Drug Class Review on Urinary Incontinence Drugs

EXECUTIVE SUMMARY

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Overview

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). Urge incontinence is the most common form of incontinence. Urge incontinence 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 that is 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 within 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. 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 know as hyperreflexia.

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

Treatment of urinary incontinence requires first a clear diagnosis of the type of incontinence, and if a mixed picture 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. 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. Oxybutynin chloride is characterized as having direct antispasmodic action on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Finally tolterodine tartrate acts as a competitive muscarinic receptor antagonist.
Reporting the Evidence

The key questions for this review were:

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?

Methodology

To identify relevant literature, we searched several electronic databases (e.g., the Cochrane Controlled Trials Registry, MEDLINE, and EMBASE) and references from retrieved articles and from material submitted by pharmaceutical manufacturers. Title and abstract were reviewed for each article to determine potential eligibility. Included were English-language reports of randomized controlled trials, in 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. 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. Characteristics of included head-to-head trials are presented in an evidence table and also described in the narrative.

We assessed the internal validity (quality) of trials and observational studies using predefined criteria based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK). External validity of trials was assessed based on the adequacy of the publication’s description of the study population, the representativeness of patients to the target population, and whether the control group treatment resembled that of standard practice. In addition to discussion of the findings of the studies overall, meta-analyses were conducted where possible. Results are reported as differences between the drugs in mean change in number of micturitions or incontinence episodes per day or per week and differences in adverse event rates and withdrawals due to adverse events.
Findings

We included 33 randomized controlled trials, seven longer-term uncontrolled studies and one systematic review. 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 there were studies that 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.

Evidence of Comparative Efficacy

We found 14 head to head trials of oxybutynin, tolterodine, and/or flavoxate. No good quality study was found. The only two flavoxate studies, one study comparing oxybutynin IR and tolterodine IR and one study comparing oxybutynin immediate and extended release 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. Studies determined to be poor quality are not discussed or included in analyses. Thus, no studies of flavoxate were included.

The included studies had similar eligibility and exclusion criteria, enrolling largely patients with only or predominantly urge incontinence. Some studies enrolled patients with hyperreflexia, but the proportions were small. 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, both of which reflect the typical characteristics of the population with urge incontinence.

Immediate release vs Immediate release. We found four fair quality studies comparing an immediate release formulation of oxybutynin to an immediate release of tolterodine. No significant differences in mean change in numbers of incontinence episodes per day or micturitions per day were found between the drugs, by intention to treat analysis, in any study.

With regard to symptoms and overall assessment of benefit, all four studies reported some measure of success based on subjective patient assessments. Two studies using a six-point scale of symptom severity (0 = no problems, 6 = severe problems) found no statistical significant differences between tolterodine 2mg twice daily and oxybutynin 5mg twice or three times daily. Using a per-protocol analysis, a study of Chinese women found that patients taking tolterodine rated severity of symptoms using a visual analog scale (VAS) statistically significantly lower than those taking oxybutynin. These differences were not statistically significant by intention to treat analysis. Finally, in a study of tolterodine 2mg twice daily versus oxybutynin 5mg twice daily, there was no statistically significant difference in the proportion of patients reporting “much benefit” after 8 weeks of treatment.
Immediate release vs Extended release. We found five fair quality studies comparing an extended release formulation of an anticholinergic urinary incontinence drug to an immediate release formulation.

One study of 10mg oxybutynin ER once daily or 5mg oxybutynin IR twice daily reported that no significant difference was found in the proportion with daytime continence (53% vs 58%). This study used a formulation of Oxy ER that is not available on the US market.

Two studies 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.

In a study of tolterodine ER 4mg once daily to tolterodine 2mg twice daily, no significant differences were found in mean absolute change in micturitions or incontinence episodes per week, number of urinary pads used per day, or overall withdrawal. An analysis of the median percent change in incontinence episodes did find a significant difference (p<0.05) favoring Tol ER. This is an unusual analysis that was not used in any other study.

In a final study using analysis of covariance that adjusted for baseline and stratum, 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) than tolterodine IR. However, because this analysis was not intention to treat and the proportions of patients excluded from the analysis are 14% in the oxybutynin ER group and 11% in the tolterodine group, the analysis presented may not reflect reductions in efficacy due to dropouts.

None of the five studies assessed subjective outcome measures.

Extended release vs Extended release. Only one study comparing extended release formulations of oxybutynin and tolterodine to each other was found. This study did not report on incontinence episodes and micturitions per 24 hours. This study used an unusual design, the study centers were allocated to either Oxy or Tol by the investigators, and then patients were randomized to dose (higher/lower) of the assigned drug.

Assessments of level of symptoms and overall assessment of benefit were reported. Using the 6-point scale described about, significantly more patients were improved on tolterodine 4mg a day compared to tolterodine 2mg and oxybutynin 5mg and 10mg (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). This finding may actually reflect confounding or selection bias, however, as a number of baseline differences discussed in detail in the review are not accounted for in the analysis.

Evidence of Comparative Efficacy: Anticholinergic incontinence drugs across active and placebo controlled trials

Incontinence episodes and micturitions per 24 hours. 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 USA. All but one trial were rated poor primarily because of
lack of important details such as eligibility and exclusion criteria. The trial that met fair quality criteria found that patients taking flavoxate experienced a mean change in number of micturitions per day for flavoxate of +1 when compared to −0.5 for those on Emepronium and −1 for those on Placebo. The mean change in the number of incontinence episodes per day was −1 for flavoxate (Emepronium -1, Placebo –2).

We found five studies comparing oxybutynin to non-drug therapy (bladder training, electrostimulation therapy) Three of these appear to be reporting different outcomes from the same trial and will be treated as one study. 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). 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 nine placebo-controlled trials and one systematic review 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. 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 oxybutynin and flavoxate to placebo that met our inclusion criteria. While actual data were not reported for the oxybutynin study, an analysis showed that a dose of 2.5mg twice daily to be better than placebo at reducing daytime frequency (p = 0.0025), but not incontinence. The flavoxate study found no difference between a dose of 200mg and placebo in the mean change in number of micturitions per day (-0.292, p = 0.95).

Quality of life. Quality of life in patients with urge incontinence has been shown to be significantly lower than among the general US population. 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)

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, and one open label extension study of tolterodine. Quality of life of tolterodine versus placebo was assessed in one randomized trial and one open label extension study. 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, 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. In the tolterodine versus placebo 12-week trial, the improvements in the tolterodine group were statistically significantly better than with placebo. These improvements were maintained, and improved after 3 months and 12 months open label treatment. 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 a tool developed for women with urge incontinence, the IQoLI. 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 three studies that were published in abstract format only, at the time of writing. Two of these may be interim analyses of included studies, and do not present enough data to compare to published studies. One study appears to be independent of the included studies. The 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 the size of effect reported.

One study of a urinary anticholinergic agent compared to another drug, and four placebo-controlled trials published in abstract form were also found. The results are comparable to results of fully published articles.

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. Only one longer-term, comparative observational study was included. A high discontinuation rate was found for both drugs at six-months based on prescription claims data, but statistically significantly higher for oxybutynin IR (68% Tol, 78% Oxy, p<0.001). In four 3- to 12-month uncontrolled, open-label studies rates of overall adverse events, dry mouth, and withdrawal due to adverse events for oxybutynin and tolterodine were similar.

Short-term comparative trials demonstrate that overall adverse event and dry mouth rates were significantly higher for oxybutynin IR compared to tolterodine IR. The proportion reporting any adverse events and dry mouth in particular 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, the change in severity of dry mouth was significantly worse with oxybutynin.
Withdrawals due to adverse effects may be the more important measure in assessing adverse events. Two of eight studies found statistically significantly more patients withdrew in the oxybutynin arms. 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 comparing the ER versus IR formulations of either drug did not show a significant difference in the withdrawal rate. The one study comparing the ER formulations reported a statistically significant difference in withdrawals favoring tolterodine. However, because this study has some concerning methodological problems, the results must be interpreted carefully.

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 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 compares oxybutynin and tolterodine, but does not state what formulations were included. This study reports that by Cox regression, the risk of discontinuation was statistically 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.

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.