Drug Class Review
on Urinary Incontinence Drugs

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INTRODUCTION

The International Continence Society (ICS) has defined urge urinary incontinence as the complaint of involuntary leakage of urine accompanied by or immediately preceded by urgency (a strong desire to void).[1] Urge incontinence is the most common form of incontinence and is often accompanied by the finding of involuntary detrusor contractions. This condition is known as detrusor instability, detrusor hyperactivity, or overactive bladder and is a urodynamic finding associated with (but not limited to) patients with neurological disorders. Detrusor instability can cause urgency and frequency with or without incontinence. Urinary continence relies heavily upon control and coordination of the smooth muscle found in the wall of the bladder. The effective storage of urine relies on detrusor muscle relaxation and contraction of internal and external sphincters found within the neck of the bladder while voiding is controlled through the contraction of the bladder's detrusor muscle and relaxation of its internal and external sphincters.[2] Bladder contraction is mediated via cholinergic muscarinic receptors in bladder smooth muscle. When a causative neurologic lesion is established (i.e. spinal cord injury), detrusor instability is known as hyperreflexia.[3]

While urge incontinence is not inevitable its incidence does increase with age.[4] It has been estimated that urinary incontinence affects 20% of community dwelling senior citizens and around 50% of the institutionalized elderly.[2, 4] Independent risk factors for the development of urinary incontinence include neurologic impairment, immobility, female gender and history of hysterectomy. It is common for urge incontinence to coexist with stress incontinence, especially in women. Institutionalized elderly are at risk of incontinence caused by detrusor hyperactivity combined with impaired bladder contractility (DHIC). Typically, however, symptoms of one form dominate.[3]

Treatment of urinary incontinence first requires a clear diagnosis of the type of incontinence. 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.[5] Pharmacological treatment for urinary incontinence includes flavoxate hydrochloride, oxybutynin chloride and tolterodine tartrate. Flavoxate hydrochloride acts as a direct spasmolytic on smooth muscle and maintains anticholinergic as well as local analgesic properties.[2, 6] Oxybutynin chloride has direct antispasmodic action on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle.[2, 6, 7] Finally tolterodine tartrate acts as a competitive muscarinic receptor antagonist.[2, 6, 8]

Scope and Key Questions

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

2. For adult patients with urinary urge incontinence/overactive bladder, do anticholinergic incontinence 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 incontinence 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 (2002, Issue 1), MEDLINE (1966-2002), EMBASE (1980-2002), 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). Subcommittee members were invited to provide additional citations. Pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the State of Oregon (http://www.ohppr.state.or.us /index.htm). All citations were imported into an electronic database (EndNote 5.0).

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 three anticholinergic urinary incontinence drugs (flavoxate, oxybutynin, or tolterodine) compared with another anticholinergic urinary incontinence drug, another incontinence drug (i.e., 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, and subjective patient 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 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.[9-11] 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 urinary incontinence drug against another provided direct evidence of comparative efficacy and adverse event rates. In theory, trials that compare these drugs to other drugs used to treat incontinence 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.

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, which were submitted to the Health Resources Commission in December 2001 and updated in February 2003. 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).[10, 11] 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.

RESULTS

Overview

Searches identified 507 citations: 95 from the Cochrane Library, 156 from MEDLINE, 221 from EMBASE, 6 from reference lists, and 29 from pharmaceutical company submissions. We included 33 randomized controlled trials, ten longer-term studies and one systematic review. Twenty-two studies were excluded for the reasons detailed in Figure 1. An additional 82 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 were repeated in October 2003, resulting in 99 new citations; 16 from the Cochrane Library, 26 from Medline, 38 from Embase, and 19 from PreMedline. In addition, one dossier was received from a pharmaceutical company. While 29 of these potentially met inclusion criteria, 8 reports of randomized controlled trials met inclusion; however three of these were re-analyses of data from trials previously included.[12-14] We excluded 9 studies for the reasons detailed in Figure 1. Additionally, we found 12 reports published in abstract form only.

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.

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

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

We found 18 head-to-head trials of oxybutynin, tolterodine, and/or flavoxate, and one re-analysis of a subgroup from a previously reported study. All included studies are summarized in Table 1. Study quality assessments are presented in Tables 2 and 3.

No good quality study was found. The only two flavoxate studies[15, 16], one study comparing oxybutynin IR and tolterodine IR[17] and one study comparing oxybutynin immediate and extended release[18], 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. Only five studies used an intention to treat analysis. The poor quality studies are not discussed here (see Tables 1, 2 and 3). 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. 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[19], and another analyzed the female subgroup of a larger trial.[12] Eight of 14 fair quality studies were conducted at least in part in the US, while the others were conducted primarily in European countries, and one each in China, and Japan and two in South Korea.

We found four fair quality studies comparing an immediate release formulation of one anticholinergic urinary incontinence drug to another.[19-21, 22] 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[19, 22] and 5mg three times daily in two.[21, 23] The study durations ranged from 8 to 12 weeks.

We found six fair quality studies comparing an extended release formulation of an anticholinergic urinary incontinence drug to an immediate release formulation.[24-29] Three studies compared oxybutynin ER to oxybutynin IR[26-28], one tolterodine ER to tolterodine IR[24] one study oxybutynin ER to tolterodine IR[30], 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 three 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.[26] The other two studies[27, 28] 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. All three 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.[24] 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 patients in 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.[25] 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.[31][Diokno, 2003 #860] In the first, oxybutynin was dosed at 5 to 10mg once daily and tolterodine at 2 to 4mg once daily. 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 second trial of the ER formulations of these two drugs[32](the OPERA trial) enrolled 790 women to take either tolterodine ER 4mg or oxybutynin ER 10mg daily for 12 weeks. The manufacturer of oxybutynin ER provided the funding for this study.

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.[33, 34] 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.[33] The other study randomized patients to 3.9mg/day TD or 4mg/day tolterodine ER. The manufacturer of the TD system funded both studies.

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[19] 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. No significant differences were found between the drugs, by intention to treat analysis, in any study.

Immediate release vs Extended release

A study of 10mg oxybutynin ER once daily or 5mg oxybutynin IR twice daily[26] used different outcome measures than the other studies: the proportion with day and nighttime *continence*, day/night micturition, and day/night incontinence episodes. No significant difference was found in the proportion with daytime continence (53% vs 58%). The results of other measures were not reported, but the authors reported no clinically significant differences between groups. The manufacturer of the extended release formulation funded the study. However the ER formulation used in this study is not available in the US. Although this study did not use an intention to treat analysis, and did not present enough data for one to be done here, only two patients were lost to follow up (one per group). The study was biased toward patients who tolerate oxybutynin IR. Out of 162 patients screened, 18 withdrew at screening and 17 during a run-in period using oxybutynin IR, 10 of those because of adverse events. Two studies[27, 28] 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)[28] and 6% (ER) and 8% (IR)[27] in, respectively. Alza, manufacturer of the oxybutynin ER formulation, funded both studies.

In a study of tolterodine ER 4mg once daily to tolterodine 2mg twice daily,[24] 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, so this result is not easily comparable. The fact that this underlying data had a skewed distribution also raises questions about the comparability between groups at baseline. 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.[12]

Oxybutynin ER was compared to tolterodine IR in one study.[25] 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.[29] 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.

Extended release vs Extended release

The OPERA trial[32]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 or mean change in micturitions per week. The proportion of patients with no incontinence in week 12 was significantly higher in the Oxybutynin ER group; 23% vs 17% in the Tolterodine ER group ($p = 0.03$). 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.[31]

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).[33] 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.[34] 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 reported some measure of success based on subjective patient assessments. Two studies[20, 21] 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,[20] 45% reported improvement on tolterodine and 41% on oxybutynin. In the study comparing tolterodine 2mg twice daily to oxybutynin 5mg three times daily,[21] 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. 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).[19] Overall symptom severity improved by 0.2 for tolterodine and 0.7 for oxybutynin. 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. 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.[22] In a per protocol analysis, 45% of tolterodine patients and 46% of oxybutynin patients reported much benefit at 8 weeks.

Immediate release vs Extended release

One study of Oxybutynin IR vs Tolterodine ER in Japanese and Korean women assessed subjective outcome measures.[29] 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%, deteriorated both groups 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. There was no significant difference on any domain in the quality of life assessment.

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[31] 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 UI (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.[33] 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".[34] 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.

b. In trials of anticholinergic incontinence 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. (Table 4).[35-40] Two used oxybutynin[39, 40] and four used flavoxate.[35-38] 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.[35] 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)[41-45] These trials are summarized in Table 5. Three of these appear to be reporting different outcomes from the same trial and will be treated as one study.[41, 43, 45] Two studies reported the mean change in number of micturitions per day (Oxy –2, and –2.1) or mean change in incontinence episodes per week (Oxy –

10.2).[41-43] These data are within the range reported in the head-to-head trials. The other studies report outcomes such as proportion with clinical cure (Oxy 73%) or change on Global Severity Index (Oxy 2.1), which were not used by other studies of oxybutynin, tolterodine or flavoxate.

We found ten placebo-controlled trials[46-54] and one systematic review[55] of anticholinergic incontinence drugs. The systematic review assessed the effectiveness of any anticholinergic incontinence drug compared to placebo, and did not present enough data to assess individual drugs. Seven of the trials that met inclusion criteria assessed tolterodine compared to placebo.[48-54] The results for these trials on mean change in number of micturitions or incontinence episodes per day are presented in Table 6. 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 -1.3. 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.

Only one study each was found comparing oral oxybutynin[47] and flavoxate[46] 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. [56]. 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 than 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.

Quality of life

Quality of life in patients with urge incontinence has been shown to be significantly lower than among the general US population.[57-59] 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,[30, 60] with one open-label extension study of tolterodine.[25] Quality of life of tolterodine IR and ER versus placebo was assessed in one randomized trial and one open label extension study.[13, 14, 61, 62] 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,[60] 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.[13, 14, 60-62]

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.[13, 14, 61, 62] 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.[62] The comparison of tolterodine ER to placebo also found improvements that favored tolterodine on six of ten domains on the KHQ.[13] 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.[14] 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.[13, 61]

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.

Another 12-week study comparing tolterodine and oxybutynin used the SF-36 and the IQoLI [63] 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.

Abstracts: Assessment of Publication Bias

In addition to the fully-published reports of head-to-head trials cited above, we found four studies that were published in abstract format only, at the time of writing (see Table 7).[64-67] Two of these may be interim analyses of included studies, and do not present enough data to compare to published studies.[65, 66] Three studies appears to be independent of the included studies.[64, 67] 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 of a urinary anticholinergic agent compared to another drug, and five placebo-controlled trials published in abstract form were also found. The results are comparable to results of fully published articles and are summarized in Table 7.

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

There are no long-term head-to-head studies designed to assess adverse events of the urinary anticholinergic incontinence drugs. No long-term studies of adverse effects of flavoxate were found. We found one study of prescription claims data that evaluated the discontinuation rate of new prescriptions for tolterodine or oxybutynin (see Table 8).[68] This 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.

We found four open label studies of tolterodine, one 12-week uncontrolled study[69] and three 9 to 12 month extension studies following RCTs.[25, 70, 71] Overall adverse event reporting was high (see Table 8). 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 classed as severe, while in the longer studies 2-3% were severe. 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[25, 71] reported that dry mouth accounted for only 1-2% of patients withdrawing overall.

In addition to these open label prospective studies, we reviewed two uncontrolled studies identifying patients by new tolterodine prescriptions.[72, 73] One study evaluated adverse events and tolerability over 12 weeks.[72] Only 4% of patients reported any adverse event, with dry mouth being the most common (2%). The other study[73]

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.

No long-term studies of oxybutynin were found. An open label 12-week study of oxybutynin reported 59% of patients with dry mouth, 23% moderate to severe.[74] Similar to the open-label tolterodine studies, withdrawals due to adverse events were 8% overall, 1.6% due to dry mouth.

Adverse events reported in short-term head-to-head trials are summarized in Table 9. 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. -0.28, 95% CI -0.34, -0.21). Two of these studies[22, 23] 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 reported severe dry mouth than those on tolterodine, but numbers were not reported. One additional study[19]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.

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 incidences of dry mouth and adverse events with the ER than IR formulation.[27, 28] These studies also reported a higher incidence of severe dry mouth with the IR formulation. 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 (see Figures 5 and 6).[26] 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.

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.[29] Overall adverse events were not reported in a way that could be directly compared.

The study of oxybutynin ER versus tolterodine IR found significantly fewer adverse events overall (risk difference –11%, 95% CI –18, -4) but 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. Tol 22.3%, p=0.02).[32] 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.[31] 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%, $p<0.001$).[33] 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 enrollment, 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.[34] Application site reactions were reported in 26% of the Oxybutynin TD group and 5.7% in the Tolterodine-placebo patch group.

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 reflects 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%.

In short-term head- to-head trials, the rate of withdrawal due to adverse events for tolterodine IR ranged from 5 to 15%, and for oxybutynin IR from 4 to 17%. 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.[21, 29, 31, 34] One study[25] 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%).[29] Three studies[24, 27, 28] 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.

In a fair quality study of Tolterodine ER and Oxybutynin ER[32] 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.[34] 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.

Drug Interactions

Clinically significant drug interactions are rare with the anticholinergic urinary incontinence drugs (see Table 10). Concomitant use of any of the three 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.[75] Dose reduction of tolterodine (to 1mg 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[76] compared Oxy IR vs Tol 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 Tol, 83% for Oxy). The other study[77] 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.[78]

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). One fair quality study enrolled only Chinese women.[19] 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[20, 22] of the IR formulations

including both men and women. A subgroup analysis of a previously reported study, assessing the subgroup of 1235 women only, from a study of Tolterodine IR vs Tolterodine ER. 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. 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.[73] 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) were 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.

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[19] 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).[79]

A study of patients from Japan and Korea[29] 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.

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.[75, 80-83]

SUMMARY AND DISCUSSION

Results for the key questions are summarized in Table 11

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.

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, Oxy ER vs Tol IR, Tol ER vs Oxy IR, Oxy IR vs Oxy ER, Tol ER vs Tol 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 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.

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 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 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 studies has some concerning methodological problems, 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. Since this studies has some concerning methodological problems, the results must be interpreted carefully.

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 Efficacy or Adverse Events in Subgroup: Oxybutynin versus Tolterodine

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.

Table 11. Summary of the Evidence

Key Question 1: Comparative Efficacy	**Quality 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 IR vs ER: Fair ER vs ER: Poor Flavoxate (Fla): Poor	Four studies of IR/IR found no difference in efficacy. Three 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.
What is the comparative efficacy of anticholinergic incontinence drugs across active and placebo controlled trials	Overall grade: Fair	UI 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. Drug versus Non-drug therapy: Four Oxy trials with results consistent to head to head trials. Placebo controlled trials: Six trials of Tol, two Oxy and one Fla. Results for Oxy and Tol show a greater effect than found in the head to head trials. Fla was not significantly better than placebo.
Key Question 2: Adverse Effects	**Quality of Evidence****	**Conclusion**
	Overall grade: Long-terms studies: Poor	The only 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.

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. The difference between drugs based on withdrawals is less clear.
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. There is insufficient evidence to indicate a difference between the UI 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

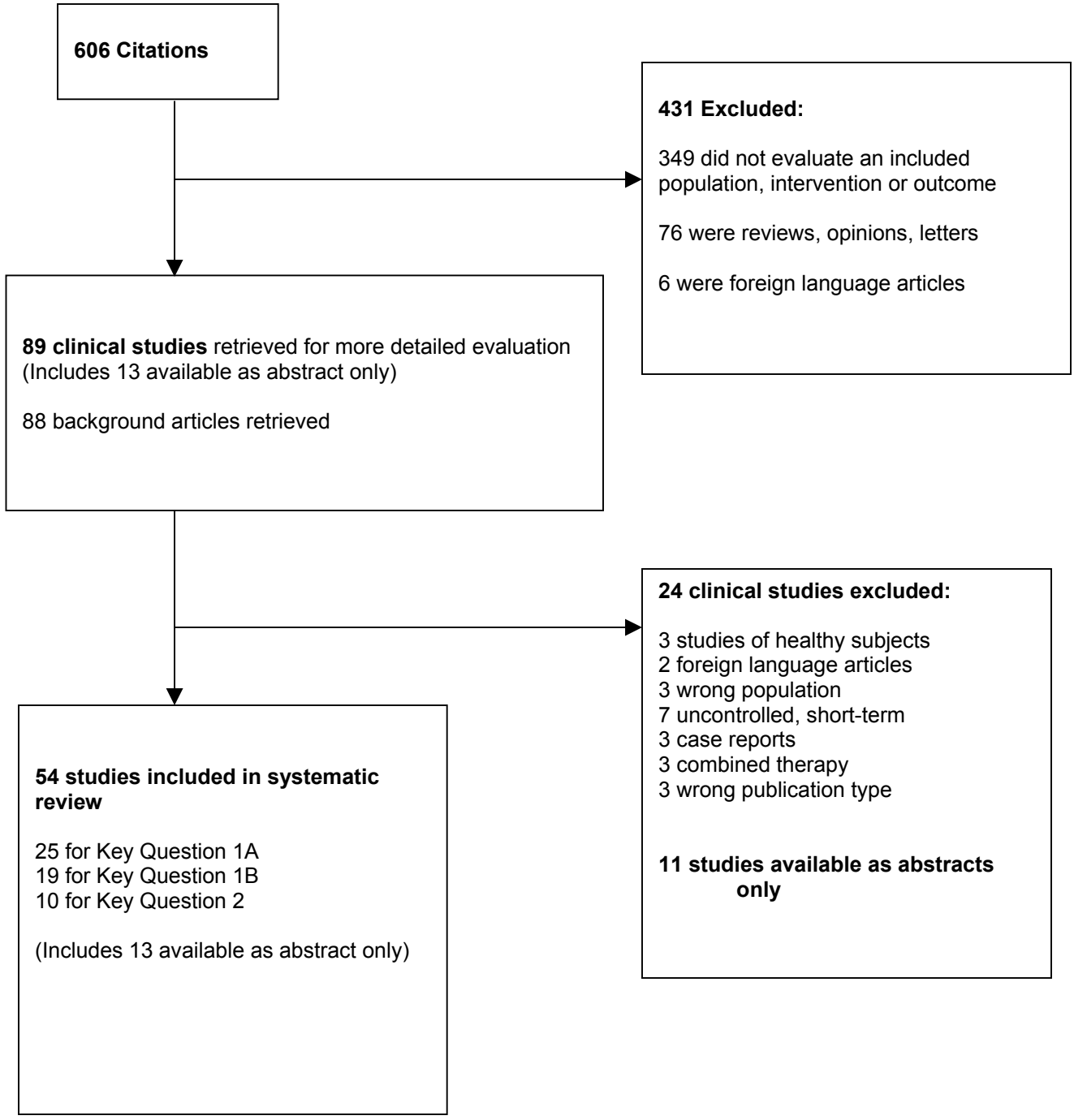

Figure 2. Incontinence episodes per day; IR versus IR

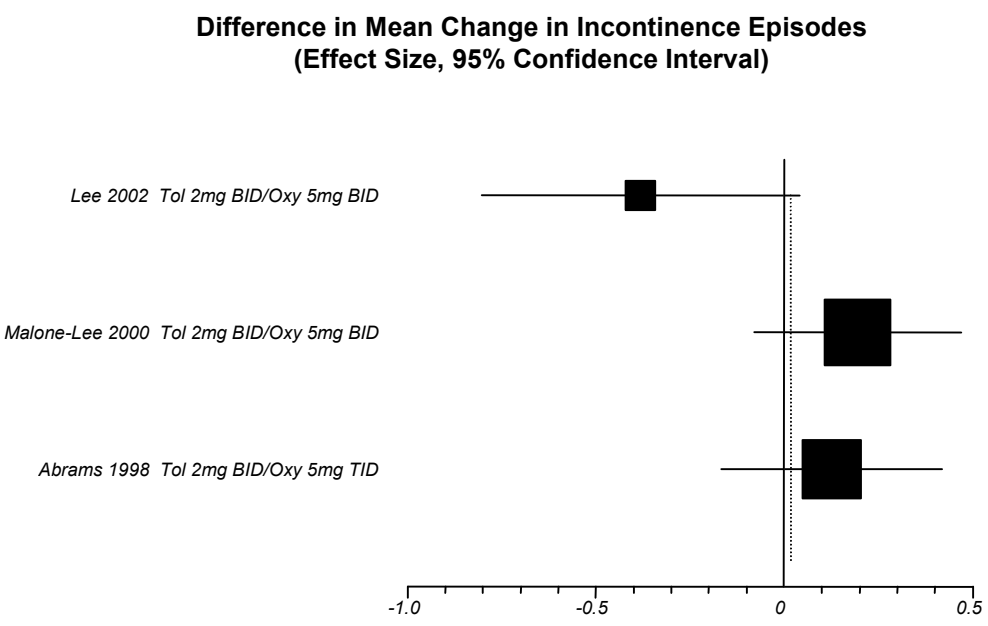

Figure 3. Micturations per day; IR versus IR

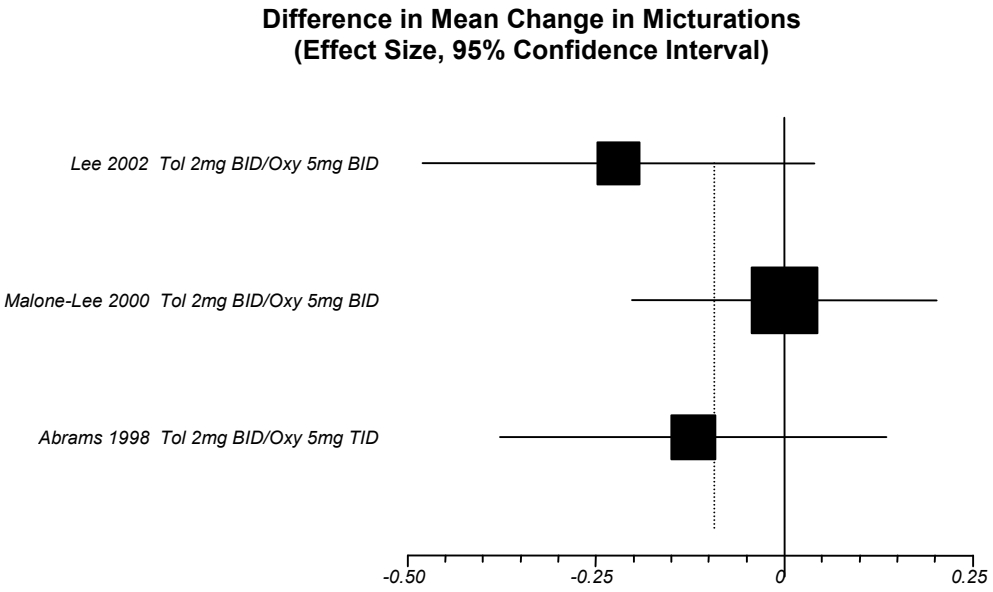

Figure 4. Tolterodine ER vs IR (Van Kerrebroeck 2001)

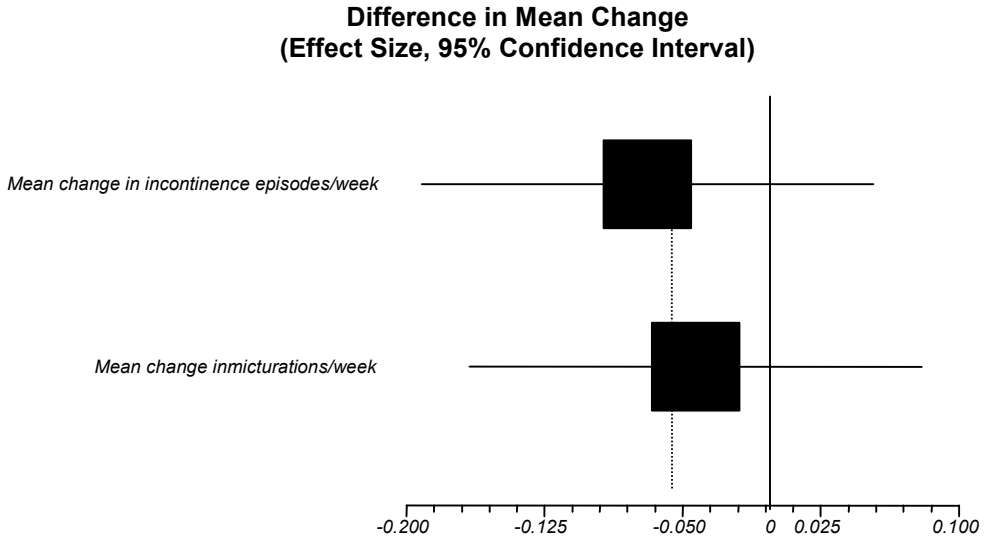

Figure 5. Difference in risk for any adverse event

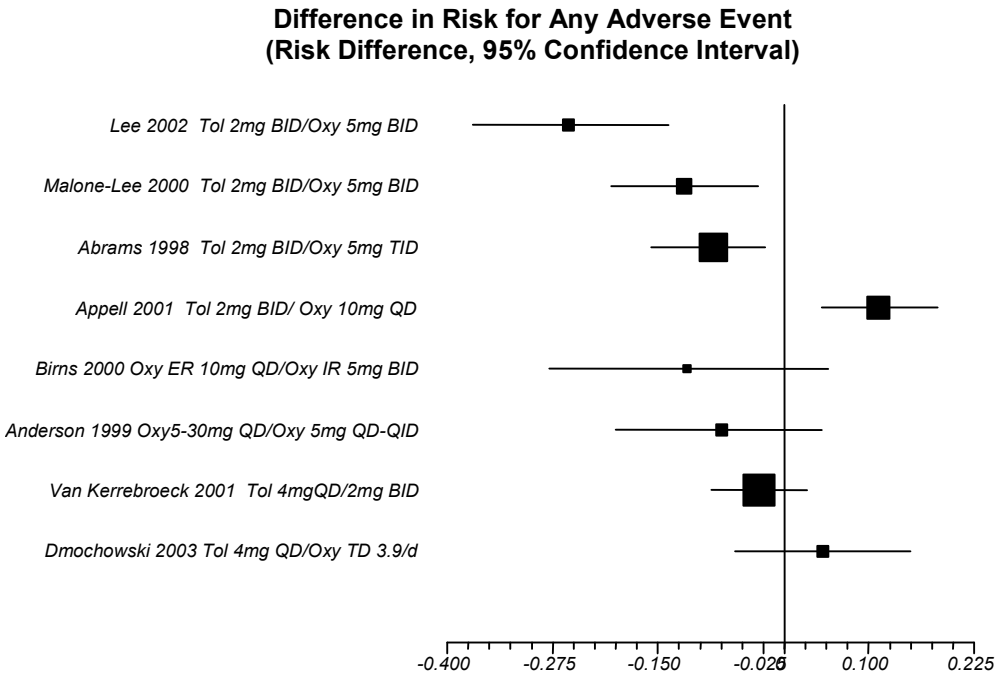

Figure 6. Difference in risk for dry mouth

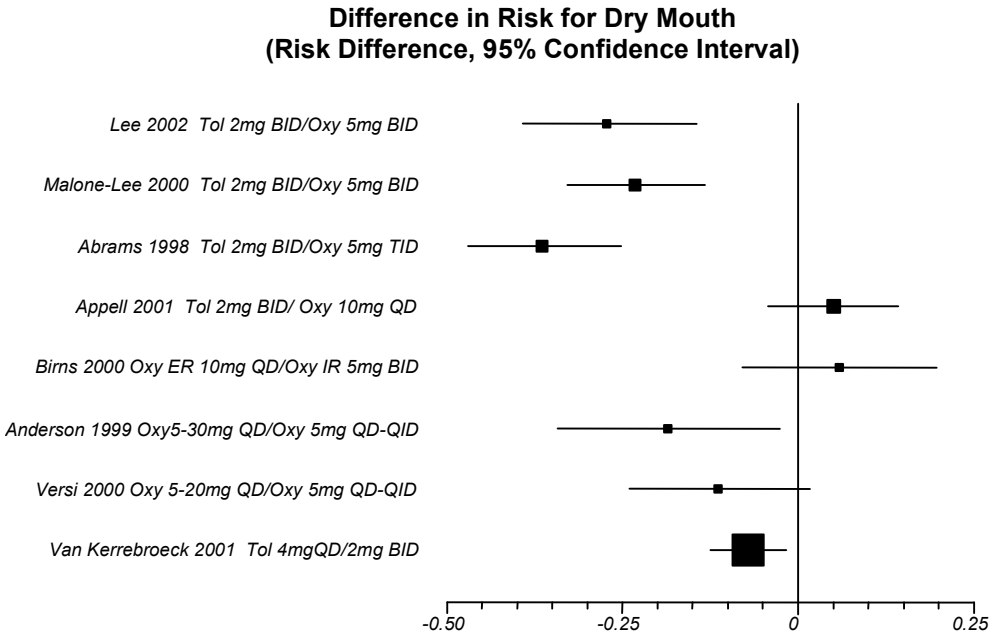

Figure 7. Risk of withdrawals due to adverse events

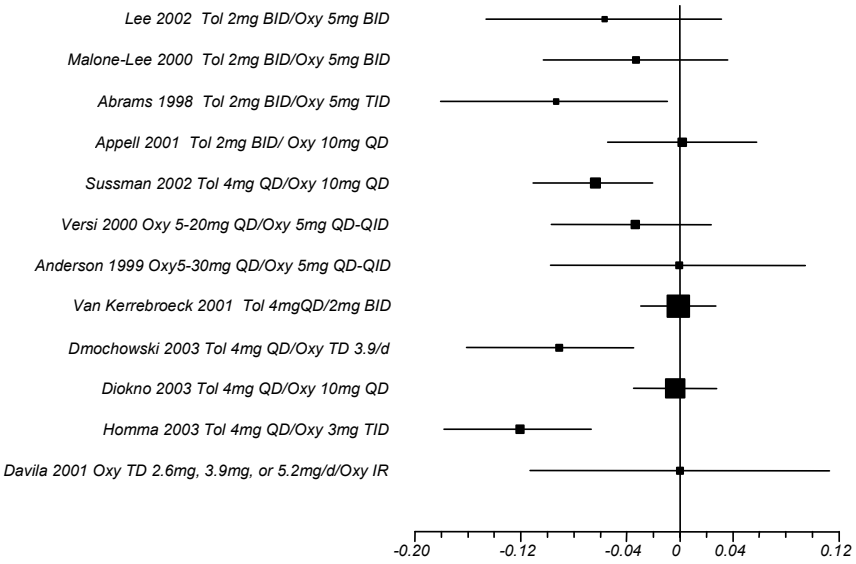

Table 1. Comparative clinical trials

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 centimeters 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Interventions (drug, regimen, duration)	Other interventions/ medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Age Gender Ethnicity
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)	Age range 43-63 yrs Median age 49.5 female
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. Compliane assessed by tablet count at 8 wks	228 enrolled (Tol 112, Oxy 116)	mean age 52 (range 20 to 86) 77% female

* 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/analyzed	Outcomes
Immediate Release vs Immediate Release (IR vs IR)			
Oxybutynin (Oxy) vs.Tolterodine (Tol)			
Leung 2002	56% postmenopausal, median parity 3	Withdrawals: Tol: 8 Oxy: 9 Number lost to follow-up not reported Number analyzed not clear	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	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	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

Table 1. Comparative clinical trials (continued)

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
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).	Compliance measured. Oxy 87.5% (11 to 99.3) Tol 75% (8.9 to 98.8) (NS)
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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Interventions (drug, regimen, duration)	Other interventions/medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Age Gender Ethnicity
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)	Age range 19-80 yrs Mean age Tol 55, Oxy 58, Pl 58 76% female
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)	mean age: Tol 63yrs, Oxy 66 yrs, placebo 62 yrs % female: Tol 81, Oxy 72, Placebo 80 % Caucasian: Tol 87, Oxy 94, Placebo 93

* 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/ analyzed	Outcomes
Abrams 1998	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'.	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	% 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	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

Table 1. Comparative clinical trials (continued)

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
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%	Dose reductions requested by 8% Tol, 32% Oxy, 2% Pl (Tol vs. Oxy p<0.001)
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%, plcebo 4% (p<0.001 Tol vs Oxy)	Tol 7 (6%), Oxy 23 (21%), placebo 4 (7%) (p = 0.002 Tol vs Oxy)	Only Allowed dose reductions in protocol, but then excluded these from analysis. Incomplete reporting of adverse events. 46 excluded from analysis due to protocol violations, but which groups assigned not reported.

* 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
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.	Severly 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Interventions (drug, regimen, duration)	Other interventions/medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Age Gender Ethnicity
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	mean age 51 (range 19 to 78) 100% female
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)	Age range 16-78 yrs Reported by center and by completer/noncompleter status rather than by treatment group. 70% female

* 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/ analyzed	Outcomes
Oxybutynin (Oxy) vs Flavoxate (Fla)			
Milani 1993	23 (46% sensory urge, 54% motor urge.	9 withdrawn: Fla: 3 poor compliance Oxy: 1 poor compliance, 5 side effects 41 analyzed	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	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	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

Table 1. Comparative clinical trials (continued)

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
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	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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Extended Release vs. Immediate Release (ER vs IR)			
Oxybutynin ER v 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Interventions (drug, regimen, duration)	Other interventions/medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Age Gender Ethnicity
Extended Release vs.Immediate Release (ER vs IR)					
Oxybutynin ER v 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	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
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	mean age: 56 yrs % female: 68% (ER 71%, IR 66%)

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Table 1. Comparative clinical trials (continued)

Author, Year	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/ analyzed	Outcomes
Extended Release vs.Immediate Release (ER vs IR)			
Oxybutynin ER v Oxybutynin IR			
Versi 2000	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	Mean change in urge incontinence episodes/wk: -15.7 ER, -15.4 IR (NS)
Birns 2000	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	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 clincally significant difference between treatment groups Exact information not given

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

Table 1. Comparative clinical trials (continued)

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
Extended Release vs.Immediate Release (ER vs IR)			
Oxybutynin ER v 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	Mean duration of treatment/follow-up not stated. Only dry mouth reported in detail.
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)	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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
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 questionaire), 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Interventions (drug, regimen, duration)	Other interventions/medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Age Gender Ethnicity
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	Mean age: ER 59yrs; IR 60yrs % Female: ER 94%, IR 90%
Nillsson 1997	Oxy ER 10mg once daily Oxy 5mg twice daily 60 days, no washout between arms	none reported	urinary diary, disability questionaire, 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	mean age 46yrs (range 37-65) 100% female

* 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/ analyzed	Outcomes
Anderson 1999	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)	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	none reported	1 "due to the sponsors' request" after first study period 16 analyzed in ER group, 17 in IR group	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

Table 1. Comparative clinical trials (continued)

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
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	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	Patients reported on a questionaire 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	Very high numbers of subjects reporting adverse events

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Table 1. Comparative clinical trials (continued)

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
Tolterodine ER vs. Tolterodine IR			
Van Kerrebroeck 2001	RCT Multicenter Multinational	Men or women, age 18+ with urinaryfrequency (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 obstruciton, 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 Multienter International	Subset of above study: women, age 18+ with urinaryfrequency (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 obstruciton, 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Interventions (drug, regimen, duration)	Other interventions/medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Age Gender Ethnicity
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	median age 60yrs 81% Female
Swift 2003	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	Mean age=59 All female 95% white 4% black 1% other

* 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/ analyzed	Outcomes
Tolterodine ER vs Tolterodine IR			
Van Kerrebroeck 2001	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%)	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	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%)	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

Table 1. Comparative clinical trials (continued)

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
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%)	Dry mouth classified as mild/moderate/severe but data only reported for ER
Swift 2003	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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Study Design Setting	Eligibility criteria	Exclusion criteria
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
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.

* 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Interventions (drug, regimen, duration)	Other interventions/medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Age Gender Ethnicity
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)	Mean Age: 59 yrs Female: 83% Ethnicity: White 87% African American 6% Hispanic 4% Asian 2% Other 1%
Tolterodine ER vs. Oxybutynin IR					
Homma 2003	Tol ER 4 mg once daily vs. Oxy IR 3 mg three times daily x 12 wks	Not allowed within 14 days of trial: anticholinergic drug or unstable dosage of any drug with anticholinergic side-effects, any drug for OAB (except estrogen started >2months), potent CYP3A4 inhibitors, or any investigational drug.	Voiding diary for 7 days at baseline and wk 12. Primary outcome, change in median number of incontinence episodes. Secondary endpoint, median number and volume of voids, number of incontinence pads used. Subjective assessment by 6-pt perception of bladder condition, 3-pt perception of urgency, and 3-pt assessment of treatment benefit. Quality of life measured by KHQ at baseline and 12 wks	Screened NR Eligible NR Enrolled = 608 Tol ER = 240 Oxy IR = 246 Pla = 122	Tol/Oxy grps Age range 26-84, mean age 59.3 Female 70.2% Ethnicity Japanese 48.2% Korean 51.8%

* 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/ analyzed	Outcomes
Oxybutynin ER v Tolterodine IR			
Appell 2001	Drug naïve Oxy ER 109 Tol 119	Overall 46 (21 Tol, 25 Oxy ER) Lost to Follow-up Oxy ER 3 Tol 3	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
Tolterodine ER vs. Oxybutynin IR			
Homma 2003	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	<u>Diaries percentage change</u> Median incontinence episodes: Tol -78.6% vs. Oxy -76.5% (p=0.4469)) Median number voids: Tol -2.0 vs. Oxy -2.1 (p=0.3132) Pad usage: median change was 0 in all groups. <u>Subjective measures</u> Improvement in bladder condition: Tol 72% vs. Oxy 73% (NS) Deterioration in bladder condition: Tol and Oxy 5% vs Pla 8% Improved ability to hold urine: Tol 49% vs. Oxy 57% Treatment beneficial (much): Tol 42% vs. Oxy 53% (NS) <u>KHQ quality of life</u> Tol vs. Oxy :no statistically significant differences on any domain

* 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

Table 1. Comparative clinical trials (continued)

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
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	
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.	Compliance ≥75% of medication: Tol 98% vs. Oxy 93%

* 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

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 $\geq$18, with documented 21-60 urge urninary incontinence episodes per week and avg $\geq$10 voids per day.	Treatable genitourinary conditions that could cause incontinence, 2 postvoid residual volumes >150 mL, pronoundced 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Interventions (drug, regimen, duration)	Other interventions/medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Age Gender Ethnicity
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)	Mean age 62.6 yrs Female 75% Caucasian 84% Black 10% Hispanic 5%
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	Mean age=60 All female Ethnicity: White 85% Black 8% Hispanic 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/ analyzed	Outcomes
Extended Release vs. Extended Release (ER vs ER)			
Oxybutynin ER vs.Tolterodine ER			
Sussman 2002	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	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	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	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

Table 1. Comparative clinical trials (continued)

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
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%).	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	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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

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 incontintent 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.
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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Interventions (drug, regimen, duration)	Other interventions/medications	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Age Gender Ethnicity
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	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	Mean age 63.5 Female 92% Ethnicity: White 95% Black 5%
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	Mean age 63.5 Female 92.8% White 94.5% Black 3.6% Other 1.9%

* 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 KHQ = King's Health Questionnaire

Table 1. Comparative clinical trials (continued)

Author, Year	Other population characteristics (diagnosis, etc)	Number withdrawn/ lost to fu/ analyzed	Outcomes
Transdermal vs. Immediate Release (TD vs. IR)			
Oxybutynin TD vs. Oxybutynin IR			
Davila 2001	NR	2/76 (2.6%) withdrawn before 4 wks	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)
Oxybutynin TD vs. Tolterodine SR			
Dmochowski 2003	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	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 disctress 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

Table 1. Comparative clinical trials (continued)

Author, Year	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
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. <u>Oxy TD vs. Oxy IR</u> 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	
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 fatique, 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 KHQ = King's Health Questionnaire

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

Table 2. Internal validity (continued)

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

Table 2. Internal validity (continued)

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

Table 2. Internal validity (continued)

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

Table 2. Internal validity (continued)

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

Table 2. Internal validity (continued)

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	Unclear	Attrition yes Adherence NR	Slightly more loss in Oxy group, including one death. Total loss 104/790 (13.2%)	Fair
Davila 2001	No, but only 1 drop out from each group	NR	Attirition: yes Adherence: "95% of expected use"	no	Fair
Dmochowski 2003	Yes	Unclear	Attrition overall 41/361 (11%) Adherence 92%	Unclear, not all withdrawals accounted for	Fair

Table 3. External validity

Author, Year	Similarity of study population to disease population	How many recruited vs enrolled	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Immediate Release vs Immediate Release						
Leung 2002	Relatively young population, age range 43-67.	Not reported	Diagnosis of stress incontinence, clinically significant voiding difficulty (max flow rate <10 ml/sec with residual volume of >200ml, recurrent or acute UTIs, require intermittent catheterization or an indwelling catheter, uninvestigated hematuria or bladder cancer, currently on treatment for an overactive bladder or on anticholinergic drugs, presence of psych disease or cognitive impairment, contraindications for antimuscarinic drugs. Patients underwent Mini Mental Status Exam and Electrocardiograph testing to rule out psychiatric or cardiovascular disease. Number for exclusion at each step unavailable	Oxy used at 5mg twice daily instead of three times daily (lower end of range), to reduce side effects.	10 weeks study duration, followed up 2 weeks after therapy to monitor side effects.	Pharmacia
Lee 2002	Good; older population, both male and female	Not stated	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. Number for exclusion at each step unavailable	yes	8 wks	Pharmacia

Table 3. External validity (continued)

Author, Year	Similarity of study population to disease population	How many recruited vs enrolled	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Malone-Lee 2000	Good; older population, both male and female	482 screened, 379 enrolled. Reasons for exclusion and larger population these drawn from not reported.	Significant stress incontinence, urinary outflow obstruction, symptomatic urinary infection, interstitial cystitis, unexplained hematuria, urinary catheterization, significant hepatic or renal disease, concomitant antimuscarinic medication, electrostimulation therapy or bladder training, treatment with Tol or Oxy in the 3 months before randomization and any investigational drug within 2 months. Number for exclusion at each step unavailable	Oxy used at 5mg twice daily instead of three times a day (lower end of range), and dose titrated up to reduce side effects. Dose allowed to be dropped if side effects occurred. No changes in Tol dose allowed.	Study duration 10 weeks, followed up 2 weeks after therapy to monitor side effects.	Pharmacia
Drutz 1999	Good; older population, both male and female	Not stated	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. Number for exclusion at each step unavailable	Yes	12 wks	Pharmacia
Abrams 1998	Good; older population, both male and female	Not reported	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 Number for exclusion at each step unavailable	Yes	12 week study duration plus 2 weeks side effects	Pharmacia
Milani 1993	unable to assess	Not stated	Severly ill, overt neurological disease, non-compliant, or taking drugs that could affect urinary symptoms. Number for exclusion at each step unavailable	Yes	4 weeks per drug	Recordati Spa, One author from company

Table 3. External validity (continued)

Author, Year	Similarity of study population to disease population	How many recruited vs enrolled	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Zeegers 1987	Unclear	60 consecutive	Kidney, liver or cardiovascular pathology, obstruction or infection, ongoing anticholinergic therapy, glaucoma or Parkinsons disease Number for exclusion at each step unavailable	Fla and Oxy - yes	3 week duration per drug	not stated
Immediate Release vs Extended Release						
Van Kerrebroeck 2001	Similar majority of pts women mean age around 60	Not stated	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,	Yes	12 wks treatment, 1 wk fu visit	Pharmacia
Appell 2001	Similar majority of pts women above age 58	Not stated	Other causes of incontinence, post void residual volume more than 150ml or delivered a baby, pelvic bladder, vaginal or prostate symptoms in past 6 months, risk of complete urinary retention, clinically important medical problems, organ abnormalities, hematuria	Yes	12 wks treatment	Alza one author from company
Birns 2000	Unable to draw conclusions	162 screened 130 randomized 128 completed study	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	Yes	4 wks	Leiras Oy, Pharmacia & Upjohn Author emplyed at Leiras Oy
Versi 2000	Majority of patients were women Ave age around 60 y/o Majority of pts were white	417 screened 226 enrolled 226 analyzed	Clinically significant medical problems, postvoid residual urine volume over 100ml, other conditions in which oxybutynin is contraindicated	Yes	Unknown	Alza

Table 3. External validity (continued)

Author, Year	Similarity of study population to disease population	How many recruited vs enrolled	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Nillsson 1997	Somewhat young population, only women	Not stated	Stress incontinence (as measured by questionaire), use of loop diuretics, prazosin, anticholinergics, or antidepressants with anticholinergic effects.	Yes	60 days - unclear when evaluations done	Leiras Oy (pharmaceuti cal company), second author worked for company
Anderson 1999	Majority of patients were women Mean age around 60	Screened 158 enrolled 105 93 complete data	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	Yes	Unknown	Alza
Homma 2003	All Asian	Screened NR Enrolled 608	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.	Yes	12 wks	Pharmacia Corp.
Swift 2003	International	NR 1235 enrolled	Demonstrable stress incontinence, total dily urine volume >3 L, any contraindications to antimuscarinic treatment, significant hepatic or renal disease, symptomatic or recurrent urinary tract infections, interstitial cystitis, hematuria or bladder outlet obstruction, current electrostimulation or bladder training therapy, indwelling catheter or intermittent self-catheterization, pregnant or nursing women, or fertile women not using reliable contraceptive methods.	Yes	12 wks	Pharmacia Corp.

Table 3. External validity (continued)

Author, Year	Similarity of study population to disease population	How many recruited vs enrolled	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Extended Release vs Extended Release						
Sussman 2002	Good; older population, both male and female	1289 consecutive patients enrolled, unclear how many attempted to recruit.	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 wk, indwelling or intermittent catheterization and any contraindication to antimuscarinic therapy. Number for exclusion at each step unavailable	Yes	8 weeks	Not Reported
Diokno 2003 OPERA	All female	Screened 1485 Eligible NR Enrolled 790	Treatable genitourinary conditions that could cause incontinence, 2 postvoid residual volumes >150 mL, pronoundced 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.	Yes	12 wks	ALZA corp & Ortho-McNeil. Several authors work for Ortho-McNeil, one for ALZA
Transdermal vs. Immediate Release						
Davila 2001	Poor - restricted to those already taking oral osybutynin	Recruited NR Enrolled 78	Allergy to oxybutynin, intolerable to transdermal, 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.	Yes	6 wks	Watson Laboratories
Transdermal vs. Extended Release						
Dmochowski 2003	No, prior use of pharmacologic treatment for overactive bladder	NR Enrolled 361		Yes	12 wks	Watson Pharma; authors attached to sponsor

Table 4. Anticholinergic UI drugs versus other drugs

Author, Year	Study Design Setting	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)	Other population characteristics (diagnosis, etc)	Eligibility criteria
Flavoxate						
Gruneberger 1984	RCT Single Center Germany	39 enrolled, others not reported	Mean age Fla 48, Cle 53 !00% female Ethnicity: not reported	Fla 200mg or Clenbuterol (Cle) 0.01mg three times daily x 6 weeks	Neurogenic cause: Fla 9 (47%), Cle 14 (70%) Mixed incontinence: Fla 3 (16%), Cle 3 (15%)	Not Reported
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	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 seconds once it had started; absent or minimal bladder suspension defect, not requiring incontinence surgery; maximum urinary flow rate above 15 ml/s; residual urine volume less than 50 ml following spontaneous voiding; mid-stream urine culture showing less than 10^5 colonies per ml

Table 4. Anticholinergic UI drugs versus other drugs (continued)

Author, Year	Exclusion criteria	Number withdrawn/ lost to fu/ analyzed	Method of outcome assessment and timing of assessment	Outcomes	Adverse effects assessed? How assessed	Withdrawals due to adverse events
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	Subjective assessments (not described)	Patients assessment: Cured/Improved: Fla 11 (58%), Cle 15 (75%)	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	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	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	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

Table 4. Anticholinergic UI drugs versus other drugs (continued)

Author, Year	Study Design Setting	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)	Other population characteristics (diagnosis, etc)	Eligibility criteria
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	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	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	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
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	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

Table 4. Anticholinergic UI drugs versus other drugs (continued)

Author, Year	Exclusion criteria	Number withdrawn/ lost to fu/ analyzed	Method of outcome assessment and timing of assessment	Outcomes	Adverse effects assessed? How assessed	Withdrawals due to adverse events
Bradley 1970	Not Reported	Withdrawals: Fla 2(8%); both due to adverse events Pro 2 (9%); 1 dizziness, 1 lost to follow-up	Subjective assessments: rating scale ranging from 'no change' to 'complete recovery'	"Complete" improvement in: Frequency: Fla 6(29%), Pro 4(38%); Urgency: Fla 7(35), Pro 2(14%) Nocturia: Fla 4(27%), Pro 1(7%);	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 Reported	Not Reported	Not Reported	Good to excellent therapeutic response: Fla 50%, Pro 30% (p-value not reported)	Not clear. Dry mouth/throat: Fla 1, Pro 13; Blurred vision: Fla 0, Pro 1; Difficulty in urinating: Fla 0, Pro 1; Drowsiness: Fla 0 Pro 1; Headache: Fla 0 Pro 1 Difficulty in concentrating: Fla 1 Pro 0 Dizziness: Fla 1 Pro 0	Not Reported
Oxybutynin						
Holmes 1989	Not Reported	Unclear	Daytime frequency: measured in total voids over 3 days; Nocturia: measured by total voids over 3 nights range; Incontinence: rated using linear analogue scale	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	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

Table 4. Anticholinergic UI drugs versus other drugs (continued)

Author, Year	Study Design Setting	Number screened/ eligible/ enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)	Other population characteristics (diagnosis, etc)	Eligibility criteria
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	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

Table 4. Anticholinergic UI drugs versus other drugs (continued)

Author, Year	Exclusion criteria	Number withdrawn/ lost to fu/ analyzed	Method of outcome assessment and timing of assessment	Outcomes	Adverse effects assessed? How assessed	Withdrawals due to adverse events
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	Bladder diary	Mean change in frequency per day: Oxy -2.4, Prov -1.9, Pl -1	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

Table 5. Anticholinergic UI drugs versus non-drug therapy

Author, Year	Study Design Setting	Number screened/ eligible/enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)	Other population characteristics (diagnosis, etc)
Goode 2002	RCT Single site USA	486 screened, 197 randomized/105 analyzed	Mean age 67	Oxy 2.5mg or Pl three times daily, increasing by 2.5mg once daily to max 5mg three times 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	48% mixed type incontinence Severity of urinary incontinence: 54% severe, 20% mild Previous drugs 28%
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	See Goode 2002
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	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

Table 5. Anticholinergic UI drugs versus non-drug therapy (continued)

Author, Year	Eligibility criteria	Exclusion criteria	Number withdrawn/ lost to follow-up/ analyzed	Method of Outcome Assessment and Timing of Assessment
Goode 2002	Age 55+, 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.	92 excluded from analysis: 28 did not complete treatment, 64 did not undergo post-treatment cystometry	Bladder diary
Burgio 2001	See Goode 2002	See Goode 2002	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"
Burgio 1998	Patients aged 55 years or older; 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)	24 withdrew/0 lost to f/u/190 analyzed	Bladder diaries, patient satisfaction and overall evaluation of perceived improvement questionnaires (2 wks post-treatment),

Table 5. Anticholinergic UI drugs versus non-drug therapy (continued)

Author, Year	Outcomes	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
Goode 2002	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%	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	Change in Global Severity Index: Oxy 2.1, Beh 3.4, Pl 1.0 (p = 0.26)	See above	See above	This is a subgroup analysis from the Burgio study, of those completing psychological analysis.
Burgio 1998	Change in incontinence episodes: Oxy 10.2/wk Beh 13/wk (p = 0.04 vs. Oxy) Pl 7/wk (p = 0.009 vs. Oxy)	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	

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

Table 5. Anticholinergic UI drugs versus non-drug therapy (continued)

Author, Year	Study Design Setting	Number screened/ eligible/enrolled	Age Gender Ethnicity	Interventions (drug, regimen, duration)	Other population characteristics (diagnosis, etc)
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.	Mean functional capacity 154
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	Detrusor instability: Oxy=14, Beh=13; Low-compliance bladder: Oxy=9, Beh=8; Sensory bladder: Oxy=15, Beh=16

Table 5. Anticholinergic UI drugs versus non-drug therapy (continued)

Author, Year	Eligibility criteria	Exclusion criteria	Number withdrawn/ lost to follow-up/ analyzed	Method of Outcome Assessment and Timing of Assessment
Soomro 2001	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	Not Reported	Voiding diary, Bristol urinary symptom questionnaire and Quality of Life questionnaire
Colombo 1995	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	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

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

Table 5. Anticholinergic UI drugs versus non-drug therapy (continued)

Author, Year	Outcomes	Adverse effects assessed? How assessed	Withdrawals due to adverse events	Comments
Soomro 2001	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	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	Clinical cure: Detrusor instability group: Oxy=93%, Beh=62% Low-compliance bladder group Oxy=67%, Beh=75% Sensory bladder group: Oxy=60%, Beh=81%	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

Table 6. Tolterodine versus placebo

Author Year	Dose	Mean Change in Number of Micturitions/24h		Mean Change in Number of Incontinence Episodes/24h	
		Tolterodine (n)	*Placebo* (n)	*Tolterodine* (n)	*Placebo* (n)
Rentzhog 1998	2mg BID	↓20% (not given)	Not reported	↓46% (not given)	Not reported
Jacquetin 2001	2mg BID	↓1.4 (103)	↓1.2 (51)	↓1.3 (79)	↓0.4 (39)
Malone-Lee 2001	2mg BID	↓0.7 (73)	0 (42)	↓0.7 (51)	0 (33)
Van Kerrebroeck 1998*	2mg BID	↓0.1 (17)	↓0.1 (16)	↓2.4 (17)	↓1.9 (16)
Millard 1999	2mg BID	↓2.3 (129)	↓1.4 (64)	↓1.7 (117)	↓1.3 (55)
Chancellor 2000	2mg BID	↓1.7 (514)	↓1.2 (507)	↓10.6 (514)	↓6.9 (507)
Zinner 2002	4mg QD <65y/o	↓2 (292)	↓1.4 (284)	↓12† (292)	↓7.4† (284)
	4mg QD +65y/o	↓1.4 (214)	↓0.9 (223)	↓11.5† (214)	↓6.3† (223)
Kelleher 2002	Tol ER 4 mg/day	NR	NR	↓15.7 (507)	↓8.9 (508)
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

*Study of patients with detrusor hyperreflexia, † Incontinence episodes per *week*

Table 6a. Transdermal oxybutynin versus placebo

Author Year	Dose	Median Change in Number of Micturitions/24h		Median Change in Number of Incontinence Episodes/24h	
		Oxybutynin TD (n)	*Placebo* (n)	*Oxybutynin TD*	*Placebo*
Dmochowksi 2002	1.3 mg/day	↓1.8 (130)	↓1.7 (132)	↓15.0 (NS)	↓14.5
	2.6 mg/day	↓1.7 (133)		↓14.0 (NS)	
	3.9 mg/day	↓2.3 (125) (p=0.0457)		↓19.0 (p=0.0165)	
	applied twice/week				

Table 7. Assessment of abstracts for publication bias

Author Year	Interventions(Drug, dose, sample size)	Micturitions mean change *(time period)*	Urge incontinence episodes mean change *(time period)*
Head-to-head			
Van Kerrebroeck 1997	A: Tolterodine 2 mg BID *(n=120)* B: Oxybutynin 5 mg TID *(n=120)*	A: -2.1 B: -2.7 *(unclear)*	A: -1.7 B: -2.1 *(unclear)*
Lee 2001	A: Tolterodine 2 mg BID (n=112) B: Oxybutynin 5 mg BID (n=116)	A: -2.6 B: -1.8 (24 hours)	A: -2.2 B: -1.4 (24 hours)
Schmidt 1998	A: Oxybutynin-XL 15 mg/day *(n=33)* B: Oxybutynin-IR 15 mg TID *(n=32)* C: Placebo *(n=15)*	Not reported	Mean percent reduction *(weekly)* A: 92% B: 72% C: 45%
Sand 2001	A: Oxybutynin-XL 10 mg/day *(n=nr)* B: Tolterodine 4 mg BID *(n=nr)* *(total n=382)*	Not reported	Not reported
Tolterodine vs. Active Control			
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
Placebo controlled			
Garely 2001	A: Tolterodine 4 mg OD *(n=507)* B: Placebo *(n=508)*	Median % decrease A: 17% B: 11%	Median % decrease A: 71% B: 33%
Millard 1997	A: Placebo B: Tolterodine 1 mg BID C: Tolterodine 2 mg BID *(n=unclear)*	A: -1.4 B: -2.3 C: -2.2 *(unclear)*	A: -1.3 B: -1.7 C: -1.8 *(unclear)*
Jonas 1997	A: Tolterodine 1 mg BID *(n=99)* B: Tolterodine 2 mg BID *(n=99)* C: Placebo *(n=44)*	A: -0.6 B: -1.4 C: -1.7 *(24 hours)*	A: -1.5 B: -1.1 C: -1.6 *(24 hours)*
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)*

**Data not provided*

Table 7. Assessment of abstracts for publication bias

Author Year	Interventions(Drug, dose, sample size)	Micturitions mean change *(time period)*	Urge incontinence episodes mean change *(time period)*
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%
Moore 1997	Same as Millard, 1997		

Comparative Observational Studies

Author Year	Interventions(Drug, dose, sample size)	Duration of Assessment	Discontinuation Rate
Boccuzzi 2002	Oxybutynin IR Tolterodine IR	12 months	Oxy 83% Tol 76%
Taira 2002			
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*

Table 8. Observational studies: adverse events

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria	Interventions	Number screened/ eligible/ enrolled
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.	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)
Michel 2002	Multicenter Germany	Open label, uncontrolled, cohort 12 weeks	Tol prescription	None specified	Tol - varying doses. Mean dose 2mg twice daily	2250 enrolled
Layton 2001	Multicenter UK	Cohort 6 months	Tol prescription	None specified	Tol - varying doses. Median dose 4mg/day	35,295 new prescriptions for Tol between April and December 1998 26,991 General Practitioners sent forms to complete 14,526 forms returned

Table 8. Observational studies: adverse events (continued)

Author, Year	Age Gender Ethnicity	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events	Comments
Tolterodine (Tol)					
Siami 2002	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	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	Mean age 61 yrs 77% female	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
Layton 2001	Mean age 62.7 69% female	General Practitioners completed forms requesting information such as age, gender, diagnosis, duration of treatment, and any significant events, any suspected drug reactions, and reasons for stopping drug if stopped, and to indicate if any adverse events were considered to be drug related.	Dry Mouth: 423 events (2.9%), 80 adverse drug reaction (0.5%) Headache/migraine 260 events (1.8%), 29 adverse drug reaction (0.19%) UTI 397 events (2.7%), 1 adverse drug reaction (.006%) Other adverse events judged to be temporarily related to drug: malaise, constipation, dyspepsia, dizziness, nausea and vomiting and pain in the abdomen (1-2% incidence) Uncommon symptoms found related to Tol: Hallucinations .06% (mean age 79, range 70 to 92 and 89% female) Palpitations/tachycardia: 0.12% (mean age 65, range 53-74) Chest pains 0.14% (mean age 67, range 33-79)	697 (4.8%) withdrawals due to adverse effects reported: dry mouth 250 unspecified 168 headache 123 constipation 78 general malaise 78	Analysis took into account the timing of the event, events occurring more distant from starting the drug were considered less likely to be drug-related.

Table 8. Observational studies: adverse events (continued)

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria	Interventions	Number screened/ eligible/ enrolled
Appell 2001	Multicenter (multinational)	Open label 9 month study	Patients completing 12 week RCT enrolled after 1-week washout period.	None specified	Tol 2mg twice daily	939 eligible/854 enrolled
Abrams 2001	Multicenter (multinational)	Open label 12 months study	Patients completing 4wk RCT enrolled after 4-week washout period.	None specified	Tol 2mg twice daily	895 elgible/714 enrolled
Kreder 2002	Multicenter (multinational)	Open label 12 month study	Patients completing 12 wk RCT enrolled	None specified	Tol ER 4mg once daily (no dose adjustments allowed)	1337 eligible/1077 enrolled

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

Table 8. Observational studies: adverse events (continued)

Author, Year	Age Gender Ethnicity	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events	Comments
Appell 2001	Age Range 19-89 Mean 60yrs 76% female	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%)	
Abrams 2001	Age range 18-92 Mean age 60yrs 69% female	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	Age range 20-93 Mean age 60 yrs 82% female	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%)	

Table 8. Observational studies: adverse events (continued)

Author, Year	Setting	Study Design	Eligibility criteria	Exclusion criteria	Interventions	Number screened/ eligible/ enrolled
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.	Oxy ER 5 to 30mg/day	Number screened not reported. 256 enrolled
Oxybutynin (Oxy) vs. Tolterodine (Tol)						
Lawerence 2000	Pharmacy Benefit Management Database USA	Pharmacy Claims Data for April - December 1998	New prescription for Tol or Oxy	Terminated coverage with plan, received more than 30 day supply, incomplete data	Tol or Oxy (IR)	1531 eligible/1020 analyzed

Table 8. Observational studies: adverse events (continued)

Author, Year	Age Gender Ethnicity	How adverse effects assessed	Adverse events reported	Withdrawals due to adverse events	Comments
Oxybutynin (Oxy)					
Gleason 1999	38.9% >65 yrs 91% female 92% white	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	
Oxybutynin (Oxy) vs. Tolterodine (Tol)					
Lawerence 2000	Median age Tol 73 (range 18-93), Oxy 70 (range 18-95) % female: Tol 68%, Oxy 97%	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%		

Table 9. Short-term comparative studies: adverse effects

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled	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	Tol 2mg twice daily Oxy 5mg twice daily	106 enrolled	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	Tol 2mg twice daily Oxy 5mg twice daily	228 enrolled (Tol 112, Oxy 116)	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	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	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

Table 9. Short-term comparative studies: adverse effects (continued)

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
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)	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	Tol 2mg twice daily Oxy 5mg three times daily Placebo three times daily Dose reduction allowed	277 enrolled (Tol 109, Oxy 112, Placebo 56)	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%, plcebo 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.
Oxybutynin (Oxy) vs Flavoxate (Fla)					
Milani 1993 Italy	Fla 400mg or Oxy 5 mg three times daily, then crossover	50 enrolled	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

* 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

Table 9. Short-term comparative studies: adverse effects (continued)

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
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)	Combined in score 15% Pl, 26% Emp, 8% Fla, 17% Oxy	Overall 20% 2 Pl, 8 Emp, 0 Fla, 2 Oxy	Poor
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	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	Oxy ER 10mg once daily or Oxy 5mg twice daily	162 screened 130 randomized	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 abnomality 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

* 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

Table 9. Short-term comparative studies: adverse effects (continued)

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
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	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
Nillsson 1997 Finland	Oxy ER 10mg once daily Oxy 5mg twice daily crossover	17 enrolled	Patients reported on a questionaire 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
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	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

* 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

Table 9. Short-term comparative studies: adverse effects (continued)

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
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	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)
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)	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
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	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

* 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

Table 9. Short-term comparative studies: adverse effects (continued)

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled	Number of adverse effects	Withdrawals due to adverse events	Quality rating and Comments
Extended Release vs. Extended Release (ER vs ER)					
Oxybutynin ER vs.Tolterodine ER					
Sussman 2002 USA	Tol ER 2mg or 4mg once daily Oxy ER 5mg or 10mg once daily	1289 enrolled 669 Tol (333 Tol 2mg, 336 Tol 4mg) 620 Oxy (313 Oxy 5mg, 307 Oxy 10mg)	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%).	Fair 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	Oxy ER 10 mg/day vs. Tol ER 4 mg/day x 12 wks	Enrolled 790 Oxy ER= 391 Tol ER = 399	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

Table 9. Short-term comparative studies: adverse effects (continued)

Author Year Setting	Interventions (drug, regimen, duration)	Number Enrolled	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	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	<u>Oxy TD vs. Oxy IR</u> 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	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	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 fatique, 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

Table 10. Clinically significant drug interactions [1]

	Flavoxate Hydrochloride	Oxybutynin Chloride	Tolterodine Tartrate
Drugs affecting hepatic enzymes (CYP 450) Inhibitors of CYP2D6, CYP3A4	Not reported	Not reported	**No significant interaction. No action required.**[2]
Fluoxetine	Not reported	Not reported	**No dose adjustment required.** May increase concentration of tolterodine by four fold[2]
Diuretics	Not reported	Not reported	**No significant interactions.**[1]
Oral Contraceptives	Not reported	Not reported	**No significant interactions. No action required.**[2]
Anticoagulants	Not reported	Not reported	**No significant interactions.**[2]
Alcohol	Not reported	**Monitor.** Increased sedation with CNS depression.[2]	Not reported
Antihistamines	Not reported	**Monitor.** Increased anticholinergic effects.[2]	Not reported
Macrolide antibiotics	Not reported	**Information not available.**[2]	Not reported
Azole antifungal agents	Not reported	**No significant interaction.** Serum concentrations of oxybutynin increased three fold when coadministered with itraconazole. However, 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]

[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.

Appendix A. Search Strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2002>
Search Strategy:
1 (oxybutinin or tolterodine or flavoxate).ti. (105)
2 from 1 keep 1-105 (105)

Database: MEDLINE
Search Strategy:
---
1 flavoxate.mp. or exp FLAVOXATE/ (125)
2 (tolterodine or oxybutinin).mp. (154)
3 1 or 2 (274)
4 limit 3 to human (218)
5 limit 4 to english language (182)
6 4 not 5 (36)
7 limit 6 to abstracts (18)
8 5 or 7 (200)
9 from 8 keep 1-200 (200)

Database: EMBASE Drugs & Pharmacology <1991 to 4th Quarter 2002>
Search Strategy:
---
1 oxybutinin.mp. or exp Oxybutynin/ (1194)
2 tolterodine.mp. or exp TOLTERODINE/ (364)
3 flavoxate.mp. or exp FLAVOXATE/ (214)
4 1 or 2 or 3 (1360)
5 limit 4 to human (1215)
6 limit 5 to english language (936)
7 5 not 6 (279)
8 limit 7 to abstracts (117)
9 6 or 8 (1053)
10 randomized controlled trial$.mp. (59792)
11 randomised controlled trial$.mp. (1276)
12 Controlled Study/ (892678)
13 controlled clinical trial$.mp. (3347)
14 10 or 11 or 12 or 13 (898901)
15 9 and 14 (235)
16 exp retrospective study/ (11916)
17 exp *OXYBUTYNIN/ae, to [Adverse Drug Reaction, Drug Toxicity] (153)
18 exp *TOLTERODINE/ae, to [Adverse Drug Reaction, Drug Toxicity] (67)
19 exp *FLAVOXATE/ae, to [Adverse Drug Reaction, Drug Toxicity] (12)
20 17 or 18 or 19 (198)

21 16 and 20 (1)
22 drug interaction.mp. or exp Drug Interaction/ (21644)
23 9 and 22 (21)
24 exp oxybutinin/it or exp tolterodine/it or exp flavoxate/it (37)
25 limit 24 to human (33)
26 evaluation studies.mp. or evaluation/ or drug evaluation.mp. or exp drug evaluation/ (19307)
27 9 and 26 (15)
28 15 or 21 or 23 or 25 or 27 (270)
29 from 28 keep 1-270 (270)

Appendix B: Methods for Drug Class Reviews for Oregon Health Plan Practitioner-Managed Prescription Drug Plan

Oregon Evidence-based Practice Center

December 14, 2001
Updated February 4, 2003

Overview

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, in developing drug class reviews for the Oregon Health Plan Practitioner-Managed Prescription Drug Plan.

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 teams 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?