% for oxybutynin IR). The other study[126]compares oxybutynin and tolterodine, but does not state what formulations were included. This study reports that by Cox regression, the risk of discontinuation was significantly lower in tolterodine users, who were 43% less likely to discontinue drug in a three-month period. The third study did not find a statistically significant difference between the drugs.[127]

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

The included studies generally enrolled ambulatory populations with more women than men, in the 50 to 60 year-old age range (mean) with the exception of one study which enrolled only spinal cord injured patients (average age = 32).[27] One fair quality study enrolled only Chinese women.[28] This study compared the IR forms of tolterodine and oxybutynin. 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 two studies[30, 32] of the IR formulations including both men and women. A subgroup analysis of a previously reported study of tolterodine IR versus tolterodine ER assessed the subgroup of 1235 women only from the study population. This analysis found a statistically significant benefit favoring tolterodine ER in the mean change in incontinence episodes per week, however the absolute difference was very small (ER -11.8, IR -10.1, p=0.036). No other significant differences were found. Dry mouth was slightly higher in the IR group (ER 25.3% vs. IR 31.2%), but withdrawal rates due to adverse events were not different.

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 event outcomes.[114] 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 and efficacy ratings and tolterodine dose as the variables. In this study, mean age was 61 years, and 77% were female. Age was associated with a decrease in efficacy in reducing frequency, urgency, and incontinence and global efficacy rating (p values <= 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 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 over the first 6 months of treatment. The number of patients reported to have hallucinations (23) or palpitations/tachycardia (42) was small out of 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. Those 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 lack of controlling for potential confounders such as co-morbidity, the results must be interpreted with discretion.

Two studies examined the efficacy of drugs for OAB in women-only populations; one was designed to examine differences in outcome based on age. The 12 week, randomized, placebo-controlled trial by Zinner and colleagues[68] investigated the differences in efficacy and safety in younger (< 65y) and older (≥65y) patients taking tolterodine ER 4 mg. The authors found no significant differences in efficacy, safety or tolerability between the age groups. A placebo-controlled study of Khullar et al.[77] found that tolterodine ER 4mg was more efficacious than placebo in reducing the number of urge incontinence episodes, the number of

micturitions/24h and the number of urgency episodes/24 hours. This study did not do a separate analysis of its population stratified by age. These findings are similar to those found in studies enrolling men and women. Neither of these studies provide comparative data, however.

A subanalysis[78] of patients in a previously published trial[34] reported data on tolterodine ER vs placebo for "nonsevere and severe" OAB patients. While greater absolute reduction was found in the more severe patients the effect was small compared to nonsevere. No data on the other arms in the study (tolterodine IR and placebo) were provided. Reductions in micturitions/day, incontinence episodes/day overall were similar to those found in other tolterodine vs. placebo trials.

An additional subanalysis of the OBJECT trial comparing oxybutynin ER to tolterodine IR in women only demonstrated that oxybutynin ER was significantly more effective with regard to urge incontinence, total incontinence episodes and micturition frequency in women aged 64 years or younger. The overall study population was largely women in this age group.[128]

The effect of co-morbidity was not well studied. The head-to-head trials allowed inclusion of patients with co-morbidities, with the exception of renal, hepatic and psychiatric illnesses in some studies, but did not analyze the effect of co-morbidity on efficacy or adverse events in a comparative way. One study[28] reported that co-existing illness was significantly associated with withdrawal from the study, but did not stratify by drug.

No head-to-head or observational studies conducted in long-term care facilities (LTCF) were found that met inclusion criteria. A placebo-controlled study of oxybutynin added to a program of prompted voiding in a LTCF found a statistically significant reduction in incontinence episodes in the oxybutynin group compared to the placebo group (-2.0 vs - 0.9).[129]

A study of patients from Japan and Korea[39]which included both men and women, compared tolterodine ER to oxybutynin IR. This study found similar efficacy, but fewer adverse events with tolterodine ER. There are no other studies of these two formulations, so making assessments across races is not possible. A recent subanalysis of only the Japanese patients in this trial used the Kings Health Questionnaire results to show that both medications improved overall quality of life in Japanese OAB patients.[91]

The study on spinal cord injured patients[27] was conducted in multiple centers in Germany. The study randomized patients to 2 week treatment of oxybutynin IR 5 mg three times daily or trospium 20 mg twice daily with a placebo at mid day. The overall rate of side effects including dry mouth was comparable in both groups. Severity of dry mouth was graded on a four point scale. "Severe" dry mouth occurred in 23% of oxybutynin IR patients and 4% in trospium patients. Withdrawal occurred more commonly with oxybutynin IR (16%) than trospium (3.6%). There were differences in demographic and urodynamic parameters between the two groups at baseline, and the numbers of randomized patients were unbalanced. Specific types or level of spinal cord injury were not provided nor was information about other medications.

Tolterodine is metabolized to an active metabolite by the CYP2D6 liver enzyme. Approximately 7% of white persons have CYP2D6 polymorphism, resulting in poor metabolism through this enzyme. 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.[124, 130-133]

SUMMARY AND DISCUSSION

Results for the key questions are summarized in Table 1.

Flavoxate

We found no fair or good quality evidence to assess flavoxate in head-to-head comparisons with oxybutynin or tolterodine. In comparison to the results found in oxybutynin or tolterodine studies, a study of flavoxate compared to another drug (emepronium) indicated a lower response on objective outcome measures, and varying response on subjective measures. Flavoxate was not superior to placebo in the two included trials. The evidence on flavoxate was inadequate to assess efficacy or adverse events compared to oxybutynin or tolterodine.

Scopolamine

There were no head-to-head studies identified for scopolamine. One two-week placebo-controlled trial in a small number of women (n=20) diagnosed with detrusor instability showed greater improvements in diurnal frequency, nocturia, urgency, and urge incontinence with scopolamine than placebo

Hyoscyamine

There were no head-to-head studies for hyoscyamine.

Evidence of Comparative Efficacy: Oxybutynin versus Tolterodine

Because both drugs are available in immediate and extended release formulations, several comparisons can be made (IR vs IR, oxybutynin ER vs tolterodine IR, tolterodine ER vs oxybutynin IR, oxybutynin IR vs oxybutynin ER, tolterodine ER vs tolterodine IR, and ER vs ER). The comparisons of the IR formulations do not demonstrate a difference based on objective or subjective efficacy measures. The strength of this evidence is good. The comparisons of the two ER formulations reported tolterodine 4mg daily to be superior based on subjective assessments of symptoms in one study, and oxybutynin ER to be superior on some outcome measures (mean micturitions, and proportion without incontinence) but not others (urge incontinence and total incontinence episodes). Because there are important concerns about selection bias and potential confounding in the first study, the strength of this evidence is fair.

The comparison of each drug's IR formulation to its ER formulation did not demonstrate important differences in efficacy measures, but there are only two studies of oxybutynin and one of tolterodine. A single study compared the ER formulation of oxybutynin to the IR formulation of tolterodine, and found statistically significant evidence that oxybutynin ER was superior based on objective measures. This study did not use an intention to treat analysis, thus the effect of dropouts on overall efficacy was not accounted for, weakening the strength of this evidence. A single study of tolterodine ER compared to oxybutynin IR found tolterodine to be equal in efficacy measures (objective and subjective).

The transdermal formulation of oxybutynin has been compared to oxybutynin IR and tolterodine ER, with no difference in efficacy measure outcomes. The comparison of TD to tolterodine ER also found no difference in efficacy measures.

Evidence of Comparative Efficacy: Oxybutynin versus Trospium

Two comparative trials were found for oxybutynin IR vs. trospium and three placebo controlled trials for trospium. One comparative trial followed patients for an average of 54 weeks. No significant differences in comparative efficacy were found in these trials. The results of placebo trials for trospium were similar to the comparative trial.

Evidence of Comparative Efficacy: Tolterodine versus Solifenacin

Two comparative trials were found for tolterodine (one with IR and the other with ER) compared to solifenacin. The comparative studies provide some mixed efficacy results. In the tolterodine IR versus solifenacin study, each drug was compared separately to placebo and then indirectly compared with each other. Both doses of solifenacin indirectly showed greater efficacy for two of four efficacy variables compared to tolterodine IR. The STAR trial also demonstrated mixed results with solifenacin showing greater efficacy than tolterodine in all but one of the secondary endpoints (nocturia was similar for both drugs). This study was designed as a "non-inferioirty" trial and found that solifenacin was non-inferior to tolterodine for the primary study endpoint, mean number of micturitions per 24 hours.

Evidence of Comparative Adverse Events: Oxybutynin versus Tolterodine

Adverse event rates for both drugs are relatively high. Dry mouth is the most commonly reported adverse event for both. Longer-term evidence is limited. A high discontinuation rate for both drugs was found in a six-month observational study of prescription claims data. But there was statistically significant evidence of a higher rate for oxybutynin IR. Adverse event, including dry mouth, and withdrawal rates were similar across 3- to 12-month uncontrolled studies.

Short-term comparative trials demonstrate that overall adverse event and dry mouth rates were significantly higher for oxybutynin IR compared to tolterodine IR. A reduction of adverse events and the proportion reporting dry mouth was reduced with the ER compared to the IR formulation of each drug. Oxybutynin ER was found to have significantly fewer adverse events overall compared to tolterodine IR, but the difference in reports of dry mouth did not reach statistical significance. In comparing the ER formulations, both studies found tolterodine ER to be slightly superior to oxybutynin ER in reports of adverse events, mainly focusing on dry mouth. Withdrawals in both studies however were similar between the groups. In a single study, comparison of oxybutynin IR was found to have higher adverse event rates than tolterodine ER. This trial found unusually high rates of reports of dry mouth with the oxybutynin compared to other studies. A separate subanalysis of CNS adverse events in a comparison of the ER formulations reported no statistically significant between-treatment differences.

The transdermal formulation of oxybutynin has been compared to oxybutynin IR and tolterodine ER. The comparison to oxybutynin IR found a significant difference only on the

incidence of dry mouth. This study titrated the dose at every visit, with dose escalation until the occurrence of side effects required dose reduction. It is unclear that the highest dose level for each group is comparable (3.9mg/day TD, 20mg/day oral). The comparison of TD to tolterodine ER found a significant difference favoring tolterodine ER in the incidence of application site reactions, although the incidence of dry mouth was lower with oxybutynin TD, but did not reach statistical significance.

Withdrawals due to adverse events may be the more important measure. Comparisons of the IR formulations did not show a significant difference when comparing tolterodine 2mg twice daily to oxybutynin 5mg twice daily, but oxybutynin 5mg three times daily did result in significantly more withdrawals due to adverse events. The studies of comparing the ER versus IR formulations of each drug did not show a significant difference in the adverse event withdrawal rate. In a single study, tolterodine ER resulted in fewer withdrawals due to adverse events than oxybutynin IR. However, this study reported unusually high rates of dry mouth in the oxybutynin group.

The study comparing oxybutynin ER to tolterodine IR did not find a difference in withdrawal rate, even though the difference in overall adverse events and dry mouth was statistically significant. Since this study has some methodological problems of some concern, the results must be interpreted carefully. The larger, randomized controlled trial of the two ER formulations found no difference in withdrawal rates, though a smaller study reported a statistically significant difference in withdrawals due to adverse events, favoring tolterodine.

Although the difference in dry mouth reports was statistically significant, withdrawals due to adverse events with oxybutynin TD was not found to be different to oxybutynin IR, with one per group. The comparison of TD to tolterodine ER found a significant difference favoring tolterodine ER in the withdrawal rate due to adverse events (largely due to application site reactions).

Evidence of Comparative Adverse Events: Oxybutynin versus Trospium

Two comparative trials reported adverse events. In one, the incidence of dry mouth was similar in both groups but more oxybutynin IR patients reported severe dry mouth.[27] This trial in which all patients had a spinal cord injury had comparable adverse events in both treatment groups with withdrawals slightly higher for oxybutynin In the other trial of 54 weeks duration, there was a higher incidence of dry mouth among oxybutynin IR patients compared to trospium patients.[45] Overall adverse events were greater for oxybutynin than trospium but overall withdrawals were similar. Withdrawals thought to be related to adverse events were more likely for oxybutynin. However the overall rate of adverse events was high for both drugs in both studies.

Evidence of Comparative Adverse Events: Darifenacin versus Oxybutynin

In a single comparative trial of darifenacin and oxybutynin IR both drugs were comparable for visual nearpoint, a measure of anticholinergic effect on vision.

Evidence of Comparative Adverse Events: Solifenacin versus Tolterodine

The STAR trial reported significantly lower rates of dry mouth for tolterodine and lower rates of constipation for tolterodine, but similar rates of blurred vision. Differences in withdrawals due to adverse events were not significantly different.

Another study comparing solifenacin 5mg or 10mg and tolterodine IR reported the percentage of patients with dry mouth was greatest in the group taking 10mg of solifenacin followed by the group taking tolterodine, then by the group taking 5mg of solifenacin and finally, placebo. The rates of constipation were greatest for solifenacin 10mg followed by solifenacin 5mg, tolterodine, and placebo. Similarly, a higher percentage of patients reported blurred vision in the solifenacin 10mg group, followed by the 5mg group., placebo, and the tolterodine group. Withdrawals due to adverse events were lowest for patients receiving tolterodine followed by solifenacin 10mg, solifenacin 5mg and highest for the placebo group.

Evidence of Comparative Efficacy or Adverse Events in Subgroup: Oxybutynin versus Tolterodine or Trospium

Insufficient evidence was found. While individual studies indicate that there may be an association between age or gender and efficacy or adverse effects, no comparative studies were found except for spinal cord injured patients. In this study trospium was found to have a lower incidence of severe dry mouth than oxybutynin IR, though overall adverse effects were comparable. Efficacy outcomes included in this review were not reported in this trial.[27]

There was fair evidence from a subanalysis comparing oxybutynin ER to tolterodine IR that the oxybutynin ER may be significantly more effective for women <65 years. This study included a greater proportion of women in this age group. The incidence of adverse events was similar for both drugs.

Table 1. Summary of the Evidence

Key Question 1: Comparative Efficacy	Quality of Body of Evidence**	Conclusion
In head to head trials of anticholinergic incontinence drugs what is the comparative efficacy?	Overall grade: Oxybutynin (Oxy), Tolterodine (Tol): IR versus IR: Fair Trospium (Tros), Oxybutynin (Oxy), IR vs IR: Fair IR vs ER: Fair ER vs ER: Poor Flavoxate (Fla): Poor Solifenacin (Sol): Sol vs. Tol IR: Fair Sol vs. Tol ER: Fair	Four studies of Oxy IR/Tol IR found no difference n efficacy. One study of Tros IR/Oxy IR found no difference in efficacy. Four studies of Oxy ER/Oxy IR and one of Tol ER/Tol IR found no difference in efficacy. One study of Oxy ER/Tol IR found Oxy superior, and one study of Tol ER/Oxy IR found Tol ER superior. Mixed results were found with Oxy ER/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 two short-term studies.
What is the comparative efficacy of anticholinergic incontinence drugs across active and placebo controlled trials	Overall grade: Fair	OAB drug versus Other drug: Results of two studies of Oxy consistent with head to head trial results. One of four Fla studies reported outcomes used by other studies. Findings indicate lower efficacy than found with Oxy or Tol in head-to-head trials. OAB drug versus Non-drug therapy: Four Oxy trials with results consistent to head to head trials. Placebo controlled trials: Twelve trials of Tol, two Oxy, three Tros, two Sol, three Dar, one Scp TD, and one Fla. Fla was not significantly better than placebo.
Key Question 2: Adverse Effects	**Quality of Evidence****	**Conclusion**
	Overall grade: Long-term studies: Poor	One comparative longer-term study assessed the discontinuation rate of Tol and Oxy over a 6-month period. This study found a higher rate, and earlier withdrawal with Oxy, but rates for both drugs were high. Uncontrolled studies reported that dry mouth is the most common adverse event, and found similar rates of adverse events and withdrawals between the drugs. One head to head trial of Tros vs Oxy found more adverse effects especially dry mouth attributed to Oxy.
Key Question 2: Adverse Effects	**Quality of Evidence****	**Conclusion**
	Short-term studies: Fair	Evidence from short-term head-to-head comparison trials indicate a higher incidence of adverse events overall, and dry mouth specifically with Oxy. The ER forms of each drug resulted in fewer adverse events, and dry mouth when compared to IR formulations. Trospium causes less severe dry mouth though overall incidence of dry mouth and short term adverse events are similar to Oxy IR. The difference between drugs based on withdrawals is less clear. Two trials of Sol vs. Tol showed similar rates of adverse events overall; one trial showed lower rates of dry mouth for Tol ER vs Sol.

Key Question 3: Subpopulations	Quality of Evidence**	Conclusion
	Overall grade: Poor	One head to head trial in Japanese and Korean patients was found, and one subgroup analysis of women from a previous trial. Another subgroup analysis of women showed that Oxy ER may be more effective for women < 65 years regarding urge incontinence, total incontinence, and micturition frequency episodes. The incidence of adverse events was similar for both drugs. One head to head trial of Tros vs. Oxy in spinal cord injured patients found comparable overall adverse events. Tros appeared to cause less severe dry mouth. There is insufficient evidence to indicate a difference between the OAB drugs based on subpopulation characteristics.

**Quality of evidence ratings based on criteria developed by the Third US Preventive Services Task Force

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Figure 1: Review Flow Diagram

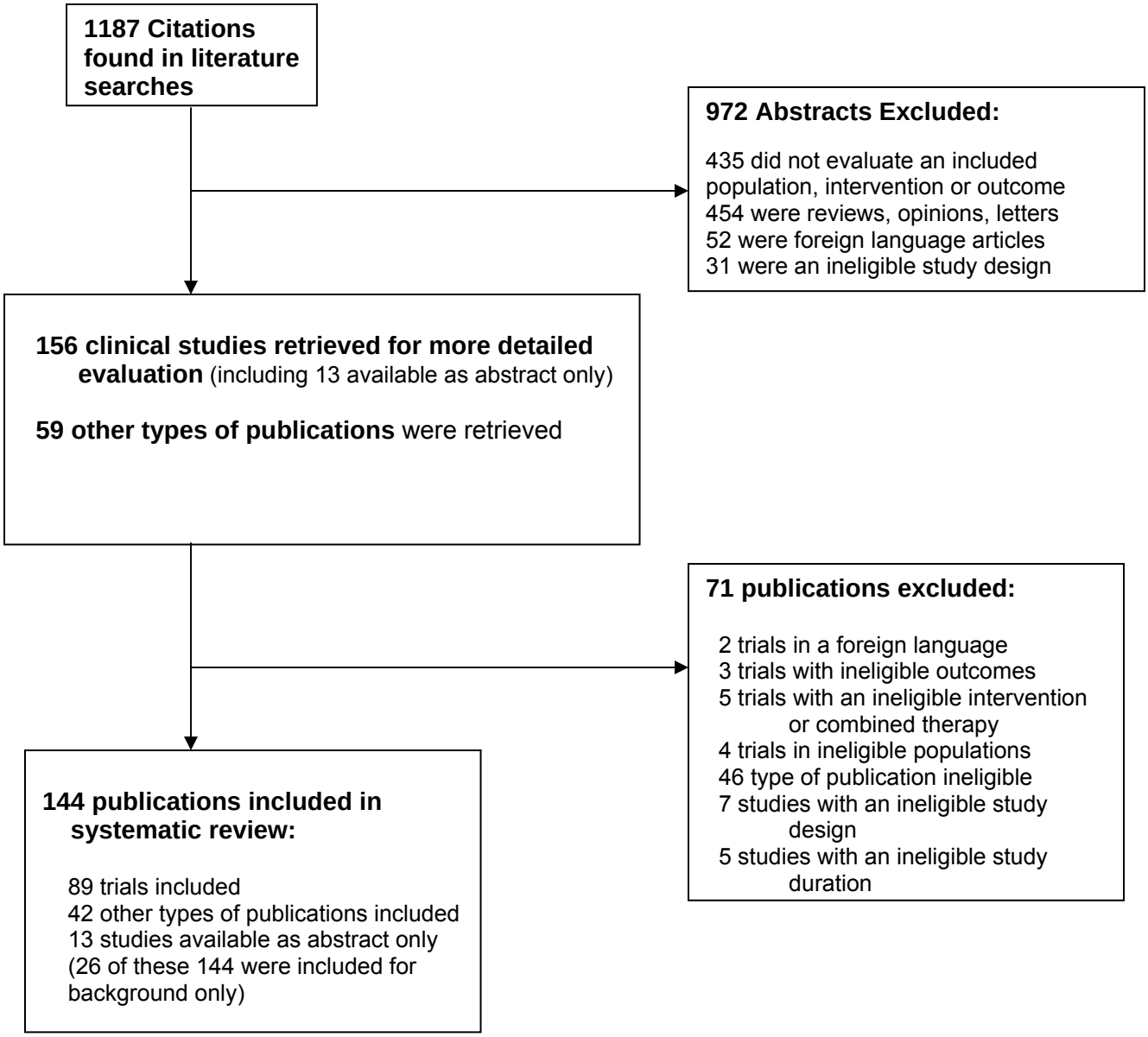


Figure 2. Incontinence episodes per day; IR versus IR

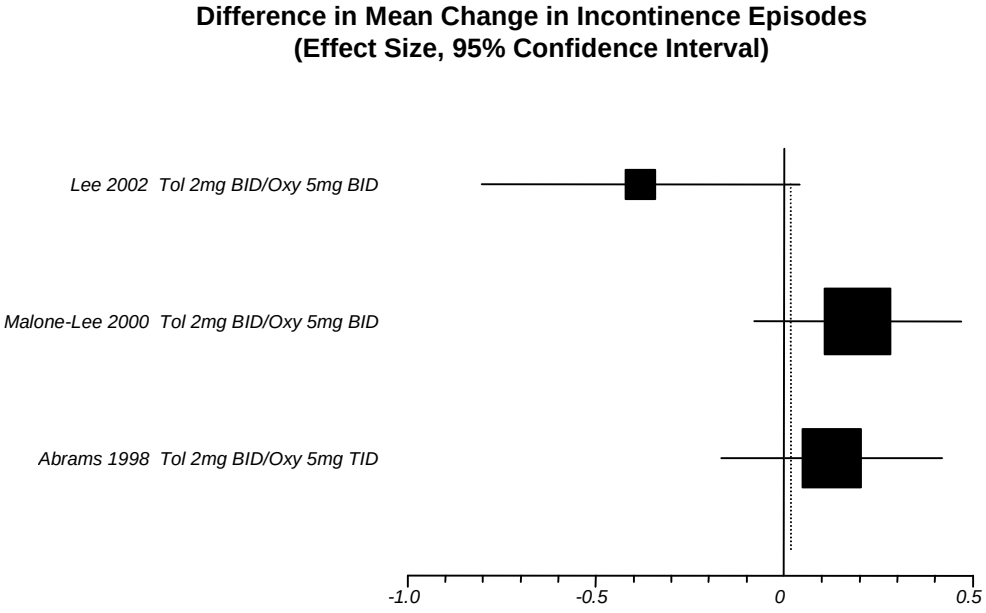


Figure 3. Micturitions per day; IR versus IR

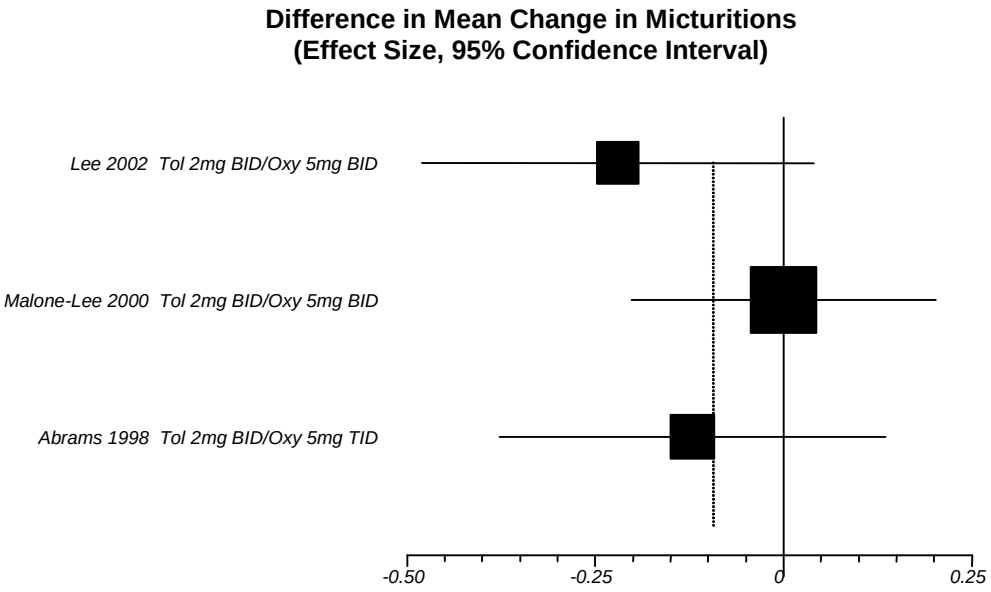


Figure 4. Tolterodine ER vs IR (Van Kerrebroeck 2001)

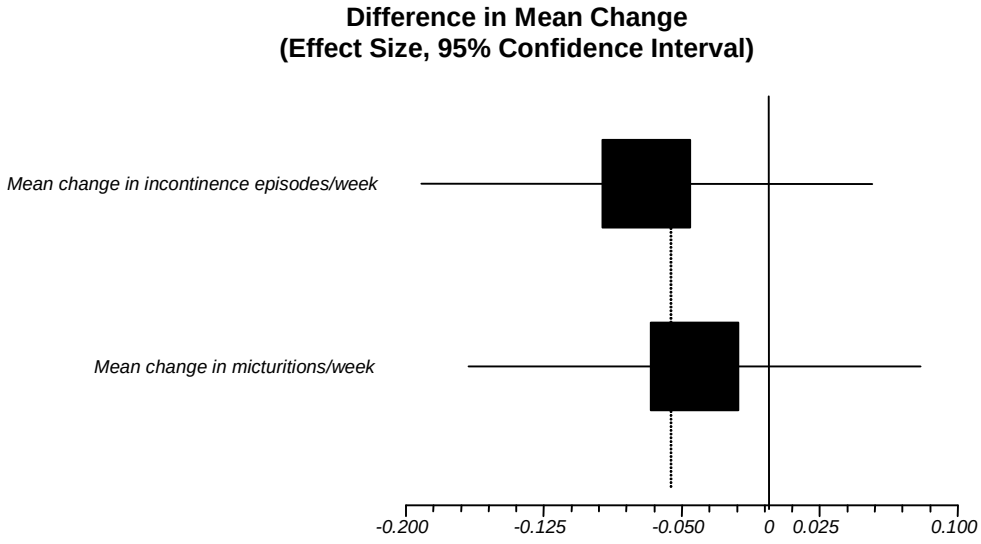


Figure 5. Risk difference in Overall Adverse Event Rates

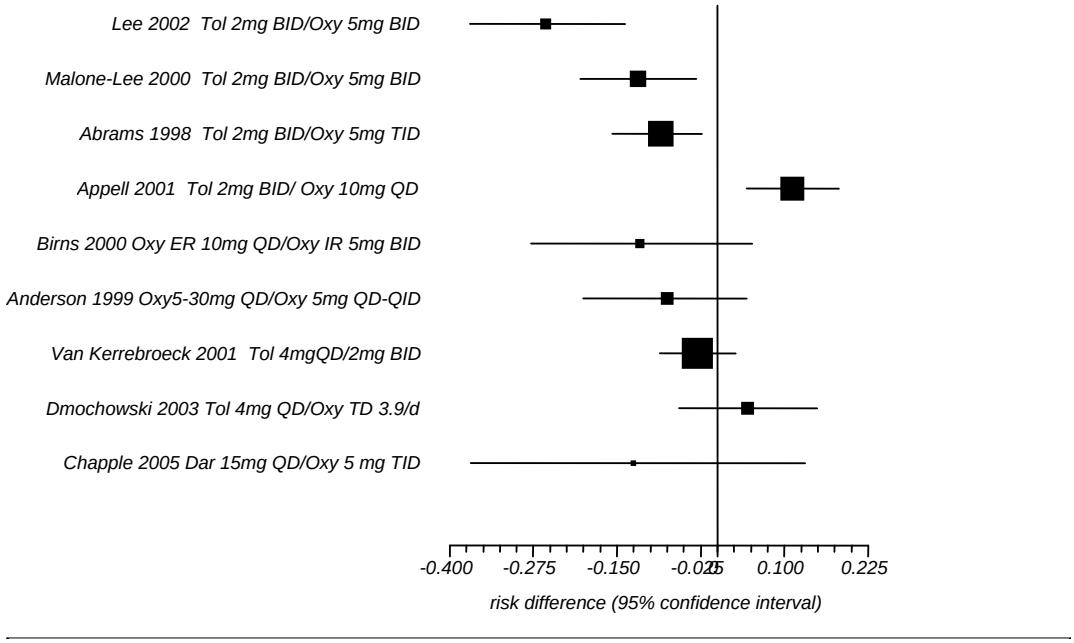


Figure 6. Risk difference in Dry Mouth Rates

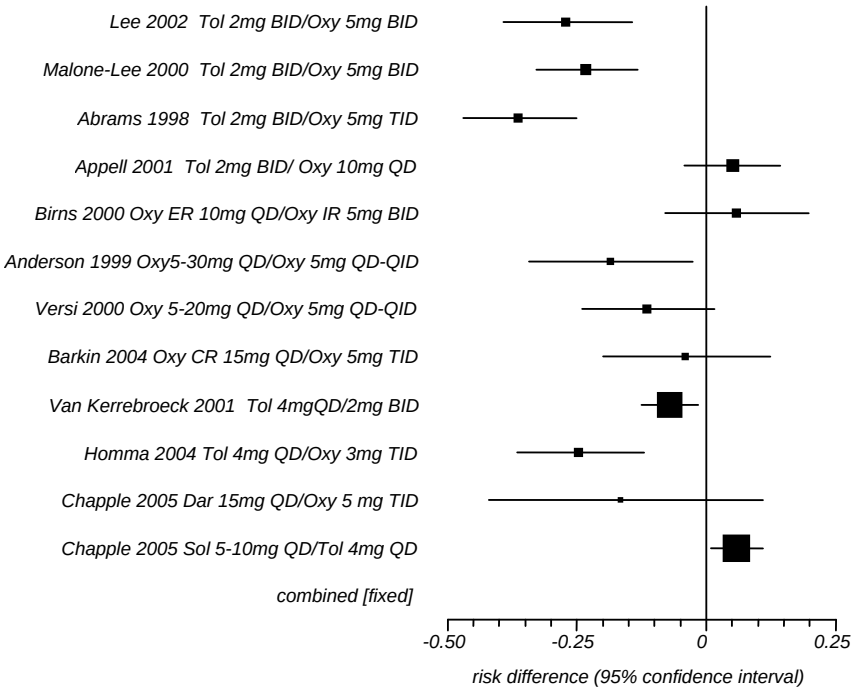
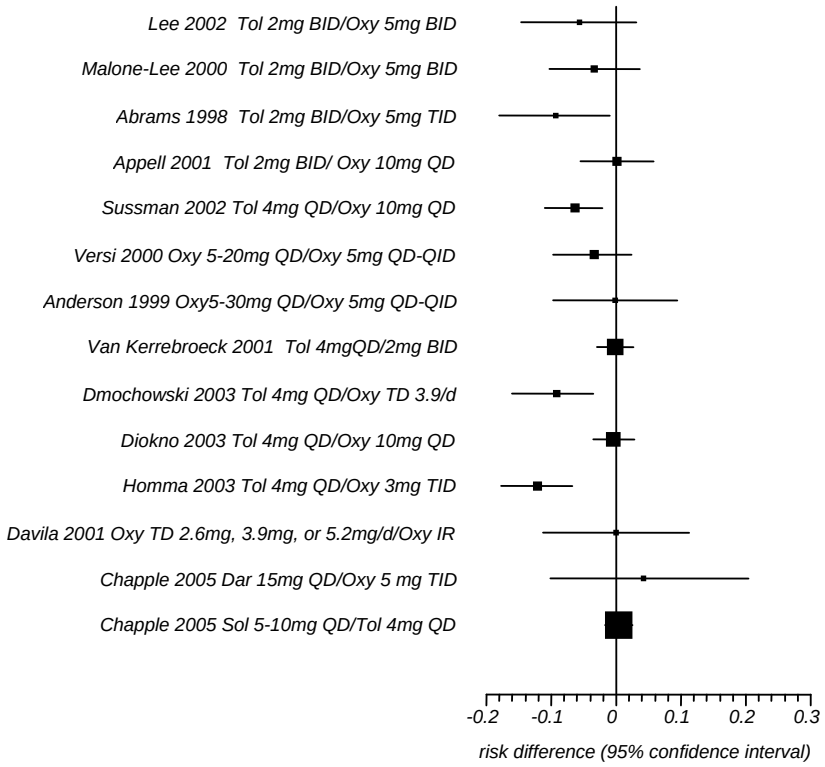


Figure 7. Risk Difference in Withdrawal Due to Adverse Events



Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Immediate Release vs Immediate Release (IR vs IR)				
Oxybutynin (Oxy) vs.Tolterodine (Tol)				
Leung 2002	Tol 2mg twice daily x 10 weeks Oxy 5mg twice daily x 10 weeks	None reported	Visual Analog Scale of patient assessment of severity of symptoms at baseline, 4 and 10 weeks, (0 = no effect, 10 = max severity), perceived changes in symptoms before and after treatment assessed at 4 and 10 weeks (+5 = max improvement, -5 = max deterioration). Voiding diary (1 week) at baseline, 4 and 10 weeks. Urinary pad test* at baseline and 10 weeks.	106 enrolled (number per group not stated)
Lee 2002	Tol 2mg twice daily Oxy 5mg twice daily x 8 wks	estrogen allowed.	Micturation diary assessed at 8 wks Patient assessment of treatment benefits as yes/no; with yes further defined as little or much. Compliance assessed by tablet count at 8 wks	228 enrolled (Tol 112, Oxy 116)

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs.Tolterodine (Tol)		
Leung 2002	Xerostomia Questionnaire at 4 and 10 weeks, independent reporting of other side effects. Significant deterioration on all measures of dryness except denture fit, for both drugs. NS between groups. Side effects reported: Oxy 49% Tol 60% (NS) Reported to be mostly abdominal aches, general malaise and urinary retention	Unclear. States that most withdrawals not due to side effects, but that patients withdrawing while on Oxy were more likely to have co-existing illnesses (p<0.012).
Lee 2002	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, and relationship to study drug. 227 patients assessed Tol: 62 patients reported 101 adverse events Oxy: 94 patients reported 154 adverse events (p = 0.001) Dry mouth: Tol 39 (35%) 72 (63%) (p<0.001) Severe dry mouth: Tol 1 (1%), Oxy 6 (5%) Micturation disorder: Tol 10 (9%), Oxy 16 (14%) Dyspepsia/abdominal pain: Tol 14 (13%), Oxy 12 (10%) Headache: Tol 4 (4%), Oxy 6 (5%)	29 : Tol 11 (6 dry mouth, 55%) Oxy 18 (16 dry mouth, 88%)

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Immediate Release vs Immediate Release (IR vs IR)	
Oxybutynin (Oxy) vs.Tolterodine (Tol)	
Leung 2002	Compliance measured. Oxy 87.5% (11 to 99.3) Tol 75% (8.9 to 98.8) (NS)
Lee 2002	

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Abrams 1998	Tol 2mg twice daily Dose could be dropped to 1mg during first 2 weeks if not tolerated Oxy 5mg three times daily Dose could be dropped to 2.5mg during first 2 weeks if not tolerated Pl three times daily Subjects >/= 65 yrs in UK and Ireland could start the dose of Oxy at 2.5mg and increase to 5mg during first 2 weeks Total trial duration 12 weeks	None reported	Micturition diary assessed at 2, 4, 8, and 12 weeks Patient assessment of severity of symptoms based on 6-point scale (0 = no problems, 6 = severe problems) Change between baseline and 12 weeks defined as decrease in score of 1 or more points.	Number screened/eligible not stated 293 enrolled (118 Tol, 118 Oxy, 57 Pl)
Drutz 1999	Tol 2mg twice daily Oxy 5mg three times daily Placebo three times daily x 12 wks Dose reduction to Tol 1mg or Oxy 5mg twice daily allowed during first 2 wks.	None reported	Change in micturations/d and incontinence episodes/d at 12 wks, assessed by micturation diary.	277 enrolled (Tol 109, Oxy 112, Placebo 56)

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

Evidence Table 1. Comparative clinical trials

Author, Year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Abrams 1998	Age range 19-80 yrs Mean age Tol 55, Oxy 58, Pl 58 76% female	Previous drug therapy: Tol 52%, Oxy 60%, Pl 75% Mean micturitions/24h: 12 Tol, 11 Oxy, 12 Pl Mean incontinence episodes/24h: 2.9 Tol, 2.6 Oxy, 3.3 Pl	37 (10 Tol, 20 Oxy, 7 Pl) reported withdrawing due to adverse effects, no other withdrawals or loss to follow-up reported, but 3 patients missing in 'evaluable patients'.
Drutz 1999	mean age: Tol 63yrs, Oxy 66 yrs, placebo 62 yrs % female: Tol 81, Oxy 72, Placebo 80 % Caucasian: Tol 87, Oxy 94, Placebo 93	% hyperreflexia: Tol 7, Oxy 7, Placebo 5 % Previous drug therapy: Tol 45, Oxy 45, Placebo 55 % with incontinence: Tol 83, Oxy 92, placebo 89 % Prior Urinary tract surgery: Tol 27, Oxy 45, placebo 34	57withdrew 147 analyzed (70 Tol, 41 Oxy, 36 placebo) 27 excluded due to dose reductions 46 excluded due to protocol violations

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Abrams 1998	All adverse events were recorded and categorized by intensity (mild, moderate, severe). The likelihood of relationship to study drug was evaluated for serious adverse events and patient withdrawn if deemed medically necessary or patient wished withdrawal. At least one adverse event reported: 89% Tol, 97% Oxy, 81% Pl (Tol vs. Oxy p = 0.023) Dry mouth: 50% Tol, 86% Oxy, 21% Pl (Tol vs. Oxy p<0.001) More patients reported dry mouth to be severe on Oxy than on Tol or Pl (numbers not given) 1 serious adverse event (syncope) was considered related to Tol	Tol 8%, Oxy 17%, Pl 2% Due to dry mouth: Tol 0.8%, Oxy 13%, Pl 3.5%
Drutz 1999	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, at visits at 2, 4, 8 and 12 wks ITT analysis: % reporting adverse events: Tol 78%, Oxy 90, placebo 75 (p = 0.013 Tol vs Oxy) Dry mouth: Tol 30%, Oxy 69%, placebo 15% (p <0.001 Tol vs Oxy) Moderate to severe dry mouth: Tol 9%, Oxy 44%, placebo 7% Other adverse events reported: headache: Tol 15%, Oxy 10% dizziness: Oxy 11% (others not reported) cardiovascular events: Tol 7%, Oxy 8% Dose reduction: Tol 7%, Oxy 23%, placebo 4% (p<0.001 Tol vs Oxy)	Tol 7 (6%), Oxy 23 (21%), placebo 4 (7%) (p = 0.002 Tol vs Oxy)

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Abrams 1998	Dose reductions requested by 8% Tol, 32% Oxy, 2% Pl (Tol vs. Oxy p<0.001)
Drutz 1999	Only Allowed dose reductions in protocol, but then excluded these from analysis. Incomplete reporting of adverse events. 46 excluded from analysis due to protocol violations, but which groups assigned not reported.

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Immediate Release vs Immediate Release (IR vs IR)				
Oxybutynin (Oxy) vs Flavoxate (Fla)				
Milani 1993	Fla 400mg or Oxy 5 mg x 4wks, then crossover after 7 d washout	not given	Diurnal and nocturnal frequency, incontinence, urgency, dysuria and pad use by diary. Symptoms scored 0,1, or 2 with 0 = best, 2 = worst. Evaluated at baseline at 4wks. Patient assessment of results at 4 wks (cured, improved, no change, worse).	50 enrolled
Zeegers 1987	Randomized to either: {Fla 200mg three times daily x 3 weeks, Emp 200mg three times daily x 3 weeks, Pl three times daily x 3 weeks} or {Oxy 5mg three times daily x 3weeks, Emp 200mg three times daily x 3 weeks, Pl three times daily x 3 weeks) with the order of drugs also randomized.	None reported	Patient and physician score at end of each 3 week period; 1 = no effect, 5 = excellent effect.	Number screened/eligible not stated; stated to be consecutive patients 60 enrolled (30 in Fla/Emp/Pl, 30 in Oxy/Emp/Pl)

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

Evidence Table 1. Comparative clinical trials

Author, Year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs Flavoxate (Fla)			
Milani 1993	mean age 51 (range 19 to 78) 100% female	23 (46% sensory urge, 54% motor urge.	9 withdrawn: Fla: 3 poor compliance Oxy: 1 poor compliance, 5 side effects 41 analyzed
Zeegers 1987	Age range 16-78 yrs Reported by center and by completer/noncompleter status rather than by treatment group. 70% female	None reported	12 withdrawn due to side effects, 5 lost to follow-up, 2 found to have non-urologic pathology 41 completed entire protocol and were analyzed

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs Flavoxate (Fla)		
Milani 1993	Adverse events were elicited at 4 wks, and rated as serious or nonserious and according to intensity. By ITT: Fla 11/50 (22%), Oxy 42/50 (84%), plus 5 patients withdrawn due to adverse events. Dry mouth: Fla 2%, Oxy 78% Abdominal or stomach pain: Fla 24%, Oxy 36%	5 (10%)
Zeegers 1987	Combined in score 15% Pl, 26% Emp, 8% Fla, 17% Oxy	12 withdrawals: 2 Pl, 8 Emp, 0 Fla, 2 Oxy

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Immediate Release vs Immediate Release (IR vs IR)	
Oxybutynin (Oxy) vs Flavoxate (Fla)	
Milani 1993	
Zeegers 1987	Analysis of the effect of the previous treatment on scores for current treatment showed no change in Oxy score. Without prior drug treatment scores are: Pl 29%, Emp 18%, Fla 44%, Oxy 63% with fair/good/excellent response

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Extended Release vs. Immediate Release (ER vs IR)				
Oxybutynin ER vs Oxybutynin IR				
Versi 2000	Oxy ER 5-20mg once daily or Oxy IR 5-20mg/d - schedule not reported doses increased in 5mg/day increments every 7 days doses decreased by 5mg if side effects were intolerable Optimal dose identified and taken for 1 week	none reported	7 day urinary diary after maintenance dose determined	screened 417 eligible/enrolled 226
Birns 2000	Oxy ER 10mg once daily or Oxy 5mg twice daily x 6 wks	none reported	Urinary diary (micturation and incontinence episodes) reviewed at visits 2, 3, 4	162 screened 130 randomized

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

Evidence Table 1. Comparative clinical trials

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

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Evidence Table 1. Comparative clinical trials

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

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Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Extended Release vs. Immediate Release (ER vs IR)		
Oxybutynin ER vs Oxybutynin IR		
Versi 2000	Reports of adverse effects recorded at each pt visit Dry mouth: ER 48%, IR 59% Kaplan Meier analysis moderate or severe dry mouth reports indicates a significant difference (p = 0.007) in favor of ER	Overall: 10 (8%) ER: 3 (3%) abdominal pain: 1 nausea/dysphagia: 1 edema/rash: 1 IR: 7 (6%) dry mouth: 1 blurred vision: 1 nausea: 1 impaired urination, edema, blood pressure changes, UTI: 1 gastric obstruction: 1 UTI: 1 edema and pain: 1
Birns 2000	Assessed during visits every two weeks 78 pts reported adverse events (60%) (ER 55%, IR 67%) Dry mouth: ER 23%, IR 17% Dizziness ER 2%, IR 9% Vision abnormality ER 7%, IR 5% Cough ER 3%, IR 5% Headache ER 0, IR 5%	1 (considered unlikely due to study drug)

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Extended Release vs. Immediate Release (ER vs IR)	
Oxybutynin ER vs Oxybutynin IR	
Versi 2000	Mean duration of treatment/follow-up not stated. Only dry mouth reported in detail.
Birns 2000	Mixed types of incontinence Study included a run-in phase to establish tolerability, patients with adverse events excluded during run-in

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Radomski 2004	Oxy IR twice daily at dose at discretion of investigator for first two weeks (if on Oxy IR prior same dose continued 3 patients, if deemed obese 5 mg twice daily otherwise 2.5 mg twice daily), followed by two week washout, followed by Oxy CR 15 mg once daily for four weeks	Subjects not permitted to use other medications to alleviate incontinence during the 8 week trial	Satisfaction rating at end of week 2 and week 8 using a four point scale.	#screened not reported. 12 included for safety analysis. 9 included for efficacy analysis (completed 8 week study)
Anderson 1999	ER Oxy 5-30mg once daily or IR Oxy 5mg once to four times daily. Doses started at 5mg and adjusted during 4 to 7 day intervals, optimal dose taken for 7 days. dose reductions allowed for adverse effects	not given	7-day voiding diary and incontinence pad use at baseline and after "final dose" achieved Duration of study varied by patient, depending on titration needs.	158 screened 105 enrolled 93 analyzed
Nillsson 1997	Oxy ER 10mg once daily Oxy 5mg twice daily 60 days, no washout between arms	none reported	urinary diary, disability questionnaire, and assessment of effect of symptoms on general welfare, work, exercise, urge, symptoms of leakage, and frequency by VAS measured at 7-8 wks	17 enrolled

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

Evidence Table 1. Comparative clinical trials

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

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Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Radomski 2004	Adverse events collected during scheduled visits and entered in diary. Mild dry mouth most frequent followed by unspecified pain	3 withdrawals due to adverse events--stomach pain (1), mild peripheral edema (1), severe vision distortion
Anderson 1999	Spontaneously reported and anti-cholinergic effects assessed at each study visit Dry mouth: ER 68%, IR 87% (p = 0.04) Moderate to severe dry mouth: ER 25%, IR 46% (p = 0.03) Somnolence: ER 38%, IR 40% Blurred vision: ER 28%, IR 17% Constipation: ER 30%, IR 31% Dizziness ER 28%, IR 38%	2 (4%) in each group due to anticholinergic adverse events
Nillsson 1997	Patients reported on a questionnaire throughout study, classified as mild, moderate, severe 14/16 on ER, 5/17 on IR reported at least one adverse event Dry mouth: ER 69%, IR 82% Headache ER 44%, 41% Dyspepsia ER 31%, IR 12% fatigue ER 13%, 24% Blurred vision 25%, IR 12% % Severe: ER 17%, IR 14% reported that these were NS, but unclear what data being compared.	none reported

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Radomski 2004	Unusual design--different treatment duration for two drugs and dosing for Oxy may have been low
Anderson 1999	Previously all pts had responded to IR oxy Very high incidence of adverse events - may reflect the aggressive dose titration Duration of study (mean) not reported, very little data on final dose in either group
Nillsson 1997	Very high numbers of subjects reporting adverse events

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Barkin 2004	No-treatment baseline period for 3 wks Oxy IR 5mg 3X/day, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks Oxy ER 15mg 1X/day, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks	Subjects not permitted to use other medications to alleviate incontinence during the 9 week trial period	24h-patient diary assessed during final 2 wks of treatment, used the Purdue Urgency Questionnaire to assess severity of urgency and frequency of urgency [severity scored on scale or 1 (no urgency or ability to delay voiding) to 5 (≥ 6 episodes of urgency or inability to delay voiding/urine leakage with urge)], used Incontinence Impact Questionnaire (evaluates effect of incontinence on 8 activities of daily living) and the Urogenital Distress Inventory (evaluates distress associated with 8 urinary symptoms) to assess changes in QoL.	NR / NR / 125 enrolled (Oxy IR 60, Oxy ER 65)

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Barkin 2004	AE data collected during scheduled visits and in diary. AE data included tolerable/not tolerable questions, # and severity of the events, lab assessments: clinical chemistry and hematological (at baseline and end of study) <u>Oxy ER vs Oxy IR (%)</u> Dry mouth: overall: 68% vs 72%; moderate or severe: 38% vs 45% Pharyngitis (dry throat): 35% vs 40% Dry skin: 17% vs 12% Diarrhea: 14% vs 5% Headache: 12 % vs 22% Uriniary tract infection: 12 % vs 18% Dizziness: 11% vs 18% Dyspepsia: 11% vs 17% Rhinitis: 11% vs 15% Abdominal pain: 9% vs 10% Asthenia: 18% vs 15% Constipation: 8% vs 10% Taste perversion: 8% vs 12% Cough increased: 6% vs 13% Dysphagia: 6% vs 13% Dry eyes: 3% vs 15% Nausea: 5% vs 17%	Oxy IR: 12 (20%) Oxy ER: 11 (17%)

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Barkin 2004	sponsored by Purdue Pharma

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Extended Release vs. Immediate Release (ER vs IR)				
Tolterodine ER vs Tolterodine IR				
Van Kerrebroeck 2001	Tol ER 4mg once daily or Tol IR 2mg or Placebo twice daily x 12 wks	none reported	micturation diary assessed at baseline and 12 wks 1 week f/u	1529 randomized into study Tol ER: 507 Tol IR: 514 placebo: 508
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Tol ER 4 mg (n=417) once daily vs. Tol IR 2 mg twice daily (n=408) vs. Pla (n=410) for 12 wks.	Other treatments for OAB not permitted, except estrogen treatment commenced >2 months prior.	micturation diary assessed at baseline and 12 wks 1 week f/u	Screened NR Eligible NR Enrolled=1235

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Extended Release vs. Immediate Release (ER vs IR)		
Tolterodine ER vs Tolterodine IR		
Van Kerrebroeck 2001	Spontaneously reported events were categorized and causation assigned dry mouth further categorized Dry mouth: ER 23%, IR 30%, Placebo 8% Constipation: ER 6%, IR 7%, Placebo 4% Headache: ER 6%, IR 4%, Placebo 5%	88 (5.7%) ER: 27 (5.3%) IR: 28 (5.5%) placebo 33 (6.5%)
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Reporting details NR. Tol ER vs. Tol IR vs. Pla: Dry mouth: 105/415 (25.3%) vs. 127/407 (31.2%) vs. 33/410 (8.0%) Dry skin: 2 (0.5%) vs. 5 (1.2%) vs.1 (0.2%) Dizziness: 7 (1.7%) vs. 7 (1.7%) vs. 4 (1.0%) Somnolence: 12 (2.9%) vs. 11 (2.7%) vs. 8 (2.0%) Abnormal vision: 5 (1.2%) vs. 4 (1.0%) vs. 2 (0.5%) Constipation: 27 (6.5%) vs. 27 (6.6%) vs. 14 (3.4%)	Tol ER 22/417 (5%) vs. Tol IR 20/408 (5%) vs. Pla 26/410 (6%)

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Extended Release vs. Immediate Release (ER vs IR)	
Tolterodine ER vs Tolterodine IR	
Van Kerrebroeck 2001	Dry mouth classified as mild/moderate/severe but data only reported for ER
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	

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

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Immediate Release (ER vs IR)			
Oxybutynin ER vs. Tolterodine IR			
Appell 2001	RCT Multicenter USA	Overactive bladder between 7 and 50 episodes per week of urge incontinence 10+ voids/24 hr mixed stress and urge incontinence if the majority of accidents were related to urinary incontinence	Other causes of incontinence; post void residual volume more than 150ml; delivered baby pelvic bladder vaginal or prostate symptoms in past 6 months; risk of complete urinary retention; clinically important medical problems; organ abnormalities; hematuria; positive urine culture; narrow angle glaucoma; pelvic organ prolapse; gastric conditions; anticholin drugs must be discontinued; known allergy; alcohol or drug abuse (current); unable to follow direction or schedules; not able to swallow tablets whole
Sand et al. 2004 OBJECT (subanalysis of women only)	RCT Multicenter USA	see Appell, 2001	see Appell, 2001

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Extended Release vs. Immediate Release (ER vs IR)				
Oxybutynin ER vs. Tolterodine IR				
Appell 2001	ER Oxy 10mg once daily Tol 2mg twice daily 12 week study	Not given	Safety monitoring patient reporting at each study visit 2,4,8,12 weeks number of urge incontinence episodes at 12 weeks vs. baseline used 7 day urinary diary	378 randomized (Oxy ER 185, Tol 193) 332 completed (Oxy ER 160, Tol 172)
Sand et al. 2004 OBJECT (subanalysis of women only)	Oxy ER 10mg once daily Tol 2mg twice daily 12 week study	see Appell, 2001	Subjects completed 7-day voiding diaries at baseline and 12-weeks	315 women enrolled/ 276 completed study

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

Evidence Table 1. Comparative clinical trials

Author, Year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Extended Release vs. Immediate Release (ER vs IR)			
Oxybutynin ER vs. Tolterodine IR			
Appell 2001	Mean Age: 59 yrs Female: 83% Ethnicity: White 87% African American 6% Hispanic 4% Asian 2% Other 1%	Drug naïve Oxy ER: 109 Tol: 119	Overall: 46 (21 Tol, 25 Oxy ER) Lost to Follow-up Oxy ER: 3 Tol:3
Sand et al. 2004 OBJECT (subanalysis of women only)	mean age: Oxy 58.4y and Tol 58.8y 100% female	Naïve to anticholinergics: Oxy 60.5% and Tol 60.7%	see Appell, 2001

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

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Extended Release vs. Immediate Release (ER vs IR)	
Oxybutynin ER vs. Tolterodine IR	
Appell 2001	Mean number of urge incontinence episodes/wk Oxy ER -19.5, Tol -16.3 Mean change in micturition frequency Oxy ER -24.7, Tol -20.1
Sand et al. 2004 OBJECT (subanalysis of women only)	see Appell, 2001 Decrease in urge incontinence episodes: Oxy ER: -21.9, Tol: -20.4 Mean decrease in micturition frequency episodes Oxy ER: -23.7, Tol: -20.4 Total decrease incontinence epidsodes Oxy ER: -17.9, Tol: -15.1

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Extended Release vs. Immediate Release (ER vs IR)		
Oxybutynin ER vs. Tolterodine IR		
Appell 2001	Patient reported dry mouth occurred in equal proportion in each group both groups had similar rates of dry mouth and other adverse effects	Oxy ER 14 Tol 15
Sand et al. 2004 OBJECT (subanalysis of women only)	see Appell, 2001 Oxy ER vs. Tol Dry mouth: 28.3% vs 33.7% Constipation: 8.6% vs 6.7% Imparied urination/urinary retention: 4.0% vs 1.2% Blurred vision: 2.6% vs 0.6% Dizziness: 3.9% vs 4.3% Somnolence: 3.3% vs 1.8% Insomnia: 0.7% vs 1.8% Nervousness: 0.0% vs 1.2% Headache: 9.2% vs 10.4% Dyspepsia: 5.3% vs 6.1% Nausea: 3.3% vs 1.8% Vomiting: 2.0% vs 1.8%	withdrawals due to AE: Oxy 11 patients and Tol 12 patients

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Extended Release vs. Immediate Release (ER vs IR)	
Oxybutynin ER vs. Tolterodine IR	
Appell 2001	
Sand et al. 2004 OBJECT (subanalysis of women only)	

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Extended Release vs. Immediate Release (ER vs IR)				
Tolterodine ER vs. Oxybutynin IR				
Homma 2003	Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks	Not allowed within 14 d of trial: anticholinergic drug or unstable dosage of any drug with anticholinergic side-effects, any drug for OAB (except estrogen started >2months), potent CYP3A4 inhibitors, or any investigational drug.	Voiding diary for 7 days at baseline and wk 12. Primary outcome, change in median number of incontinence episodes. Secondary endpoint, median number and volume of voids, number of incontinence pads used. Subjective assessment by 6-pt perception of bladder condition, 3-pt perception of urgency, and 3-pt assessment of treatment benefit. Quality of life measured by KHQ at baseline and 12 wks	Screened NR Eligible NR Enrolled = 608 Tol ER = 240 Oxy IR = 246 Pla = 122
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks	See Homma 2003	Micturation diary completed during 7 days of run-in (baseline and the last 7days of treatment (week 12) King's Health Questionnaire (KHQ) was used to determine health related quality of life (HRQoL) at baseline and week 12	293 enrolled: Tol 114, Oxy 122, Placebo 57

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Extended Release vs. Immediate Release (ER vs IR)		
Tolterodine ER vs. Oxybutynin IR		
Homma 2003	Directly observed and spontaneously reported at visits 3 through 6, rated as mild, moderate or severe. (Tol vs. Oxy) Dry mouth: 80 (33.5%) vs. 131 (53.7%) p<0.001 Severe dry mouth: 0.4% vs 8.2% Dry eyes: 3 (1.3%) vs. 7 (2.9%) Blurred vision: 3 (1.3%) vs. 8 (3.3%) Constipation: 17 (7.1%) vs. 15 (6.1%) Somnolence: 1 (0.4%) vs. 4 (1.6%) Difficulty in micturition: 3 (1.3%) vs. 21 (8.6%)	Dry mouth: Tol 0.4% vs. Oxy 9.4% All events: Tol 5.0% vs. Oxy 17.1% p<0.001 Serious event, possibly drug related: 1 Oxy cardiac failure. No deaths and no clinically significant changes in lab or ECG values.
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	*Tol ER vs Oxy vs Pla* Dry mouth: 36.9% vs 61.5% vs 5.3% (p=0.002 for Tol vs Oxy) Severity of dry mouth: mild: 31.6% vs 45.1% vs 5.3% moderate: 5.3% vs 13.1% vs 0% severe: 0% 3.3% vs 0%	See Homma, 2003 for overall withdrawals due to AE. Withdrawals due to AEs in Japanese pts: Oxy: 16.4% Tol: 5.3%

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Extended Release vs. Immediate Release (ER vs IR)	
Tolterodine ER vs. Oxybutynin IR	
Homma 2003	Compliance ≥75% of medication: Tol 98% vs. Oxy 93%
Homma 2004 subanalysis of HRQoL in Japanese OAB patients	

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Extended Release vs. Extended Release (ER vs ER)				
Oxybutynin ER vs.Tolterodine ER				
Sussman 2002	Tol ER 2mg or 4mg once daily Oxy ER 5mg or 10mg once daily x 8 weeks No dose adjustments allowed	None reported	Patient assessment of symptoms based on 6-point scale (0 = no problems, 6 = severe problems) at baseline and 8 weeks Patient and Physician rated benefit (No, yes - a little, and yes-very much) at 8 weeks	Number screened/eligible not stated. 1289 enrolled 669 Tol (333 Tol 2mg, 336 Tol 4mg) 620 Oxy (313 Oxy 5mg, 307 Oxy 10mg)
Diokno 2003 OPERA	Oxy ER 10 mg/day vs. Tol ER 4 mg/day x 12 wks	None reported	Diaries at baseline week, and weeks 2, 4, 8, 12. Outcomes: total incontinence episodes, total incontinence episodes, micturition frequency.	Screened 1485 Eligible NR Enrolled 790 Oxy ER= 391 Tol ER = 399

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Extended Release vs. Extended Release (ER vs ER)		
Oxybutynin ER vs.Tolterodine ER		
Sussman 2002	Dry mouth evaluated on 100 mm Visual Analog Scale(0 - least problem, 100 - most severe) at baseline and 8 weeks Change in dry mouth severity was dose dependent for both drugs. Tol 2mg vs. Tol 4mg p = 0.09, Oxy 5mg vs. Oxy 10mg p=0.05 Change in severity of dry mouth:(100 point VAS) Tol 2mg 2.3 Tol 4mg 6.0 Oxy 5mg 6.3 Oxy 10mg 11.3 (p=0.03 Tol 4mg vs. Oxy 10mg)	Only reported for Tol 4mg (19, 6%) and Oxy 10mg 37 (13%).
Diokno 2003 OPERA	Data collected at each visit or any time reported by participant, rated as mild, moderate, severe. Dry mouth: Oxy 116/391 (29.7%) vs. Tol 89/399 (22.3%) (p=0.02) mild: oxy 87/391 (22.3%) vs Tol 69/399 (17.3%) mod-severe: Oxy 29/391 (7.4%) vs Tol 20/399 (5%) Constipation: Oxy 25/391(6.4%) vs. 31/399 (7.8%) (NS)	All events: Oxy 20/391 (5.1%) vs. Tol 19/399 (4.8%) Due to dry mount: Oxy 7, Tol 4

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Extended Release vs. Extended Release (ER vs ER)	
Oxybutynin ER vs.Tolterodine ER	
Sussman 2002	Report does not make clear why subjects excluded from intention to treat analysis, does not report all withdrawal reasons, does not report adverse event withdrawals for all doses, reports no side effect data other than change in dry mouth. Clinical significance of change in dry mouth not clear.
Diokno 2003 OPERA	

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

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	RCT, Multicenter, USA	see Diokno 2003	see Diokno 2003
Trospium chloride versus oxybutynin			
Halaska 2003	RCT Multi center Europe	Patients with urge syndrome or urge incontinence	Absolute tachycardia, Closed-angle glaucoma, myasthenia gravis, severe arteriosclerosis of the cerebral vessels, stress incontinence, undue frequency of micturition due to heart failure, renal failure or diuretic therapy, bladder outlet obstruction, acute UTI at the beginning of the trial, hiatus hernia in combination with reflux esophagitis, stenosis in the GI tract, megacolon, colonic ulceration, allergy or intolerance towards atropine, Oxy, trospium or other consitutuents of trial medications, concurrent medication with anticholinergics, tricyclic or tetracyclic antidepressants, alpha-blockers or beta-sympathomimetics within the last 7d before starting the trial, urological or gynecological operations within the last 3 mos before starting the trial, serious illnesses or conditions which would preclude participation in any clinical trial (malignant neoplasms, alcoholism, drug misuse), pregnancy or lactation, participation in any other study
Madersbacher 1995	RCT Multi center Germany	Patients with spinal cord injuries and detrusor hyper-reflexia	Acute urinary tract infection, glaucoma, known allergy to atropine, Oxy or Trospium, tachycardia, renal, hepatic and/or cardiovascular insufficiency, intake of other anticholinergic drugs,body weight over 90 kg, age below 18 years.

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	Oxy ER 10mg/day vs. Tol ER 4mg/day x 12 weeks	see Diokno 2003	Data collected at each visit or anytime reported by participant. AE cited as reasons for withdrawal were specifically identified for analysis. AE were coded the the FDA "Coding Symbols for Thesaurus of Adverse Reaction Terms" (COSTART V). Focus on AE that COSTART includes under the CNS classification. For additional information see Diokno, 2003	see Diokno 2003
Trospium chloride versus oxybutynin				
Halaska 2003	Average 54 weeks of treatment with either Oxy 5 mg twice daily or Trospium 20 mg twice daily. Multiple appointments for evaluation through the course of the trial	None	Micturition diaries reported at 0, 2, 26, and 52 weeks. Efficacy also reported by doctor and patient as follows: cured, definite improvement, slight improvement, no improvement or deterioration.	Screened NR Eligible 358 Enrolled 357
Madersbacher 1995	Initial one week washout followed by 2 weeks of treatment with either Oxy 5 mg three times daily or Trospium 20 mg twice daily. To maintain double blind conditions the Trospium group received a placebo at midday	None	Twenty "well being" items were the subject of direct questioning before and at the end of the trial--specifically dry mouth, blurred/double vision, palpitation, constipation, difficulty in swallowing. Severity graded on 4 point scale.	Screened NR Eligible NR Enrolled 95 Trospium=52 ; Oxy=43 .

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

Evidence Table 1. Comparative clinical trials

Author, Year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	see Diokno 2003	see Diokno 2003	see Diokno 2003
Trospium chloride versus oxybutynin			
Halaska 2003	Mean age 53.7 Female 86% Ethnicity NR	Smokers: 13% Previous illnesses: 70% Previous medication: 41% Mean body weight: 71.8 Kg	91 withdrew (Trospium 67, Oxy 24)
Madersbacher 1995	Mean age=`32. Female 50% Ethnicity NR	Type of spinal cord injury not specified. Differences in baseline urodynamic measures for maximum bladder capacity and compliance	10/NR/88

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

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	COSTART V CNS AEs including dizziness, insomnia, somnolence, anxiety, hypertonia, nervousness, tremor and confusion (reported in mild, moderate or severe categories). Oxy ER (n=391) vs Tol ER (n=399) (p=NS for all comparisons) Any CNS AE: 9.0% vs 8.3% Dizziness: 3.8% vs 2.5% Somnolence: 1.0% vs 2.3% Insomnia: 1.8% vs 0.8% Depression: 1.3% vs 0.8% Hypertonia: 0.5% vs 1.0%
Trospium chloride versus oxybutynin	
Halaska 2003	Baseline incontinence episodes Trospium: 1.5; Oxy: 2.1. Treatment in both arms resulted in "the frequency of incontinence episodes diminshed by about one episode at each follow-up attendance." Frequency of micturition/day at baseline: Trospium:11.4; Oxy:12.5. Assessed at 2, 26, 52 weeks. Reduction for Trospium 1.2, 2.9, 3.5; Oxy 1.5, 3.4, 4.2. Baseline episodes of urgency:Trospium: 10.2 ;Oxy: 11.0. Reduction for Trospium: 1.6, 3.2, 3.5; Oxy: 1.7, 3.2, 3.6. Subjective appraisal of efficacy after 52 weeks of treatment by physicians 29% Trospium rated as "cured", Oxy 17%. Patient ratings "similar."
Madersbacher 1995	Not reported. "Severe" dry mouth present in 4% trospium, 23% Oxy. Withdrawal less in trospium (6%) than Oxy (16%). Overall side effect rate comparable. No change in lab parameters.

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	Incidence and severity of AEs judged possible or probably related to Oxy ER and Tol ER during OPERA study: All comparisons are for Oxy ER (miild, moderate, severe) vs Tol ER (miild, moderate, severe) Dizziness: (1.8% , 0.8%, 0%) vs (1.5%, 0.5% , 0%) Insomnia: (0.8%, 0.5%, 0%) vs (0%, 0%, 0%) Somnolence: (0.5%, 0.3%, 0%) vs (1.5%, 0.5%, 0%) Anxiety: (0.5%, 0.3%, 0%) vs (0%, 0%, 0%) Hypertonia: (0%, 0.3%, 0%) vs (0%, 0%, 0%) Nervousness: (0%, 0.3%, 0%) vs (0%, 0%, 0%) Tremor: (0.3%, 0%, 0%) vs (0.3%, 0%, 0%) Confusion: (0.3%, 0%, 0%) vs (0%, 0%, 0%) Not judged to be related to treatment: Oxy ER: depression, increased libido, or vertigo. Tol ER: abnormal dreams, anxiety, depression, facial paralysis, hypertonia, insomnia, paresthesia, or	Withdrawals due to CNS AEs: Oxy: 6 (1.5%) Tol: 2 (0.5%)
Trospium chloride versus oxybutynin		
Halaska 2003	Follow up appointments at 2, 6, 12, 20, 26, 32, 40, 52 weeks to assess safety and tolerability. 20 item questionnaire used to assess tolerabiilty at 26 and 52 weeks. 4 point scale used to measure severity. Subjective tolerability recorded by doctor and patient using very good, good, satisfactory or poor scale. Overall withdrawal 25% Tros, 26.7% Oxy. Adverse events occurred in 64.8% Tros, 76.7% in Oxy. Tros vs. Oxy Dry Mouth: 33% vs 50% Constipation: 7% vs 4% Visual disturbance: 3% vs 6%	Trospium 16 (6%) Oxy 9 (10%)
Madersbacher 1995	Adverse effects assessed via interview focused on "well being" items. Severity grading done--methodology for grading based on a four point scale. Dry mouth: 56% Oxy vs 54% Trospium. "Severe" dry mouth: in 23% Oxy vs 4% Trospium. Withdrawal less in Trospium (6%) than Oxy (16%). Overall side effect rate comparable. No change in lab parameters.	Trospium 3 (6%) Oxy 7 (16%)

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Chu et al, 2005 OPERA Extension (subanalysis of CNS AEs)	
Trospium chloride versus oxybutynin	
Halaska 2003	
Madersbacher 1995	No information on nature of spinal cord injury or duration of injury. No information on other medications patients on during trial.

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

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Transdermal vs. Immediate Release (TD vs. IR)			
Oxybutynin TD vs. Oxybutynin IR			
Davila 2001	RCT Multicenter USA	Men and women, aged ≥18, with history of urge or mixed urinary incontinence, previously diagnosed, with symptomatic improvement during treatment with oral oxybutynin for ≥6 weeks. During 2-wk washout from current treatment, min. 3 incontinent episodes and increase >30%. Diagnosis of detrusor instability based on symptoms and urodynamic study confirming involuntary bladder contractions.	Allergy to oxybutynin, intolerable of transdermal system, pregnancy or lactation, overflow incontinence secondary to underactive or noncontractile detrusor or outlet obstruction, impaired bladder compliance, including tonic increase in pressure greater than 15 cm during filling cystometry, current medical conditions or therapies that could contribute to UI, or medical conditions that could worsen due to oxybutynin.
Transdermal vs. Sustained Release (TD vs.SR)			
Oxybutynin TD vs. Tolterodine SR			
Dmochowski 2003	RCT Multicenter USA	Men and women, aged ≥18, taking current pharmacologic treatment for overactive bladder with beneficial response (by patient response). Post-washout: >/= 4 urge urinary incontinent episodes, with either pure urge or predominant urge, 24 or more voids, and an average urinary void volume of 350ml or less over 3 days.	History of urinary tract surgery in previous 6 months, diagnosis of interstitial cystitis, urethral syndrome, painful bladder syndrome, or overflow urinary incontinence.

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Transdermal vs. Immediate Release (TD vs. IR)				
Oxybutynin TD vs. Oxybutynin IR				
Davila 2001	Starting dose assigned depending on prior oral oxybutynin dose of </= 10mg, 11-15mg, or >/= 20mg daily: Oxy TD 2.6mg, 3.9mg, or 5.2mg daily (2, 3 or 4 patches per day), patch applied twice weekly Oxy IR 10 mg, 15mg or 22,5mg total daily x 6 wks Dose titrated up if no side effects after 2 wks	NR	3-day diary of daily incontinence episodes, recorded at prestudy, washout, and wks 2,4,6. Questionnaire of anticholinergic symptoms, VAS for efficacy at wks 2,4,6.	Screened NR Eligible NR Enrolled 76 Oxy TD = 38 Oxy IR = 38
Transdermal vs. Sustained Release (TD vs.SR)				
Oxybutynin TD vs. Tolterodine SR				
Dmochowski 2003	Oxybutynin transdermal (Oxy TD) 3.9 mg/day (applied twice weekly): n=121 Tolterodine sustained release (Tol SR) 4 mg/day: n=123 Placebo: n=117 12 wk treatment period	Maintain any nonpharmacologic incontinence management program.	Diary of urine volume, urge and incontinence episodes; measured at 0, 2, 6, 12 wks. QOL instrument and VAS "periodically."	Screened NR Eligible NR Enrolled 361

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

Evidence Table 1. Comparative clinical trials

Author, Year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Transdermal vs. Immediate Release (TD vs. IR)			
Oxybutynin TD vs. Oxybutynin IR			
Davila 2001	Mean age 63.5 Female 92% Ethnicity: White 95% Black 5%	NR	2/76 (2.6%) withdrawn before 4 wks
Transdermal vs. Sustained Release (TD vs.SR)			
Oxybutynin TD vs. Tolterodine SR			
Dmochowski 2003	Mean age 63.5 Female 92.8% White 94.5% Black 3.6% Other 1.9%	Prior treatment median duration >1 yr (range 6 wks to 20 years) Oxy 49.6% Tol 47.4%	41 withdrawn 1 lost to followup 361 analyzed

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

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Transdermal vs. Immediate Release (TD vs. IR)	
Oxybutynin TD vs. Oxybutynin IR	
Davila 2001	Oxy TD vs Oxy IR Reduction in mean incontinence episodes at 6 wks: 4.8/7.2 (66.7%) vs. 4.6/7.2 (63.9%)(NS) Zero incontinence: 8/38 (21%) vs.10/38 (26%) VAS score improvement 5.8 vs 6.0 (p<o.0001)
Transdermal vs. Sustained Release (TD vs.SR)	
Oxybutynin TD vs. Tolterodine SR	
Dmochowski 2003	Mean change in incontinence episodes per day at 12 wks: Oxy -2.9, Tol -3.2, Pla -2 (Oxy vs Tol p=0.5878) Mean decrease in urinary frequency per day: Oxy -1.9, Tol -2.2, Pla -1.4 (Oxy vs Tol p=0.2761) Frequency reduction greater for patients with 14+ micturitions/day; reduction NS for <10/day. Avg urinary volume: Oxy +24 mL, Tol +29 mL vs. Pla +5.5 mL (Oxy vs. Tol p=0.7690) Global Assessment of Disease State scores: Oxy vs. Tol p =0.1861 IIQ (qol scale): -22 vs -23 (NS) Urogenital distress Inventory: -25 vs -28 (NS)

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Transdermal vs. Immediate Release (TD vs. IR)		
Oxybutynin TD vs. Oxybutynin IR		
Davila 2001	Unvalidated questionnaire to evaluate titration for presence and severity of 10 symptoms assessed at 2, 4 and 6 wks. Oxy TD vs. Oxy IR Dry mouth: 15 (39%) vs. 31 (82%) (p<0.001) Reduction in severity of dry mouth vs prior treatment: 67% vs. 33% Worse dry mouth: 5% vs. 33% Constipation: 8 (21%) vs. 19 (50%) Somnolence 7 (18%) vs. 14 (37%) Blurred vision: 7 (18%) vs. 9 (24%) Impaired urination: 9 (24%) vs. 9 (24%)	Oxy IR: 1 (dry mouth) Oxy TD: 1 contact dermatitis due to patch
Transdermal vs. Sustained Release (TD vs.SR)		
Oxybutynin TD vs. Tolterodine SR		
Dmochowski 2003	Method of assessment not reported Application site reactions: Oxy 32/121 (25.4%; 5% severe), Tol 7/123 (5.7%), Pla 8/117 (6.9%) Systemic adverse events: Oxy 23/121 (19%), Tol 29/123, Pla 14/117 (12%) Anticholinergic side effects (% only, numbers NR) Dry Mouth Oxy TD 4.1% vs Tol SR 7.3% Constipation Oxy TD 3.3%, Tol SR 5.7%	Oxy TD l= 13/121 (10.7%; 12 due to application site reaction, 1 hot flushes). Tol SR = 2/123 (1.6%; 1 fatigue, 1 dizziness).

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Transdermal vs. Immediate Release (TD vs. IR)	
Oxybutynin TD vs. Oxybutynin IR	
Davila 2001	
Transdermal vs. Sustained Release (TD vs.SR)	
Oxybutynin TD vs. Tolterodine SR	
Dmochowski 2003	

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

Evidence Table 1. Comparative clinical trials

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Tolterodine vs. Solifenacin			
Chapple et al. 2003	RCT Multicenter International	Patients ≥18 with OAB symptoms (including urgency, urge incontinence, or frequency) for ≥3 months; post-run-in eligibility included an average frequency of ≥8 voids /24 h and 3 episodes of urgency and/or 3 episodes of incontinence during 3-day voiding period.	Patients with clinically significant BOO, a postvoid residual vol. of >200ml, stress incontinence, presence of a neurological cause for detrusor muscle overactivity, evidence of UTI or of bladder stones, previous pelvic irradiation, previous or current malignant disease of the pelvic organs, any medical condition contraindicating the use of anti-muscaric medication (including narrow-angle glaucoma and urinary or gastric retention), nonpharmalogical OAB treatment including electrostimulation therapy or start of a bladder traning program during the 2 wks before or during the study, diabetic neuropathy, use of drugs intended to treat incontinence, use of any drugs with cholnergic or anti-cholinergic side effects, participation in a clinical trial within 30 days prior to study entry, pregnant or nursing women, women intending to become pregnant during the study, and women not using reliable contraceptive methods.
Chapple, et al. 2005 STAR trial	RCT, Europe	Men and women aged ≥18y, OAB Symptoms for ≥ 3m, outpatient, demonstrated UI (≥1 episode/24h) and urinary frequency (≥8 micuritions/d) and ≥1 Urgency episodes/24h during 3-day voiding diary period	Stress Incontinence (SI) or Mixed Incontinence where SI was predominant and neurogenic DO

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Tolterodine vs. Solifenacin				
Chapple et al. 2003	Placebo BID; Tolterodine IR 2mg BID (Tol); Solifenacin 5 mg QD (Sol 5); Solifenacin 10 mg QD (Sol 10)		Patient-reported voiding diary (episodes of urgency and incontinence, times of voiding, volume voided/void, pad use, and episodes of sleep disturbance/nocturia) at wks 0,4,8, & 12	1281 enrolled; 1081 randomized; 1033 evaluated
Chapple, et al. 2005 STAR trial	Weeks 0-4: Solifenacin 5mg once/d Tolterodine ER 4mg once/d Weeks 5-12 (after pts chose if they wanted to increase their dosage): Solifenacin 5mg once/d (Sol 5) Solefenacin 10mg once/d (Sol 10) Tolterodine ER 4mg once/d (Tol 4)	none reported	3-day micturition diary presented at scheduled visits at wks 4, 8 and 12. Symptoms assessed include: micturition frequency (primary endpoint), episodes of urgency, incontinence with and without urgency, nocturia, pad usage/24h, volume voided per micturition. Health related QoL: validated 6-point categorical scale to assess patient Perception of Bladder Condition.	1355 screened/1200 randomized and enrolled / Full analysis set (FAS): 1177

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

Evidence Table 1. Comparative clinical trials

Author, Year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed
Tolterodine vs. Solifenacin			
Chapple et al. 2003	Mean age: Placebo: 57.8; Tolterodine (2 mg): 56.9; Solifenacin (5 mg): 58.1; Solifenacin (10mg): 57.2 25% male >98% white	Mean no. of voids/24 h: 12.07; Urge incontinence only: 653/1033; No incontinence: 67/1033; Mixed stress and urge incontinence: 313/1033; Prior drug therapy: 670/1033; Any non-drug therapy: 348/1033	Withdrawn: 36/1077 (3.6%); Lost to fu: 11/1077 (1.0%)
Chapple, et al. 2005 STAR trial	Mean Age: Sol 5 & 10: 56.5y Tol ER: 56.4y Age range: NR Sol: 85.3% female Tol ER: 88.3% female Sol: 99.3% Caucasian 0.7% Other Tol ER: 99.5 Caucasian 0.5% Other	Sol: 70.8% ≤65y; 29.2% >65y; and 6.7% >75y Tol ER: 70.6% ≤65y; 29.4% >65y; and 6.0% >75y	Withdrawls: Sol: 3.5% Tol ER: 3.0%

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

Evidence Table 1. Comparative clinical trials

Author, Year	Outcomes
Tolterodine vs. Solifenacin	
Chapple et al. 2003	Change in mean number of urgency episodes/24 h: **Tolterodine:** -38%, p=0.0511 **Solifenacin:** 5mg once daily: -52%, p<0.001 10mg once daily: -55%, p<0.001 **Placebo:** -33%, no p-value reported.
Chapple, et al. 2005 STAR trial	Primary endpoint: micturition frequency Secondary endpoints: episodes of urgency, incontinence with and without urgency, nocturia, pad usage/24h, volume voided per micturition. Health related QoL: validated 6-point categorical scale to assess Perception of Bladder Condition. <u>Sol (5 & 10 combined) vs Tol ER (reductions are endpoint minus baseline numbers)</u> Mean reduction in number of urgency episodes/24h: 2.85 vs 2.42 episodes Mean reduction in numober of urge incontinence episodes/24h: 1.42 vs 0.83 episodes Mean reduction in number of incontinence episodes/24h: 1.60 vs 1.11 episodes Mean reduction in number of pads used/ 24h: 1.72 vs 1.19 pads Mean recution in number of nocturia epsiodes/night: 0.71 vs 0.63

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

Evidence Table 1. Comparative clinical trials

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Tolterodine vs. Solifenacin		
Chapple et al. 2003	Dry mouth: placebo=13 (4.9%),Sol 5mg=39 (14%),Sol 10mg=57 (21.3%), Tol=49 (18.6%); Constipation: placebo=5 (1.9%), Sol 5mg=20 (7.2%), Sol 10mg=21 (7.8%), Tol=7 (2.6%); Blurred vision: Placebo=7 (2.6%), Sol 5mg=10 (3.6%), Sol 10mg=15 (5.6%), Tol=4 (1.5%)	31/1077 (2.9%) for withdrawals due to all adverse events
Chapple, et al. 2005 STAR trial	AE were evaluted at each clinic visit in response to general and non-specific questioning by the investigator or volunteered by patient Comparisons: Sol (mild%, moderate%, severe% AEs) vs Tol (mild%, moderate%, severe% AEs) Dry Mouth: (17.5%, 10.8%, 1.7%) vs (14.8%, 7.7%, 1.5%) Constipation: (3.2%, 2.7%, 0.5%) vs (1.3%, 1.0%, 0.2%) Blurred Vision: (0.7, 0%, 0%) vs. (0.7%, 1.0%, 0%)	Withdrawals due to AEs: Sol: 3.5% Tol ER: 3.0%

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Tolterodine vs. Solifenacin	
Chapple et al. 2003	
Chapple, et al. 2005	Overall withdrawal rates are unclear.
STAR trial	Study funded by Yamanouchi Pharmaceutical Co.

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled
Darifenacin vs. Oxybutinin				
Chapple & Abrams 2005	Three Cohorts: 1) Dar IR 2.5mg three times/d or Oxy IR 2.5mg three times/d 2) Dar ER 15mg once/d or Oxy IR 5mg three times/d 3) Dar ER 30mg once/d or Oxy IR 5mg three times/d each treatment period was for 7 days	none reported	Visual Nearpoint measured at baseline, pre-dose and 2 an 4 hours after the final dose on day 7 of each treatment period using a standard instrument, the RAF nearpoint ruler.Symptoms diary for OAB symptoms and adverse events	103 screened/ 65 eligible/ 65 enrolled

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Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

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

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

Evidence Table 1. Comparative clinical trials

Author, Year	Comments
Darifenacin vs. Oxybutinin	
Chapple & Abrams 2005	sponsored by Pfizer

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

Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Immediate Release vs Immediate Release							
Leung 2002	Adequate	Not reported	Some differences, Not statistically significant. Menopausal: 45% Oxy, 66% Tol Coexisting illness: 58.5% Oxy, 50.9% Tol Concomitant drugs: 60% Oxy, 72% Tol	Yes	Yes	Yes	No
Lee 2002	Adequate	Not reported	Some differences, Previously treated with drug for incontinence: Tol 32%, Oxy 22%; stratification of drugs used Not reported.	Yes	Yes	Yes	Yes
Malone-Lee 2000	Adequate	Not reported	Similar	Yes	Yes	Yes	Yes
Drutz 1999	Not reported	Not reported	Some differences, mean age and % male higher in Oxy group, Oxy group had more patients with incontinence, and significantly more in Oxy group had prior urinary tract surgery,	Yes	Yes	Yes	Yes
Abrams 1998	Not reported	Not reported	Some differences, Not statistically significant. Previously treated with drug for incontinence: 52% Tol, 60% Oxy, 75% Pl Some characteristics Not stratified by group, i.e. concomitant disease or drugs, prior urinary tract surgery.	Yes	Not reported (method of blinding in light of dose adjustments and varying schedules not stated)	Not reported (method of blinding in light of dose adjustments and varying schedules not stated)	Yes
Milani 1993	Not reported	Not reported	Not reported	Yes	Yes	Yes	Yes
Zeegers 1987	Not reported	Not reported	Not clear	Yes	Yes	Yes	Yes

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

Evidence Table 2. Internal validity

Author, Year	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)
Immediate Release vs Immediate Release					
Leung 2002	Stated ITT, but actual numbers analyzed not reported	No, of those withdrawing a higher proportion of those on Oxy had coexisting disease or concomitant drugs, were slightly older and had higher mean parity.	Withdrawals reported clearly Cross over Not reported Compliance: Oxy 88% Tol 75%	No	Fair
Lee 2002	Yes	Not clear	Yes	18% withdrew from study, 97% of these due to adverse events with higher number in Oxy group.	Fair (+)
Malone-Lee 2000	Yes	Not clear	Attrition reported clearly, crossovers Not reported, adherence measured but Not reported.	No	Fair
Drutz 1999	Only for adverse events	Not clear	Attrition reported clearly, others Not reported	47% of original patients excluded from analysis, 20% withdrew overall, with 12% of original group withdrawing due to adverse events.	Poor
Abrams 1998	Yes	Not clear	Withdrawals due to adverse effects reported clearly Others Not reported	No	Fair
Milani 1993	No	Not clear	Yes	18% drop out rate, higher in Oxy group due to adverse effects	Poor
Zeegers 1987	No	Not clear	Withdrawals due to adverse effects reported clearly Others Not reported	Yes, high loss to follow-up in Emp group	Poor

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

Evidence Table 2. Internal validity

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

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

Evidence Table 2. Internal validity

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

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

Evidence Table 2. Internal validity

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

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

Evidence Table 2. Internal validity

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

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Evidence Table 2. Internal validity

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

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Evidence Table 2. Internal validity

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

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Evidence Table 2. Internal validity

Author, Year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Barkin, 2004	NR	NR	similar	yes	yes, method NR	yes, method NR	yes, method NR
Chapple et al, 2005	yes	NR	similar	yes	NR	NR	yes
Chapple & Abrams, 2005	yes	NR	similar	yes	NR	NR	yes
Chapple, Rechberger et al, 2003	NR	NR	some differences, prior drug therapy: placebo 32%, Sol 5mg 34.9%, Sol 10mg 40.1%, Tol 30.8%, types of incontinence: Tol group had more mixed incontinence than all other groups and placebo has the most UI only.	yes	NR	NR	NR

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Evidence Table 2. Internal validity

Author, Year	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)
Barkin, 2004	no	not clear	withdrawals reported clearly, crossover not reported, Compliance reported in withdrawal reasons: 2 patients in Oxy group, contamination NR	no	fair
Chapple et al, 2005	yes	not clear	withdrawals reported clearly, crossover not reported, Compliance not reported, contamination NR	NR	fair
Chapple & Abrams, 2005	no	not clear	withdrawals reported clearly, crossover reported clearly, Compliancedescribed but not reported, contamination NR	no	fair
Chapple, Rechberger et al, 2003	yes	not clear	withdrawals reported clearly, other NR	no	fair

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Evidence Table 2. Internal validity

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

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Evidence Table 2. Internal validity

Author, Year	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)
Extended Release vs Extended Release					
Sussman 2002	Stated to be ITT, to be included patients had to have received at least one dose of study drug AND had a least one post-randomization efficacy assessment. Missing data were imputed by last observation carried forward method.	Not clear	Withdrawals due to adverse effects reported clearly for Tol4mg and Oxy10mg only. Reported loss to follow-up, withdrawal of consent, withdrawal due to lack of efficacy, and due to side effects. Others Not reported	Unable to calculate for Tol 2mg and Oxy 5mg. For Tol 4mg loss to follow-up other than side effects = 6%, for Oxy 10mg = 9%.	Fair (-)
Diokno 2003 OPERA	Yes (using last observation carried forward)	Unclear	Attrition yes Adherence NR	Slightly more loss in Oxy group, including one death. Total loss 104/790 (13.2%)	Fair
Transdermal vs. Immediate Release					
Davila 2001	No, but only 1 drop out from each group	NR		no	Fair
Transdermal vs. Extended Release					
Dmochowski 2003	Yes	Unclear	Attrition overall 41/361 (11%) Adherence 92%	Unclear, not all withdrawals accounted for	Fair

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Evidence Table 3. Trials with OAB drugs versus another drug

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

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Evidence Table 3. Trials with OAB drugs versus another drug

Author, Year	Other population characteristics (diagnosis, etc)	Eligibility criteria
Flavoxate		
Gruneberger 1984	Neurogenic cause: Fla 9 (47%), Cle 14 (70%) Mixed incontinence: Fla 3 (16%), Cle 3 (15%)	Not Reported
Meyhoff 1983	Comorbid stress incontinence: 10/20(50%); One or more previous operations: 5/20(25%); detrusor instability: 14/20(70%); unable to suppress voluntarily induced detrusor contraction: 5/20(25%)	Rapid fill CO2 cystometry revealing detrusor instability as defined according to definitions of the International Continence Society or was considered present if the patient did not have uninhibited detrusor contractions during filling cystometry but was unable to suppress a voluntarily induced detrusor contraction within 50 sec. once it had started; absent or minimal bladder suspension defect, not requiring incontinence surgery; maximum urinary flow rate <15 ml/s; residual urine volume <50 ml following spontaneous voiding; mid-stream urine culture showing <105 colonies/ml
Bradley 1970	Urinary Tract Infection: Fla 6(25%), Pro 5(23%); Symptoms only: Fla 4(17%), Pro 2(9%); Cystitis alone or mixed: Fla 10(42%), Pro 12(54.5%); Bladder carcinoma alone or mixed: Fla 2(8%), Pro 0; Benign Prostatic hypertrophy: Fla 1(4%), Pro 1(4.5%); Post-Prostatectomy: Fla 0, Pro 1(4.5%); Enuresis: Fla 0, Pro 1(4.5%); Bladder neck obstruction: Fla 1(4%), Pro 0	Not Reported
Herbst 1970	Cystitis/urethrocystitis: 13/43(30%); Symptoms only : 6/43(14%); Post Prostatectomy: 7/43(16%); Urethral calculus: 6/43(14%); Trigonitis/urethrotrigonitis: 5/43(12%); Prostatitis: 4/43(9%)	Not Reported

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Evidence Table 3. Trials with OAB drugs versus another drug

Author, Year	Exclusion criteria	Number withdrawn/ lost to fu/ analyzed
Flavoxate		
Gruneberger 1984	Not Reported	Withdrawals: Fla 5 (25%) due to little or no efficacy and strong side effects, Cle 1 (5%) due to drug interaction
Meyhoff 1983	Patients with detrusor sphincter dyssynergia; bladder stone or bladder tumor; neurological disease; glaucoma or severe heart failure; concomitant use of drugs affecting the autonomic nervous system or smooth muscles	1 withdrawal due to unspecified disease unrelated to treatment
Bradley 1970	Not Reported	Withdrawals: Fla 2(8%); both due to adverse events Pro 2 (9%); 1 dizziness, 1 lost to follow-up
Herbst 1970	Not Reported	Not Reported

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Evidence Table 3. Trials with OAB drugs versus another drug

Author, Year	Method of outcome assessment and timing of assessment	Outcomes
Flavoxate		
Gruneberger 1984	Subjective assessments (not described)	Patients assessment: Cured/Improved: Fla 11 (58%), Cle 15 (75%)
Meyhoff 1983	Patient-reported drug preferences measured at end of trial; Urinary diary (diurnal and nocturnal micturition patterns, total number of voidings, incontinence)	Micturations/24h: Fla +1, Eme -0.5, Pl -1 (NS) Incontinence episodes: Fla -1, Eme -1, Pl -2 (NS) Drug preferences: Fla 3 (16%), Eme 4 (21%), Pl 9 (47%) NS
Bradley 1970	Subjective assessments: rating scale ranging from 'no change' to 'complete recovery'	"Complete" improvement in: Frequency: Fla 6(29%), Pro 4(38%); Urgency: Fla 7(35), Pro 2(14%) Nocturia: Fla 4(27%), Pro 1(7%);
Herbst 1970	Not Reported	Good to excellent therapeutic response: Fla 50%, Pro 30% (p-value not reported)

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Evidence Table 3. Trials with OAB drugs versus another drug

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

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Evidence Table 3. Trials with OAB drugs versus another drug

Author, Year	Study Design Setting	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)
Oxybutynin				
Holmes 1989	RCT Crossover Single center London	23 enrolled, others not reported	Age: Oxy 39.6, Pro 44.5 100% female Ethnicity: not reported	Oxy 5 mg or Pro 15 mg three times daily 1 month intervention, 1 week washout, then crossover
Madersbacher 1999	RCT Multicenter Austria	366 enrolled; others not reported	Age: Prov 49.6, Oxy 50.3; Pl 47.6 Prov 9(21%) male, 117(79%) female; Oxy 8(22%) male, 113(78%) female; Pl 4(18%) male, 59(82%) female Ethnicity: not reported	Oxy 2.5 mg or Prov 15 mg three times daily x 4 weeks
Hycoscyamine				
Serels 1998	Unclear Cross-over Single Center USA	34 enrolled; Others not reported	Mean age: 62 yrs Range: 28-91 100% female Ethnicity: NR	Hyoscyamine 0.375 mg bid; Doxazosin 2 mg QHS; Hyo + Dox (combination) Pts got each therapy for a month, unless they were unwilling to cross-over

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

Evidence Table 3. Trials with OAB drugs versus another drug

Author, Year	Other population characteristics (diagnosis, etc)	Eligibility criteria
Oxybutynin		
Holmes 1989	Daytime frequency: Oxy 38.6 total voids/3 days, Pro 29.1 total voids/3 days; Nocturia: Oxy 5 total voids/3 nights, Pro 7 total voids/3 nights	Not Reported
Madersbacher 1999	Sensory urge (overall) 196(54%); Motor urge (overall): 78(21%) Years of urge incontinence: Prov 2.4, Oxy 2.4, Pl 2.0 Previous treatment or urge incontinence: Prov 32, Oxy 32, Pl 21	History of urgency or urge incontinence, a maximum cystometric bladder capacity of < or equal to 300 ml.; age 18 or older; body weight 45 kg. or greater
Hycoscyamine		
Serels 1998	NR	NR

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

Evidence Table 3. Trials with OAB drugs versus another drug

Author, Year	Exclusion criteria	Number withdrawn/ lost to fu/ analyzed
Oxybutynin		
Holmes 1989	Not Reported	Unclear
Madersbacher 1999	Detrusor hyperreflexia; postoperative incontinence; infravesical obstruction; a postvoid residual urine of > 15% of the maximal cystometric bladder capacity; acute Urinary Tract infections; angina pectoris; glaucoma; megacolon; clinically relevant cardiac, renal or hepatic dysfunctions; tachy/dysrhythmias; frequency or nocturia due to heart or renal insufficiency; overt cerebral sclerosis	Unclear
Hycoscyamine		
Serels 1998	NR	NR

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Evidence Table 3. Trials with OAB drugs versus another drug

Author, Year	Method of outcome assessment and timing of assessment	Outcomes
Oxybutynin		
Holmes 1989	Daytime frequency: measured in total voids over 3 days; Nocturia: measured by total voids over 3 nights range; Incontinence: rated using linear analogue scale	Mean change in micturations/24h: Oxy -2.5, Pro -1.2 Mean change in Visual Analog Scale of severity of incontinence symptoms: Oxy -22.2, Pro -17.6
Madersbacher 1999	Bladder diary	Mean change in frequency per day: Oxy -2.4, Prov -1.9, Pl -1
Hycoscyamine		
Serels 1998	NR	Improvement on AUA symptom score: Hyo = 68%; Dox = 68%; Combination= 77% Mean improvement in American Urological Assoc.(AUA) symptom score over baseline (p value: baseline vs endpoint score): Hyo: 34% (p<0.001) Dox: 30% (p=0.002) combination: 48% (p=0.004) Increased Voiding Pressure: % (n) Hyo: 53%(20), Dox: 66% (15), Combin: 72% (8) Decreased Compliance: Hyo: 53% (9), Dox: 61% (8), Combin: 100%(3)

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

Evidence Table 3. Trials with OAB drugs versus another drug

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Oxybutynin		
Holmes 1989	Unclear. Dry mouth: Oxy 29.8, Pro 18.4; Constipation: Oxy 10.1, Pro 9.3; Blurred vision: Oxy 12.1, Pro 16.2	Withdrawals: 3
Madersbacher 1999	Total incidence: Prov 64%, Oxy 72%, Pl 42% Frequency of severe dry mouth: Oxy>Prov (p 0.0093) Visual disturbance: Prov 27%, Oxy 18%, Pl 14% Nausea: Prov 4.1%, Oxy 9.9%, Pl 8.3% Vomiting: Prov 2.1%, Oxy 1.4%, Pl 2.8%	Withdrawals: Pro 13%, Oxy 11%, Pl 9.7
Hycoscyamine		
Serels 1998	*Percentages are in order: Hyo, Dox, combination* Moderate -to-severe side effects: 19 (61%), 8 (47%), 8 (61%) These percentages are estimated from a graph: Dry mouth: 70 %, 20%, 58% Fatigue: 33%, 31%, 8% Dizziness: 25%, 20%, 23% Headaches: 22%, 8%, 8% Constipation: 26%, 11%, 8% Diarrhea: 10%, 8%, 0% Vaginal dryness: 3%, 0%, 0% Night sweats: 3%, 0%, 0% Leg edema: 0%, 3%, 8%	Not Reported

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

Evidence Table 4. OAB drugs versus non-drug therapy

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

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

Evidence Table 4. OAB drugs versus non-drug therapy

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

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

Evidence Table 4. OAB drugs versus non-drug therapy

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

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

Evidence Table 4. OAB drugs versus non-drug therapy

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

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

Evidence Table 4. OAB drugs versus non-drug therapy

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

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

Evidence Table 4. OAB drugs versus non-drug therapy

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

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

Evidence Table 4. OAB drugs versus non-drug therapy

Author, Year	Number withdrawn/ lost to follow-up/ analyzed	Method of Outcome Assessment and Timing of Assessment	Outcomes
Soomro 2001	Not Reported	Voiding diary, Bristol urinary symptom questionnaire and Quality of Life questionnaire	Reduction in voiding frequency/24h: Oxy -2, ENS: -2 Symptoms by Bristol urinary symptom questionnaire : significant changes in score in both groups on frequency, and dissatisfaction with spending rest of life with current symptoms compared to baseline No difference on leaking or hesitancy compared to baseline Oxy only had significant change in score for incomplete emptying compared to baseline SF-36: No significant differences compared to baseline Patients finding treatment effective: Oxy 10, ENS 4
Colombo 1995	6 withdrawn: Oxy=4 due to anticholinergic adverse events; Beh=2 consent withdrawals	Clinical cure: total disappearance of urge incontinence and did not require protective pads or further therapies	Clinical cure: Detrusor instability group: Oxy=93%, Beh=62% Low-compliance bladder group Oxy=67%, Beh=75% Sensory bladder group: Oxy=60%, Beh=81%

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

Evidence Table 4. OAB drugs versus non-drug therapy

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
Soomro 2001	Post-treatment side effects questionnaire (at 6 wks) Dry mouth Oxy 87%, ENS 6% Blurred vision Oxy 53%, ENS 6% Dry skin Oxy 30%, ENS 28% Skin irritation Oxy NA, ENS 11% Difficulty using machine ENS 13%	Not reported	
Colombo 1995	Unclear. Oxy: Dry mouth=15; constipation=6; Nausea=5; Dizziness=2; Decrease in visual acuity=1; Tachycardia=1; Beh = none reported	Oxy = 4(3 due to dry mouth; 1 due to glaucoma) Beh = none reported	

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

Evidence Table 5. OAB drugs versus placebo

Author Year	Dose	Mean Change in Number of Micturitions/24h		Mean Change in Number of Incontinence Episodes/24h	
		OAB drug (n)	*Placebo* (n)	*OAB drug* (n)	*Placebo* (n)
Rentzhog 1998	TOL 2mg BID	↓20% (not given)	Not reported	↓46% (not given)	Not reported
Jacquetin 2001	TOL 2mg BID	↓1.4 (103)	↓1.2 (51)	↓1.3 (79)	↓0.4 (39)
Malone-Lee 2001	TOL 2mg BID	↓0.7 (73)	0 (42)	↓0.7 (51)	0 (33)
Van Kerrebroeck 1998*	TOL 2mg BID	↓0.1 (17)	↓0.1 (16)	↓2.4 (17)	↓1.9 (16)
Millard 1999	TOL 2mg BID	↓2.3 (129)	↓1.4 (64)	↓1.7 (117)	↓1.3 (55)
Chancellor 2000	TOL 2mg BID	↓1.7 (514)	↓1.2 (507)	↓1.5 (514)	↓1.0 (507)
Zinner 2002	TOL 4mg QD <65y/o	↓2 (292)	↓1.4 (284)	↓1.7 (292)	↓1.1 (284)
	TOL 4mg QD +65y/o	↓1.4 (214)	↓0.9 (223)	↓1.6 (214)	↓0.9 (223)
Chapple 2004	TOL 2 mg BID	↓1.9 (263)	↓1.2 (267)	↓1.1 (263)	↓0.8 (267)
Chapple 2004	TOL 2 mg BID	↓1.8 (37)	↓1.0 (36)	↓0.4 (37)	↓0.3 (36)
Kelleher 2002	TOL ER 4 mg/day	NR	NR	↓2.2 (507)	↓1.3 (508)
Khullar 2004	TOL ER 4mg/day	↓1.2 (569)	↓0.9 (285)	↓1.5 (569)	↓1.1 (285)
Landis 2004	TOL ER 4 mg/day	↓1.9 (492)	↓0.4 (494)	↓1.3 (492)	↓0.7 (494)
Szonyi 1995	OXY 2.5mg BID	Daytime frequency lower with Oxy (p = 0.0025)		Not reported	Not reported
Chapple 1990	Flavoxate 200mg TID	Difference in mean change = -0.292 p = 0.95		Not reported	Not reported
Zinner 2004	TROS 20 mg BID	↓2.4 (256)	↓1.3 (256)	↓2.3 (256)	↓1.9 (256)

Author Year	Dose	Mean Change in Number of Micturitions/24h		Mean Change in Number of Incontinence Episodes/24h	
		OAB drug (n)	*Placebo* (n)	*OAB drug* (n)	*Placebo* (n)
Alloussi 1999	TROS 20 mg BID	Efficacy assessment done by investigator favored trospium		NR	NR
Cardozo 2000	TROS 20 mg BID	Efficacy assessment done by investigator favored trospium		NR	NR
Dmochowksi 2002	OXY TD 1.3 mg/day 2.6 mg/day 3.9 mg/day applied twice/week	↓1.8 (130) ↓1.7 (133) ↓2.3 (125) (p=0.0457)	↓1.7 (132)	↓2.1 (NS) ↓2.0 (NS) ↓2.7 (p=0.0165)	↓2.1
Muskat 1996	SCP TD Changed every 3 days (4 patches total)	Diurnal frequency: ↓7.5 (10) p<0.05	Diurnal frequency: ↓0.7 (10)	NR	NR
Cardozo 2004	SOL 5 mg 10 mg	↓2.4 (286) ↓2.8 (290)	↓1.6 (281)	↓1.6 (173) ↓1.6 (165)	↓1.3 (153)
Cardozo 2005	DAR 30 mg QD	↓0.8 (35) p=NS	↓0.3 (36)	NR	NR
Haab 2004	DAR A: 3.75mg QD B:7.5 mg QD C: 15 mg QD	Median change: A: ↓1.7 (49), p=NR B: ↓1.6 (219) C: ↓1.7 (106) (p<0.001 for both B & C vs placebo)	Median change: ↓0.8 (152)	Median change A: ↓1.2 (49) B: ↓1.3 (219) C: ↓1.5 (106)	↓1.1 (152)
Steers 2005	DAR A: 7.5 mg B: 7.5 for 2 wks then 15 mg for 12 wks	A: ↓2.0 (104) B: ↓1.9 (157) (p≤ 0.001 for both combined vs. placebo)	↓1.0 (123)	A: ↓1.1 (104) B: ↓1.2 (156)	↓0.3 (123)
Unpublished data no date	DAR A: 15mg B; 30 mg for 12 weeks	Median change: A: ↓1.9 (109) (p=NS) B: ↓1.9 (225) (p=0.047 vs. placebo)	↓1.2 (113)	Median change: A: ↓0.5 (p=NS) B: ↓0.7 (p<0.05 vs placebo)	Median change ↓0.5

All weekly rates were divided by 7 and reported as daily rates

Abbreviations: TROS = trospium chloride; OXY = oxybutynin; DAR = darifenacin; TOL = Tolterodine tartrate; SOL = solifenacin; SCP = scopolamine; IR = immediate release; ER = extended release; TD = transdermal;

*****Study of patients with detrusor hyperreflexia

Evidence Table 6. Assessment of abstracts for publication bias

Author Year	Interventions (Drug, dose, sample size)	Micturitions mean change *(time period)*	Urge incontinence episodes mean change *(time period)*
Head-to-head trials			
Van Kerrebroeck 1997	A: Tolterodine 2 mg BID *(n=120)* B: Oxybutynin 5 mg TID *(n=120)*	A: -2.1 B: -2.7 *(unclear)*	A: -1.7 B: -2.1 *(unclear)*
Lee 2001	A: Tolterodine 2 mg BID (n=112) B: Oxybutynin 5 mg BID (n=116)	A: -2.6 B: -1.8 (24 hours)	A: -2.2 B: -1.4 (24 hours)
Schmidt 1998	A: Oxybutynin-XL 15 mg/day *(n=33)* B: Oxybutynin-IR 15 mg TID *(n=32)* C: Placebo *(n=15)*	Not reported	Mean percent reduction *(weekly)* A: 92% B: 72% C: 45%
Sand 2001	A: Oxybutynin-XL 10 mg/day *(n=nr)* B: Tolterodine 4 mg BID *(n=nr)* *(total n=382)*	Not reported	Not reported
Junemann 2000	A: Trospium Chloride 20 mg BID *(n=57)* B: Tolterodine 2 mg BID *(n=63)* C: Placebo *(n=60)*	A: -3.4 B: -2.6 C: -1.9 *(24 hours)*	Not reported
Zinner 2004	A: Oral darifenacin CR 15 mg QD (*n=58)* B: Oxybutynin 5 mg TID (*n=58)* C: Placebo (*n=58)*	NR	NR

**Data not provided*

Evidence Table 6. Assessment of abstracts for publication bias

Author Year	Interventions (Drug, dose, sample size)	Micturitions mean change *(time period)*	Urge incontinence episodes mean change *(time period)*
Placebo-controlled trials			
Garely 2001	A: Tolterodine 4 mg OD *(n=507)* B: Placebo *(n=508)*	Median % decrease A: 17% B: 11%	Median % decrease A: 71% B: 33%
Millard 1997	A: Placebo B: Tolterodine 1 mg BID C: Tolterodine 2 mg BID *(n=unclear)*	A: -1.4 B: -2.3 C: -2.2 *(unclear)*	A: -1.3 B: -1.7 C: -1.8 *(unclear)*
Jonas 1997	A: Tolterodine 1 mg BID *(n=99)* B: Tolterodine 2 mg BID *(n=99)* C: Placebo *(n=44)*	A: -0.6 B: -1.4 C: -1.7 *(24 hours)*	A: -1.5 B: -1.1 C: -1.6 *(24 hours)*
Moore 1997	A: Tolterodine 1 mg BID B: Tolterodine 2 mg BID C: Placebo (*Total n=306*)	A: -1.7 B: 1.8 C: not reported *(24 hours)*	Not reported
Whishaw 1997	A: Tolterodine 1 mg BID *(n=unclear)* B: Tolterodine 2 mg BID *(n=unclear)* C: Placebo *(n=unclear)* *(Total n=316)*	A>C* B>C* *(24 hours)*	A=B=C *(24 hours)*
Van Kerrebroeck 2000	A: Tolterodine 4 mg/day *(n=507)* B: Placebo *(n=508)*	Percent change A: -17% B: -11%	Percent change A: -53% B: -30%
Hill 2004	A: Darifenacin CR 7.5 mg QD (*n=108)* B: Darifenacin CR 15 mg QD (*n=107)* C: Darifenacin CR 30 mg QD (*n=115)* D: Placebo (*n=109)*	NR	Median % Change A: -9.8 B: -10.9 D: -6.6 (*weekly)*
Rudy 2004	A: Trospium chloride 20 mg BID (*n=329)* B: Placebo (*n=329)*	A: -2.67 B: -1.76	A: -65.9 B: -43.6
Comparative Observational Studies			
Boccuzzi 2002	Oxybutynin IR Tolterodine IR	12 months	Oxy 83% Tol 76%
Taira 2002	Tol, Oxy, Oxy XL, Hyoscyamine, Flavoxate, imipramine, propantheline		
Juzba 2001	Oxybutynin Tolterodine (formulations not stated)	3 months	Cox regression the risk of discontinuation was statistically significantly lower in Tol users, who were 43% less likely to discontinue

**Data not provided*

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Tolterodine (Tol)				
Siami 2002	Multicenter USA	Open label, uncontrolled 12 weeks	Men and women age 18+ with diagnosis of overactive bladder with symptoms of urinary frequency (8+ micturations/24h), urgency (strong and sudden desire to urinate), with or without urge incontinence	Pure or predominantly stress incontinence, indwelling or intermittent catheter, symptomatic or recurrent UTI, hepatic or renal dysfunction, program of electrostimulation, bladder training or pelvic floor exercises within 4 weeks.
Michel 2002	Multicenter Germany	Open label, uncontrolled, cohort 12 weeks	Tol prescription	None specified
Appell 2001	Multicenter (multinational)	Open label 9 month study	Patients completing 12 week RCT enrolled after 1-week washout period.	None specified

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Tolterodine (Tol)			
Siami 2002	Tol 4mg ER once daily	Number screened not reported. 1147 enrolled 1138 analyzed (9 took no drug) 735 drug naïve 403 previously treated (not with Tol)	Age range 18-91 Mean age drug naive 60yr Mean age prior treatment 62.5yrs Drug naïve;70% female, Prior Treatment; 79% female Drug naïve; 87% white, Prior treatment; 90% white
Michel 2002	Tol - varying doses. Mean dose 2mg twice daily	2250 enrolled	Mean age 61 yrs 77% female
Appell 2001	Tol 2mg twice daily	939 eligible/854 enrolled	Age Range 19-89 Mean 60yrs 76% female

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events	Comments
Tolterodine (Tol)				
Siami 2002	Spontaneously reported and elicited during visits (1, 4 and 12 wks). Investigator classified adverse events as mild (does not interfere with patient's usual function), moderate (interferes to some extent), or severe (interferes significantly).	Dry mouth was the most common adverse event reported, at 16%. Of these events 8% were severe, 20% moderate, and 72% were mild. No other adverse events were reported in greater than 6% of patients.	90 (8%)	Short-term
Michel 2002	Spontaneously reported and elicited during visits (6 and 12 wks). Patients asked to rate tolerability at 12 wks (very good, good, moderate, poor)	127 events were reported by 93 patients (4.1%). Dry mouth was the most common (2%). Tolerability ratings: very good 39% good 56% moderate 4% poor 0.9% Logistic regression showed no association between tolerability rating and age, gender and baseline symptoms, but did show improved tolerability related to higher dose (4mg)	61	Realistic setting, but unclear if tolerability assessment is made by physician or patient
Appell 2001	Spontaneously reported adverse events, withdrawals, and dose reductions (by patient as needed). Adverse events classified as mild, moderate, severe. Severe Adverse events were assessed for relationship to Tol. Blood chemistry/hematology. Patients seen at 3 and 9 months.	76% of patients reported adverse events. Dry Mouth 28% (2% of all patients had severe dry mouth) UTI 12% Constipation 7% Headache 7% Abdominal pain 6% 13% reduced dosage 3 serious adverse events were judged possibly or probably related to Tol (constipation, abdominal pain, and tachycardia) 3 cases of urinary retention (0.4%)	73 (9%), of these 12 due to dry mouth (1%)	

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Abrams 2001	Multicenter (multinational)	Open label 12 months study	Patients completing 4wk RCT enrolled after 4-week washout period.	None specified
Kreder 2002	Multicenter (multinational)	Open label 12 month study	Patients completing 12 wk RCT enrolled	None specified
Abrams, 2001	Multicenter, Europe	Open label, uncontrolled, 12 months	male and female patients, age >18 (≥65y in one 4-week study), urodynamically proven overactive baldder and symptoms of urinary frequency (average (≥8 micturitions/24h), urgency, an/or urge incontinence (average(≥ 1 incontinence episode/24h).	clinically significant stress incontinence, hepatic or renal disease, recurrent or symptomatic UTI, conditions contraindicating antimuscarinic therapy, clinically significant voiding difficulty with risk of urinary retention, treatment with or initiation during the study of, any antimuscarinic drug or any drug for bladder control problems or bladder training, within 14d prior to the baseline visit.
Michel, 2005	Multicenter, Germany	Open label, uncontrolled, 9 months	none	none

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Abrams 2001	Tol 2mg twice daily	895 elgible/714 enrolled	Age range 18-92 Mean age 60yrs 69% female
Kreder 2002	Tol ER 4mg once daily (no dose adjustments allowed)	1337 eligible/1077 enrolled	Age range 20-93 Mean age 60 yrs 82% female
Abrams, 2001	Tol 2mg twice daily with optional reduction to 1mg twice daily	screened NR/895 eligible after completion of 4-week RCT studies/714 enrolled	mean age 59.7y, 68.5% women, ethnicity NR
Michel, 2005	Tol 4mg once daily	screened NR/ eligible not applicable/ 3824 enrolled	overall mean age 64.8y. 75.8% female. mean age/gender incontinent patients, 66.3y/ 81.7% female and continent patients, 61.4y/ 62.6% and Ethnicity not reported

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events	Comments
Abrams 2001	Spontaneously reported adverse events, withdrawals, and dose reductions (by patient as needed). Adverse events classified as mild, moderate, severe. Severe Adverse events were assessed for relationship to Tol. Blood chemistry/hematology. Patients seen at 6 and 12 months.	77% reported an adverse event. Dry mouth 289 (41%) (27% mild, 3% severe) UTI 10% Headache 6% Abdominal pain 6% 5 serious adverse events were considered related to Tol (hernia, dyspepsia, pulmonary edema, and acute urinary retention) 167 (23% reduced dosage).	105 (15%)	
Kreder 2002	Spontaneously reported adverse events, withdrawals, and dose reductions (by patient as needed). Adverse events classified as mild, moderate, severe. Severe adverse events were assessed for relationship to Tol. Blood chemistry/hematology. Patients assessed by phone at 1 month, and seen at 3, 6, 9 and 12 months, and again by phone 1 week after end of study.	Dry mouth 139 (12.9%) UTI 44 (4.1%) URI 43 (4%) 4 serious adverse events considered possibly related to Tol ER: urinary retention (2), aggravated MS (1), 'medication error' (1)	107 (10%) Most common reason: dry mouth 19 (18%)	
Abrams, 2001	spontaneously reported AE, withdrawals and dosage reductions and at 6 month assessment visit. AE were classified as mild (easily tolerated), moderate (sufficient discomfort for interference with normal daily activities) or severe (incapacitating in terms of work and normal daily activities)	41% dry mouth (27% mild, 10% moderate and 35 severe) Other AE: autonomic nervous system disorders, general body disorders, gastrointestinal disorders and urinary disorders.	105 patients (15%)	62% of patients completed 12months' treatment with tol
Michel, 2005	Physician observed and reported at baseline, 1, 3, 6, and 9 months	overall AE: 13%, dry mouth: 7.8%	2.8% due to lack of tolerability	post-marketing surveillance of Tol ER sponsored by Pharmacia (now Pfizer)

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Takei, 2005	extension of Homma, 2003, a comparative controlled RCT	open label, uncontolled, 12 months	Eligible Japanese pts who completed a 12wk double blind trial: patients were ≥ 20 years with OAB symptoms including urinary urgency, urinary frequency (≥ 8 micturitions/24h) and urge incontinence (.= 5 episodes/wk) for .= 6 months. Pts were recruited based solely on OAB symptoms, irrespective of prior antimuscarinic treatment or response to such therapy	demonstrable stress incontinence, total daily uring volume >3L, average volume voided/micturition >200mL, significant hepatic or renal disease, any contraindication for anticholingeric treatment, symptomatic or recurrent UTI, inserstitial cystits, hematuria or BOO, indwelling catheter or intermittent self-catheterization, electrostimulation or bladder training within 14days before randomization or expected to commence during study. Pts who were poorly compliant (missed >25% of prescribed medication), had an ongoing serious AE and pregnant or nursing women and women of childbearing potential not using reliable contraception also excluded.
Oxybutynin (Oxy)				
Gleason 1999	Multicenter USA	Open label 12 week study	Men and women with idiopathic urge incontinence or mixed incontinence with clinically significant urge component, with at least 6 urge incontinence episodes weekly.	Uncontrolled medical condition, post void residual volume >100ml or significant berurua or pyuria.
Salvatore, 2004	Kings College Hospital London, UK	open label, random allocation to starting dose (not described), open ended continuation, follow-up after 2y	women with videourodynamic diagnosis of DO or low bladder compliance	NR

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Takei, 2005	Tol 4mg once daily	188 out of 293 continued open label	mean age 63.6y, 65.4% female, all Japanese
Oxybutynin (Oxy)			
Gleason 1999	Oxy ER 5 to 30mg/day	Number screened not reported. 256 enrolled	38.9% >65 yrs 91% female 92% white
Salvatore, 2004	Oxy IR 2.5mg twice daily or Oxy IR 5mg nightly. These doses were to be self adjusted by the patients to a level where side effects were considered acceptable. The maximum recommended dose was 5mg tid.	screened NR/ eligible NR/ 96 enrolled	mean age 57.5y (range 32-80y), all female, no ethnicity reported

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events	Comments
Takei, 2005	safety was assessed at 4, 12, 24, 36 and 52 weeksof the continuation study and at post-treatment follow-up. AE were recorded at each visit. Clinical lab assessment (serum chem, hematology and urinanysis) at 12, 24, and 52 weeks. ECG at baseline, and 12 and 52 weeks or upon withdrawal	total incidence of dry mouth 33.5%, mild in all but one case. Nasopharyngitis (26.6%) considered unrelated to treament.	19 (10.1%) patients withdrew due to AEs	
Oxybutynin (Oxy)				
Gleason 1999	Reports of adverse events were solicited at visits at weeks 1, 4, 8 and 12.	Dry mouth 59% (36% mild, 23% moderate to severe) 2 serious adverse events possibly related to Oxy were related to pre-existing gastric reflux disease.	20 (8%) Most commonly nausea, dry mouth and somnolence, urinary retention, and increased post-void residual	
Salvatore, 2004	phone or postal questionnaire at 2y after baseline. Questionnaire intended to assess efficacy, acceptability and compliance of two regimens. Not clear if questionnaire was administered prior to treatment.	34.8% complained of side effects. No serious AE reported.	43.2% of women who ceased treatment cited AE as reason for temination.	68.75% responded to questionnaire

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria
Oxybutynin (Oxy) vs. Tolterodine (Tol)				
Lawrence 2000	Pharmacy Benefit Management Database USA	Pharmacy Claims Data for April - December 1998	New prescription for Tol or Oxy	Terminated coverage with plan, received more than 30 day supply, incomplete data
Solifenacin (Sol)				
Haab, 2005	extension of Cardozo, 2004 a placebo-controlled trial and Chapple 2004, a trial with a placebo arm	open label, uncontrolled, 40 weeks	in addition to criteria for original study: informed consent and completion of treatment in the previous double-blind studies within </= 14d prior to entry into extension study.	clinically significant outflow obstruction, postvoid residual urine≥ 200mL, persistent or recurrent UTI, bladder stones, chronic interstitial cystitis, previous pelvic radiation or previous or current malignant disease of the pelvic organs and any medical condition contraindicating use of anticholinergic medication. Women of childbearing potential, pregnant or nursing or intended to become pregnant during study or unreliable contraception method.

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	Interventions	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Oxybutynin (Oxy) vs. Tolterodine (Tol)			
Lawrence 2000	Tol or Oxy (IR)	1531 eligible/1020 analyzed	Median age Tol 73 (range 18-93), Oxy 70 (range 18-95) % female: Tol 68%, Oxy 97%
Solifenacin (Sol)			
Haab, 2005	Sol 5mg once daily for weeks 12-16 (week 12 of trial=week 1 of open-label study);pts could chose to increase to Sol 10mg once daily at weeks 16, 28 and 40.	Screened and eligible NR/ 1633 enrolled in safety analysis	mean age 56.4y with a range of 18-82y, 78% women, 98.1% white, 0.5% black, 0.8% Asian, 0.6% other

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 7. OAB observational studies: Adverse events

Author, Year	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events	Comments
Oxybutynin (Oxy) vs. Tolterodine (Tol)				
Lawrence 2000	Determined discontinuation of medication by gap in refill data, assessed time to discontinuation.	Continuing therapy for 6 months: Tol 164 (32%), Oxy 111 (22%) (p<0.001) Difference remains significant after controlling for age and co-payment amount. Patients discontinued Oxy significantly earlier (mean 45 days) than Tol (mean 59 days) (p<0.001). Never refilling prescription: Oxy 68% Tol 55%		
Solifenacin (Sol)				
Haab, 2005	safety was assessed at 4, 16, 28, 40 and 52 weeks of the extension study. At each visit patients were assessed: vital signs, physical examination, serum chem, hematology and urinanysis, 3-day diary, and QoL questionnaire. ECG and bladder ultrasound were performed week 28 and end of study.	total incidence of dry mouth 21%, with 10% of the lower dose group and 17% of the higher dose group. About 10% reported constipation and 7% reported blurred vision. The majority (> 50%) of the episodes of dry mouth, constipation and blurred vision were mild in severity.	4.7% withdrew due to AE	81% of enrolled patients completed 40 weeks of open label treatment

Tol = Tolterodine, Oxy = Oxybutynin, IR = Immediate release, ER = Extended release, RCT = Random Controlled Trial, UTI = Urinary tract infection

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs. Tolterodine (Tol)		
Leung 2002 Hong Kong	Tol 2mg twice daily Oxy 5mg twice daily	106 enrolled
Lee 2002 South Korea	Tol 2mg twice daily Oxy 5mg twice daily	228 enrolled (Tol 112, Oxy 116)
Malone-Lee 2000 UK and Ireland	Tol 2mg twice daily Oxy 5mg twice daily x 8 weeks Dose reduction allowed in Oxy group	482 screened 379 randomized 378 analyzed (1 received no drugs) Tol 190, Oxy 188

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs. Tolterodine (Tol)			
Leung 2002 Hong Kong	Xerostomia Questionnaire at 4 and 10 weeks, independent reporting of other side effects. Significant deterioration on all measures of dryness except denture fit, for both drugs. NS between groups. Side effects reported: Oxy 49% Tol 60% (NS) Reported to be mostly abdominal aches, general malaise and urinary retention	Unclear. States that most withdrawals not due to side effects, but that patients withdrawing while on Oxy were more likely to have co-existing illnesses (p<0.012).	Fair Compliance measured. Oxy 87.5% (11 to 99.3) Tol 75% (8.9 to 98.8) (NS)
Lee 2002 South Korea	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, and relationship to study drug. 227 patients assessed Tol: 62 patients reported 101 adverse events Oxy: 94 patients reported 154 adverse events (p = 0.001) Dry mouth: Tol 39 (35%) 72 (63%) (p<0.001) Severe dry mouth: Tol 1 (1%), Oxy 6 (5%) Micturation disorder: Tol 10 (9%), Oxy 16 (14%) Dyspepsia/abdominal pain: Tol 14 (13%), 12 (10%) Headache: Tol 4 (4%), Oxy 6 (5%)	Overall 29 (13%) Tol 11 (6 dry mouth, 55%) Oxy 18 (16 dry mouth, 88%)	Fair
Malone-Lee 2000 UK and Ireland	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity. Special attention to reporting of dry mouth. No description of scale for assessment of intensity or seriousness. At least one adverse event: 69% Tol, 81% Oxy Severe intensity: 13% Tol, 28% Oxy Serious and considered drug-related: 3 patients (1.6%) Tol, 0 Oxy Dry Mouth: overall 37% Tol, 61% Oxy (p<0.0001) Severe: 4% Tol, 15% Oxy (NS)	Overall 50 (13%) 22 (12%) Tol, 28 (15%) Oxy Due to dry mouth: 3% Tol, 7% Oxy	Fair Dose reductions requested by 6% Tol, 25% Oxy (p<0.0001)

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Abrams 1998 UK, Ireland and Sweden	Tol 2mg twice daily Oxy 5mg three times daily Placebo three times daily Subjects >/= 65 yrs in UK and Ireland could start the dose of Oxy at 2.5mg and increase to 5mg during first 2 weeks Dose reduction allowed	293 enrolled (118 Tol, 118 Oxy, 57 Pl)
Drutz 1999 USA/Canada	Tol 2mg twice daily Oxy 5mg three times daily Placebo three times daily Dose reduction allowed	277 enrolled (Tol 109, Oxy 112, Placebo 56)

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Abrams 1998 UK, Ireland and Sweden	All adverse events were recorded and categorized by intensity (mild, moderate, severe). The likelihood of relationship to study drug was evaluated for serious adverse events and patient withdrawn if deemed medically necessary or patient wished withdrawal. At least one adverse event reported: 89% Tol, 97% Oxy, 81% Pl (Tol vs. Oxy p = 0.023) Dry mouth: 50% Tol, 86% Oxy, 21% Pl (Tol vs. Oxy p<0.001) More patients reported dry mouth to be severe on Oxy than on Tol or Pl (numbers not given) 1 serious adverse event (syncope) was considered related to Tol	Overall: 10% Tol 8%, Oxy 17%, Pl 2% Due to dry mouth: Tol 0.8%, Oxy 13%, Pl 3.5%	Fair Dose reductions requested by 8% Tol, 32% Oxy, 2% Pl (Tol vs. Oxy p<0.001)
Drutz 1999 USA/Canada	Spontaneously reported adverse events were reported and rated as serious or nonserious and according to intensity, at visits at 2, 4, 8 and 12 wks ITT analysis: % reporting adverse events: Tol 78%, Oxy 90, placebo 75 (p = 0.013 Tol vs Oxy) Dry mouth: Tol 30%, Oxy 69%, placebo 15% (p <0.001 Tol vs Oxy) Moderate to severe dry mouth: Tol 9%, Oxy 44%, placebo 7% Other adverse events reported: headache: Tol 15%, Oxy 10% dizziness: Oxy 11% (others not reported) cardiovascular events: Tol 7%, Oxy 8% Dose reduction: Tol 7%, Oxy 23%, placebo 4% (p<0.001 Tol vs Oxy)	Overall 12% Tol 7 (6%), Oxy 23 (21%), placebo 4 (7%) (p = 0.002 Tol vs Oxy)	Poor Only Allowed dose reductions in protocol, but then excluded these from analysis. Incomplete reporting of adverse events. 46 excluded from analysis due to protocol violations, but which groups assigned not reported.

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Immediate Release vs Immediate Release (IR vs IR)		
Oxybutynin (Oxy) vs Flavoxate (Fla)		
Milani 1993 Italy	Fla 400mg or Oxy 5 mg three times daily, then crossover	50 enrolled
Zeegers 1987 Netherlands, Austria	Randomized to either: Fla 200mg or Emp 200mg or Pl three times daily x 3 weeks each or Oxy 5mg or Emp 200mg or Pl three times daily x 3 weeks each Order of drugs also randomized.	Stated to be consecutive patients 60 enrolled (30 in Fla/Emp/Pl, 30 in Oxy/Emp/Pl)

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs Flavoxate (Fla)			
Milani 1993 Italy	Adverse events were elicited at 4 wks, and rated as serious or nonserious and according to intensity. By ITT: Fla 11/50 (22%), Oxy 42/50 (84%), plus 5 patients withdrawn due to adverse events. Dry mouth: Fla 2%, Oxy 78% Abdominal or stomach pain: Fla 24%%, Oxy 36%	5 (10%) not clear when these occurred.	Poor
Zeegers 1987 Netherlands, Austria	Combined in score 15% Pl, 26% Emp, 8% Fla, 17% Oxy	Overall 20% 2 Pl, 8 Emp, 0 Fla, 2 Oxy	Poor

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Immediate Release vs Immediate Release (IR vs IR)		
Trospium chloride IR vs Oxybutynin IR		
Halaska 2003	Average 54 weeks of treatment with either Oxy 5 mg twice daily or Trospium 20 mg twice daily. Multiple appointments for evaluation through the course of the trial	Screened NR Eligible 358 Enrolled 357
Maderspacher 1995	Initial one week washout followed by 2 weeks of treatment with either Oxy 5 mg three times daily or Trospium 20 mg twice daily. To maintain double blind conditions the Trospium group received a placebo at midday	Screened NR Eligible NR Enrolled 95 52 Trospium, 43 Oxy.

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Immediate Release vs Immediate Release (IR vs IR)			
Trospium chloride IR vs Oxybutynin IR			
Halaska 2003	All adverse events: Trospium 68%, Oxy 77% All adverse events possibly/probably connected with treatment: Trospium 48%, Oxy 59%, p=0.02. All gastrointestinal adverse events possibly/probably connected with treatment: Trospium 39%, Oxy 51%, p=0.02. Dryness of mouth: Trospium 33%, Oxy 50%, p<0.01. "Time to event" reported as significant in favor of Trospium (p<0.01). Withdrawal due to adverse events classified as having at least a possible association: Trospium 3.7%, Oxy 6.7% Withrawal due to adverse events classified as having no association: Trospium 0.7%, Oxy 0%. Withrawal due to other serious adverse events: Trospium 1.5%,Oxy 3.3% Tolerability assessed by subjective appraisal of physicians at 26 & 52 wks:Trospium rated very good by 49% (26 wks) and 63% (52 wks); Oxy rated at 36%(26 wks) and 42%(52 wks). Appraisal by patients reported as "almost identical."	91 withdrew: Trospium 67 (25%), Oxy 24 (26.7%)	Fair. Long FU. Significant number of withdrawals for multiple reasons.
Maderspacher 1995	Analysis of tolerance carried out on all 95 subjects. Twenty "well being" items asked directly by investigator before and at end of trial. Severity grading assessed using 4 point scale. Overall rate of side effects reported as "almost comparable" in both groups. Dry mouth: Trospium 54%, Oxy 56% Severe dry mouth: Trospium 4%, Oxy 23%	10 withdrawals Trospium 3 (6%) Oxy 7 (16%)	Fair. All patients spinal cord injured. Type and level of injury not specified. Concurrent medications not noted.

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Oxybutynin ER v Oxybutynin IR		
Versi 2000 USA	Oxy ER 5-20mg once daily or Oxy IR 5-20mg/d - schedule not reported	screened 417 eligible/enrolled 226
Birns 2000 UK	Oxy ER 10mg once daily or Oxy 5mg twice daily	162 screened 130 randomized
Anderson 1999 USA	ER Oxy 5-30mg once daily or IR Oxy 5mg once to four times daily. . dose reductions allowed for adverse effects	158 screened 105 enrolled 93 analyzed

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Oxybutynin ER v Oxybutynin IR			
Versi 2000 USA	Reports of adverse effects recorded at each pt visit Dry mouth: ER 48%, IR 59% Kaplan Meier analysis moderate or severe dry mouth reports indicates a significant difference (p = 0.007) in favor of ER	Overall: 10 (8%) ER: 3 (3%) IR: 7 (6%)	Fair Mean duration of treatment/follow-up not stated. Only dry mouth reported in detail.
Birns 2000 UK	Assessed during visits every two weeks 78 pts reported adverse events (60%) (ER 55%, IR 67%) Dry mouth: ER 23%, IR 17% Dizziness ER 2%, IR 9% Vision abnormality ER 7%, IR 5% Cough ER 3%, IR 5% Headache ER 0, IR 5%	1 (considered unlikely due to study drug)	Fair Mixed types of incontinence Study included a run-in phase to establish tolerability, patients with adverse events excluded during run-in
Anderson 1999 USA	Spontaneously reported and anti-cholinergic effects assessed at each study visit Dry mouth: ER 68%, IR 87% (p = 0.04) Moderate to severe dry mouth: ER 25%, IR 46% (p = 0.03) Somnolence: ER 38%, IR 40% Blurred vision: ER 28%, IR 17% Constipation: ER 30%, IR 31% Dizziness ER 28%, IR 38%	2 (4%) in each group due to anticholinergic adverse events	Fair Previously all pts had responded to IR oxy Very high incidence of adverse events - may reflect the aggressive dose titration Duration of study (mean) not reported, very little data on final dose in either group

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Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Nillsson 1997 Finland	Oxy ER 10mg once daily Oxy 5mg twice daily crossover	17 enrolled
Radomski 2004	Oxy IR twice daily at dose at discretion of investigator for first two weeks (if on Oxy IR prior same dose continued 3 patients, if deemed obese 5 mg twice daily otherwise 2.5 mg twice daily), followed by two week washout, followed by Oxy CR 15 mg once daily for four weeks	# screened not reported. 12 included for safety analysis. 9 included for efficacy analysis (completed 8 week study)
Barkin 2004	Oxy IR 5mg tid, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks Oxy ER 15mg tid, dose titration in 5mg increments in 2 wks followed by stable-dose phase for 4 wks	125 enrolled (Oxy IR 60, Oxy ER 65)

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Nillsson 1997 Finland	Patients reported on a questionnaire throughout study, classified as mild, moderate, severe 14/16 on ER, 5/17 on IR reported at least one adverse event Dry mouth: ER 69%, IR 82% Headache ER 44%, 41% Dyspepsia ER 31%, IR 12% fatigue ER 13%, 24% Blurred vision 25%, IR 12% % Severe: ER 17%, IR 14% reported that these were NS, but unclear what data being compared.	None reported	Poor Very high numbers of subjects reporting adverse events
Radomski 2004	Adverse events collected during scheduled visits and entered in diary. Dry mouth: ER vs IR (mild, moderate, severe): 25%,25%,8% vs 58%,8%,8%. Constipation: ER 8%, IR 8% Back Pain: ER 8%, IR 8% Pain-unspecified: ER 42%, IR 17% Increased salivation: ER 17%,IR 8% Asthenia: ER 8%, IR 17% Peripheral edema: ER 8%, IR 8%	2 withdrawals in OXY IR phase. 1 withdrawal in Oxy ER phase. Events reported: severe stomach pain, mild peripheral edema, severe vision distortion	Poor All subjects exposed to Oxy IR first, exposed to longer duration of ER. Study open label
Barkin 2004	<u>Oxy ER vs Oxy IR (%)</u> Dry mouth: overall: 68% vs 72%; moderate or severe: 38% vs 45% Pharyngitis (dry throat): 35% vs 40% Dry skin: 17% vs 12% Diarrhea: 14% vs 5% Headache: 12 % vs 22% Uriniary tract infection: 12 % vs 18% Dizziness: 11% vs 18% Dyspepsia: 11% vs 17% Rhinitis: 11% vs 15% Abdominal pain: 9% vs 10% Asthenia: 18% vs 15% Constipation: 8% vs 10% Taste perversion: 8% vs 12% Cough increased: 6% vs 13% Dysphagia: 6% vs 13% Dry eyes: 3% vs 15% Nausea: 5% vs 17%	Oxy IR: 12 (20%) Oxy ER: 11 (17%)	Fair

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Tolterodine ER vs Tolterodine IR		
Van Kerrebroeck 2001 Multinational	Tol ER 4mg once daily or Tol IR 2mg or Placebo twice daily	1529 enrolled Tol ER: 507 Tol IR: 514 placebo: 508
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Tol ER 4 mg (n=417) once daily vs. Tol IR 2 mg twice daily (n=408) vs. Pla (n=410) for 12 wks.	1235 enrolled Tol ER: 417 Tol IR: 408 placebo: 410
Extended Release vs.Immediate Release (ER vs IR)		
Oxybutynin ER v Tolterodine IR		
Appell 2001 USA	ER Oxy 10mg once daily Tol 2mg twice daily	378 enrolled (Oxy ER 185, Tol 193) 332 completed (Oxy ER 160, Tol 172)

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Tolterodine ER vs Tolterodine IR			
Van Kerrebroeck 2001 Multinational	Spontaneously reported events were categorized and causation assigned dry mouth further categorized Dry mouth: ER 23%, IR 30%, Placebo 8% Constipation: ER 6%, IR 7%, Placebo 4% Headache: ER 6%, IR 4%, Placebo 5%	Overall 88 (5.7%) ER: 27 (5.3%) IR: 28 (5.5%) placebo 33 (6.5%)	Fair Dry mouth classified as mild/moderate/severe but data only reported for ER
Swift 2003 Re-analysis of data for women only in Van Kerrebroeck 2001 study (above)	Reporting details NR. Tol ER vs. Tol IR vs. Pla: Dry mouth: 105/415 (25.3%) vs. 127/407 (31.2%) vs. 33/410 (8.0%) Dry skin: 2 (0.5%) vs. 5 (1.2%) vs.1 (0.2%) Dizziness: 7 (1.7%) vs. 7 (1.7%) vs. 4 (1.0%) Somnolence: 12 (2.9%) vs. 11 (2.7%) vs. 8 (2.0%) Abnormal vision: 5 (1.2%) vs. 4 (1.0%) vs. 2 (0.5%) Constipation: 27 (6.5%) vs. 27 (6.6%) vs. 14 (3.4%)	Tol ER 22/417 (5%) vs. Tol IR 20/408 (5%) vs. Pla 26/410 (6%)	Fair Dry mouth classified as mild/moderate/severe Reporting details NR Patients excluded from AE assessment (Tol ER=2; Tol IR=1)
Extended Release vs.Immediate Release (ER vs IR)			
Oxybutynin ER v Tolterodine IR			
Appell 2001 USA	Patient reported dry mouth occurred in equal proportion in each group both groups had similar rates of dry mouth and other adverse effects	Overall 7.7% Oxy ER 14 Tol 15	Fair

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Tolterodine ER vs. Oxybutynin IR		
Homma 2003	Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks	Enrolled = 608 Tol ER = 240 Oxy IR = 246 Pla = 122
Extended Release vs.Immediate Release (ER vs IR)		
Solifenacin IR vs. Tolterodine ER		
Chapple 2005 STAR trial	Flexible dosing, Weeks 0-4: Sol 5mg qd Tol ER 4mg qd Stable-dose phase,Weeks 5-12: Sol 5mg qd (Sol 5) Sol 10mg qd (Sol 10) Tol ER 4mg qd (Tol 4)	Full analysis set (FAS): 1177

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Tolterodine ER vs. Oxybutynin IR			
Homma 2003	Dry mouth: Tol 0.4% vs. Oxy 9.4% All events: Tol 5.0% vs. Oxy 17.1% p<0.001 Serious event, possibly drug related: 1 Oxy cardiac failure. No deaths and no clinically significant changes in lab or ECG values.	Compliance >75% of medication: Tol 98% vs. Oxy 93%	Fair Adverse events undefined; ascertainment techniques NR
Extended Release vs.Immediate Release (ER vs IR)			
Solifenacin IR vs. Tolterodine ER			
Chapple 2005 STAR trial	AE evaluted at each clinic visit in response to questioning by the investigator or volunteered by patient Comparisons: Sol (mild%, moderate%, severe% AEs) vs Tol (mild%, moderate%, severe% AEs) Dry Mouth: (17.5%, 10.8%, 1.7%) vs (14.8%, 7.7%, 1.5%) Constipation: (3.2%, 2.7%, 0.5%) vs (1.3%, 1.0%, 0.2%) Blurred Vision: (0.7, 0%, 0%) vs. (0.7%, 1.0%, 0%)	Withdrawals due to AEs: Sol: 3.5% Tol ER: 3.0%	Fair

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Extended Release vs.Immediate Release (ER vs IR)		
Darifenacin IR and Darifenacin ER vs. Oxybutynin IR		
Chapple and Abrams 2005	1) Dar IR 2.5mg tid or Oxy IR 2.5mg tid 2) Dar ER 15mg qd or Oxy IR 5mg tid 3) Dar ER 30mg qd or Oxy IR 5mg tid each treatment period was 7 days	65 enrolled
Diokno 2003 OPERA	Oxy ER 10 mg/day vs. Tol ER 4 mg/day x 12 wks	Enrolled 790 Oxy ER= 391 Tol ER = 399

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs.Immediate Release (ER vs IR)			
Darifenacin IR and Darifenacin ER vs. Oxybutynin IR			
Chapple and Abrams 2005	*Cohort 1% (Dar: # of pts; Oxy: # of pts) vs. Cohort 2% (D: #; O: #) vs. Cohort 3% (D:#; O:#)* All AEs: 43% (D:5, O 8) vs 73% (D:16; O;19) vs 98% (D:22; O:24) Treatment-related AEs: 40% (D:4; O:8) vs 68% (D:14; O:19) vs 98% (D:22; O:24) Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2) Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1) Dry mouth: 40% (D: 4; O:8) vs 62.5% (D:13; O:17) vs 94%(D:21; O:23) Constipation: 6.7% (D:1; O:1) vs 29.2% (D:8; O:6) vs 25.5% (D:10; O:2) Dyspepsia: 3.3% (D:1; O:0) vs 16.7% (D:3; O:5) vs 8.5% (D:2; O:2) Headache: 3.3% (D:1; O:0) vs 8.3% (D:1; O:3) vs 10.6% (D:2; O:3) Abnormal vision: 6.7% (D:1; O:1) vs 8.3% (D:1; O:3) vs 12.8% (D:4; O:2) Somnolence: 3.3% (D:0; O:1) vs 4.2% (D:1; O:1) vs 4.3% (D:2; O:1) Asthenia: 3.3% (D:0; O:1) vs 0% vs 6.4% (D:3; O:1) Pharyngitis: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:2; O:1) Dysphagia: 0% vs 8.3%(D: 1; O:3) vs 0% Pruritus: 0% vs 2.1% (D:O; O:1) vs 4.3% (D:3; O:0) Dry eyes: 0% vs 0% vs 6.4% (D:1; O:3) Urinary tract disorder: 0% vs 6.3%(D: 2; O:1) vs 0% Confusion: 0% vs 0% vs 4.3% (D:3; O:0) Epistaxis: 0% vs 0% vs 4.3% (D:1; O:2) Dysuria: 0% vs 0% vs 4.3% (D:1; O:2)	Discontinued due to AEs: 3.3% (D:0; O:1) vs 2.1% (D:1; O:0) vs 6.4% (D:1; O:2) Discontinued due to treatment-related AEs: 0% vs 2.1% (D:1; O:0) vs 4.3% (D:1; O:1)	Fair
Diokno 2003 OPERA	Dry mouth: Oxy 116/391 (29.7%) vs. Tol 89/399 (22.3%) (p=0.02) mild: oxy 87/391 (22.3%) vs Tol 69/399 (17.3%) mod-severe: Oxy 29/391 (7.4%) vs Tol 20/399 (5%) Constipation: Oxy 25/391(6.4%) vs. 31/399 (7.8%) (NS)	All events: Oxy 20/391 (5.1%) vs. Tol 19/399 (4.8%) Due to dry mount: Oxy 7, Tol 4	Fair Data collected at each visit or any time reported by participant, rated as mild, moderate, severe by investigator

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled
Transdermal vs. Immediate Release (TD vs. IR)		
Oxybutynin TD vs. Oxybutynin IR		
Davila 2001	Starting dose assigned depending on prior oral oxybutynin dose of </= 10mg, 11-15mg, or >/= 20mg daily: Oxy TD 2.6mg, 3.9mg, or 5.2mg daily (2, 3 or 4 patches per day), patch applied twice weekly Oxy IR 10 mg, 15mg or 22,5mg total daily x 6 weeks Dose titrated up if no side effects after 2 weeks	Enrolled 76 Oxy TD = 38 Oxy IR = 38
Dmochowski 2003	Oxybutynin transdermal (Oxy TD) 3.9 mg/day (applied twice weekly) Tolterodine sustained release (Tol SR) 4 mg/day Placebo 12 wk treatment period	Enrolled 361 Oxy TD: 121 Tol SR: 123 Placebo: 117

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

Evidence Table 8. Short-term comparative studies: adverse effects

Author Year Setting	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Transdermal vs. Immediate Release (TD vs. IR)			
Oxybutynin TD vs. Oxybutynin IR			
Davila 2001	Oxy TD vs. Oxy IR Dry mouth: 15 (39%) vs. 31 (82%) (p<0.001) Reduction in severity of dry mouth vs prior treatment: 67% vs. 33% Worse dry mouth: 5% vs. 33% Constipation: 8 (21%) vs. 19 (50%) Somnolence 7 (18%) vs. 14 (37%) Blurred vision: 7 (18%) vs. 9 (24%) Impaired urination: 9 (24%) vs. 9 (24%)	Oxy IR: 1 (dry mouth) Oxy TD: 1 contact dermatitis due to patch	Fair Unvalidated questionnaire to evaluate titration for presence and severity of 10 symptoms assessed at 2, 4 and 6 wks.
Dmochowski 2003	Application site reactions: Oxy 32/121 (25.4%; 5% severe), Tol 7/123 (5.7%), Pla 8/117 (6.9%) Systemic adverse events: Oxy 23/121 (19%), Tol 29/123, Pla 14/117 (12%) Anticholinergic side effects (% only, numbers NR) Dry Mouth Oxy TD 4.1% vs Tol SR 7.3% Constipation Oxy TD 3.3%, Tol SR 5.7%	Oxy TD l= 13/121 (10.7%; 12 due to application site reaction, 1 hot flushes). Tol SR = 2/123 (1.6%; 1 fatigue, 1 dizziness).	Fair Method of assessment not reported

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

Evidence Table 9. Clinically significant drug interactions. [1]

	Flavoxate Hydrochloride	Oxybutynin Chloride	Tolterodine Tartrate	Darifenacin	Solifenacin Succinate	Trospium Chloride
Drugs affecting hepatic enzymes (CYP 450) Inhibitors of CYP2D6, CYP3A4	Not reported	Not reported	**No significant interaction. No action required.**[2]	**No dose adjustment needed for CYP2D6 and moderate CYP3A4 inhibitor.** Dosage should not exceed 7.5 mg when co-administered with potent CYP3A4 inhibitor.[6]	**Further studies needed.**[5]	Not reported
Fluoxetine	Not reported	Not reported	**No dose adjustment required**. May increase concentration of tolterodine by four fold.[2]	Not reported	Not reported	Not reported
Diuretics	Not reported	Not reported	**No significant interactions.**[1]	Not reported	Not reported	Not reported
Oral Contraceptives	Not reported	Not reported	**No significant interactions. No action required.**[2]	Not reported	Not reported	Not reported
Anticoagulants	Not reported	Not reported	**No significant interactions.**[2]	Not reported	Not reported	Not reported
Alcohol	Not reported	**Monitor**. Increased sedation with CNS depression.[2]	Not reported	Not reported	Not reported	Not reported
Antihistamines	Not reported	**Monitor**. Increased anticholinergic effects.[2]	Not reported	Not reported	Not reported	Not reported

Evidence Table 9. Clinically significant drug interactions. [1]

	Flavoxate Hydrochloride	Oxybutynin Chloride	Tolterodine Tartrate	Darifenacin	Solifenacin Succinate	Trospium Chloride
Macrolide antibiotics	Not reported	**Information not available.**[2]	Not reported	Not reported	Not reported	Not reported
Azole antifungal agents	Not reported	**No significant interaction**. Serum concentrations of oxybutynin increased three fold when coadministered with itraconazole. Half-life was unaffected and the interaction is of only minor significance.[3]	**Dose adjustment required**. May inhibit metabolism of tolterodine. Doses of >1mg twice daily should be avoided.[2]	Not reported	**Monitor.** Co-administration with a single 10 mg solifenacin dose increased solifenacin's concentration by 40%. Half-life increased by 55% and AUC increased by 100%.[5]	Not reported

1 AHFS Drug Information, ASHP, 2002.
2 Drug Information Handbook 7th Ed. Lexi-Comp, 1999-2000.
3 Benedetti et al. Drug Metabolism Reviews, 1999.
4 Epocrates Version 6.02, 2003.
5 Drug Facts and Comparisons, Wolters Kluwer Company. 2004.
6 Drugs@FDA, 2005.

Appendix A. Search Strategy

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:

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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:

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

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

Appendix B. Quality Assessment Methods for Drug Class Reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD. To ensure scientific rigor and relevance of the work, the Oregon EPC develops key questions and criteria for admissible evidence, and uses these to create a literature search strategy that best captures the appropriate evidence. To consider papers identified by the searches, the teams use the criteria for admissible evidence (explicit inclusion and exclusion criteria) to select papers that provide information to help answer the key questions. They abstract key data from these selected papers. The team's use established criteria to assess the internal validity of the evidence in each paper, as well as the total internal validity, external validity, and coherence of the evidence for each key question.

Key Questions and Inclusion/Exclusion Criteria

Key questions are essential in focusing the literature review on a manageable and clinically relevant topic. All key questions are reviewed and approved by the topic team in the process of assessing and refining the topic before the detailed literature review. The EPC teams work with the subcommittee members of the Oregon Health Resources Commission assigned to a particular drug class to finalize the key questions for that drug class.

We clearly document the criteria by which the team chooses to admit evidence on a given key question. Such criteria might include, for example, study design (e.g., randomized controlled trials, cohort studies), setting, sample size, population studied, language(s) of publication, and year(s) of publication.

No generic criteria for admissible evidence have been established. Rather, the criteria are determined on a topic-by-topic and key question-by-key question basis, depending on the questions involved and the amount and quality of evidence available. All inclusion/exclusion criteria are reviewed and approved by the entire topic team.

Databases to Be Searched and Documenting Search Terms

At a minimum, all topics include a review of the English-language literature in MEDLINE and EMBASE bibliographic databases and the Cochrane Controlled Trials Register. Other databases (e.g., nursing or psychology databases) are searched as deemed necessary by the topic team. Evidence reviews document the databases used.

Search terms used for each key question, along with the yield associated with each term, are documented in a table or set of tables; these appear in the final evidence review.

Database of Abstracts

The EPC, for each review, establishes a database of all abstracts (i.e., both those included and those eventually excluded from the final set of full-text articles reviewed). Information captured in the database includes the key question(s) associated with each included abstract and reason for exclusion if the abstract does not meet inclusion criteria.

Abstraction Forms

Although the EPC has no standard or generic abstraction form, the following broad categories are always abstracted from included articles: study design, study participant description, quality information, and outcomes. Each team uses these (and, if indicated, other) general categories to develop an abstraction form specific to the topic at hand.

Double Abstraction of Included Articles

The EPC teams abstract only those articles that, after review of the entire article, meet criteria for both quality and focus on the key question at hand. Key articles are always read and checked by more than one team member. All reviewers are trained in the topic, the analytic framework and key questions, and the use of the abstraction instrument. Initial reliability checks are done for quality control.

Quality Criteria

Assessment of Internal Validity
To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the US Preventive Services Task Force and the NHS Centre for Reviews and Dissemination.

For 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 numbers, birth dates or week days
    - 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
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record numbers, birth dates or week days
        - 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 the 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 (i.e., 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 followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Reports of Complications/Adverse Effects

Assessment of Internal Validity

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

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in 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 non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

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

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Economic Studies

Assessment of Internal Validity

Framing

1. Was a well-defined question posed in answerable form?

2. Was a comprehensive description of the competing alternatives given?

3. Are the interventions and populations compared appropriate?

4. Is the study conducted from the societal perspective?

5. Is the time horizon clinically appropriate and relevant to the study question?

Effects

1. Are all important drivers of effectiveness included?

2. Are key harms included?

3. Is the best available evidence used to estimate effectiveness?

4. Are long-term outcomes used?

5. Do effect measures capture preferences or utilities?

Costs

1. Are costs and outcomes measured accurately?

2. Are costs and outcomes valued credibly?

3. Are costs and outcomes adjusted for differential timing?

4. Are all appropriate downstream medical costs included?
5. Are charges converted to costs appropriately?
6. Are the best available data used to estimate costs? (like first question)
7. Are all important and relevant costs and outcomes for each alternative identified?

Results

1. Are incremental cost-effectiveness ratios presented?
2. Are appropriate sensitivity analyses performed?
3. How far do study results include all issues of concern to users?

Assessment of External Validity

1. Are the results generalizable to the setting of interest in the review?

Systematic Reviews:

1. Is the systematic review recent and relevant?
2. Is the review comprehensive in considering sources and in searching databases to find all relevant research?
3. Are inclusion/exclusion criteria reported relating to the primary studies that address the review question? If so, are they explicit and relevant?
4. Are the primary studies summarized appropriately?
5. Is sufficient detail of the primary studies presented?
6. Is there standard appraisal of the primary studies?
7. Is the validity of primary studies adequately assessed?
8. Are there valid conclusions in the systematic review?

Appendix C. 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.