

Drug Class Review on Overactive Bladder

Update #4: Preliminary Scan Report 2

March 2008

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

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

Update scan prepared by Susan Severance, MPH



OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

Update # 3, December 2005 (searches through July 2005)

Date of Last Update Scan

March 2007

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Questions

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

Inclusion Criteria

Population

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

Interventions

Active ingredients	Form	Brand name
Darifenacin	Oral tablet	Enablex
Flavoxate hydrochloride	Oral tablet	Urispas
Hyoscyamine sulfate	Oral tablet	Levsin
Oxybutynin chloride	Oral tablet and syrup	Ditropan
Oxybutynin chloride	Extended release oral tablet	Ditropan XL
Oxybutynin	Transdermal system	Oxytrol
Scopolamine (hyoscine) butylbromide	Oral tablet	Buscopan
Solifenacin succinate	Oral tablet	Vesicare
Tolterodine tartrate	Oral tablet	Detrol
Tolterodine tartrate	Extended release oral capsule	Detrol LA
Trospium chloride	Oral tablet	Sanctura

Effectiveness outcomes

- Change in mean number of incontinence episodes/24 h
- Change in mean number of micturitions/24 h
- Change in mean number of pads/24 h
- Subjective patient assessments of symptoms (i.e. severity of problems caused by bladder symptoms, extent of perceived urgency, global evaluation of treatment)
- Quality of life

Safety outcomes

- Overall adverse effects reported
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events or withdrawals due to specific adverse events (e.g., dry mouth)

Study designs

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

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from February 2007 through March Week 3, 2008, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/index_e.html) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 67 citations. Of those, there are 8 new potentially relevant trials (see Appendix A, attached). Table 1 provides details of the treatment comparisons addressed in the new trials.

Table 1. Summary of new trials identified in Scan #2

Study	Treatment comparisons
Chapple 2007	Darifenacin vs placebo in older adults
Chapple 2007	Tolterodine ER vs placebo
Chapple 2007	Solifenacin vs tolterodine ER (STAR study)
Dmochowski 2007	Tolterodine ER vs placebo
Dmochowski 2007	Tolterodine ER vs placebo
Robinson 2007	Tolterodine ER vs placebo
Staskin 2007	Trospium chloride vs placebo
Yamaguchi 2007	Solifenacin succinate vs placebo

Taken together with the 20 trials identified in the first preliminary update scan (Table 2), there are now a total of 28 trials to consider in deciding whether or not a full update is warranted.

Table 2. Summary of new trials identified in Scan #1

Study	Treatment comparisons
Hill 2006	Darifenacin vs placebo
Zinner 2006	Darifenacin vs placebo
Zinner 2005	Darifenacin vs placebo
Anderson 2006	Oxybutynin ER vs tolterodine ER

Armstrong 2005	Oxybutynin ER vs tolterodine ER
Fader 2007	Oxybutynin vs intravesical atropine
Wang 2006	Oxybutynin vs placebo
Karademir 2005	Oxybutynin+SANS vs SANS alone
Kelleher 2006	Solifenacin vs placebo
Chapple 2005	Solifenacin vs tolterodine ER (STAR study)
Kaplan 2006	Tolterodine ER vs placebo
Nitti 2006	Tolterodine ER vs placebo
Roehrborn 2006	Tolterodine ER vs placebo
Rackley 2006	Tolterodine ER vs placebo (night-time dosing)
Horstmann 2006	Tolterodine ER vs trospium
Song 2006	Tolterodine vs bladder training
Junemann 2005	Tolterodine vs propiverine
Kaplan 2006	Tolterodine vs tamsulosin
Rudy 2006	Trospium chloride vs placebo
Rudy 2006	Trospium chloride vs placebo

New Drugs

Trospium chloride (Sanctura XR) was approved 8/3/07 as an extended release oral capsule formulation.

New Indications

No new indications were identified.

New Safety Alerts

New information was added to the product safety labels for one drug. Details of these changes are listed in the table below.

Drug	Source	Date of change	Type of change	Details
solifenacin	FDA	Date: 7/07	Label Change: Adverse Reactions	VESIcare (solifenacin succinate) Tablets ADVERSE REACTIONS Postmarketing Surveillance Central Nervous Hallucinations

Appendix A. Abstracts of potentially relevant new trials of drugs to treat overactive bladder

Chapple, C., C. DuBeau, et al. (2007). "Darifenacin treatment of patients \geq 65 years with overactive bladder: results of a randomized, controlled, 12-week trial." *Current Medical Research & Opinion* 23(10): 2347-58.

BACKGROUND: Overactive bladder (OAB) increases in prevalence with advancing age. This study specifically investigated patients \geq 65 years, evaluating the efficacy, tolerability, safety and quality of life (QoL) outcomes from darifenacin treatment. **METHODS:** Patients (n = 400, mean age 72 years) with OAB were randomized (2:1) to receive 12 weeks of double-blind treatment with darifenacin (7.5 mg once daily for 2 weeks, then optional titration to 15 mg daily) or placebo (with sham titration). Efficacy, tolerability and safety were assessed from patient diary data, adverse events and discontinuations and QoL outcomes using specific questionnaires. **RESULTS:** Mean urgency urinary incontinence episodes (UUIEs) decreased significantly from baseline to Week 12 with both darifenacin (-88.6%) and placebo (-77.9%; $p > 0.05$), with 70% and 58% patients responding with \geq 50% reductions, respectively ($p = 0.021$). This was accompanied by significant differences between groups in reductions in micturition frequency (-25.3% with darifenacin vs. -18.5% placebo; $p < 0.01$). QoL assessments revealed significant improvements with darifenacin versus placebo at Week 12 in OAB-q, Patient Perception of Bladder Condition, and patient and physician assessments of treatment benefit (all $p < 0.001$). The most commonly reported adverse events were dry mouth and constipation. **CONCLUSIONS:** This study demonstrated that marked improvements in OAB symptoms can be achieved in patients \geq 65 years, with significant treatment differences in responder rates, micturition frequency and QoL. Reduction in UUIEs may not be the optimal endpoint in this population, whereas QoL appears to be a sensitive and relevant patient-oriented measure of treatment effect.

Chapple, C., P. Van Kerrebroeck, et al. (2007). "Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder." *European Urology* 52(4): 1204-12.

OBJECTIVE: To determine the efficacy, tolerability, and safety of fesoterodine in subjects with overactive bladder (OAB). **METHODS:** This was a multicentre, randomised, double-blind, placebo- and active-controlled trial with tolterodine extended release (ER) to assess the efficacy and safety of fesoterodine. Eligible subjects (\geq 18 yr) with increased micturition frequency and urgency and/or urgency urinary incontinence (UUI) were randomised to placebo, fesoterodine 4 mg, fesoterodine 8 mg, or tolterodine ER 4 mg for 12 wk. The primary efficacy variable was a change from baseline to week 12 in micturitions per 24 h. Co-primary end points included change from baseline to week 12 in UUI episodes per 24 h and Treatment Response ("yes" or "no," based on four-point treatment benefit scale). Secondary efficacy variables included mean volume voided per micturition, continent days per week, and number of urgency episodes. **RESULTS:** At the end of treatment, subjects taking fesoterodine 4 and 8 mg had significant ($p < 0.05$) and clinically relevant improvements versus placebo in the primary, co-primary, and most secondary efficacy variables. Tolterodine ER (active control) also provided significantly greater improvement than placebo for most efficacy variables, confirming the sensitivity of the study design. A more pronounced effect was observed with fesoterodine 8 mg at most end points. **CONCLUSIONS:** Both doses of

fesoterodine were significantly better than placebo in improving the symptoms of OAB and produced a significantly greater Treatment Response versus placebo. Efficacy was more pronounced with fesoterodine 8 mg compared with the other treatments. Active treatments were well tolerated.

Chapple, C. R., A. Fianu-Jonsson, et al. (2007). "Treatment outcomes in the STAR study: a subanalysis of solifenacin 5 mg and tolterodine ER 4 mg." *European Urology* 52(4): 1195-203.

OBJECTIVE: To compare OAB symptom outcomes following initial randomised treatment with solifenacin 5 mg or tolterodine ER 4 mg at the 4-week clinic-visit and again at 12 weeks for patients choosing to remain on this treatment dose from 4 weeks. **METHODS:** A prospective, double blind, double-dummy, two-arm, parallel-group, 12-week study (The STAR study) was conducted to compare the efficacy and safety of solifenacin 5/10 mg and tolterodine extended release (ER) 4 mg in OAB patients. **RESULTS:** At 4 weeks mean improvements in OAB symptoms, including urgency, frequency (primary variable), incontinence and nocturia, were larger in patients randomised to solifenacin 5 mg; with the difference for incontinence being statistically significant (mean reduction in incontinence episodes/24 hrs in the solifenacin group of -1.30 vs. -0.90 (p=0.0181); the mean result for solifenacin 5 mg amounted to a 44% additional improvement.) There was an associated significant reduction in pad use (reduced by -1.21 vs. -0.80; p=0.0089); the mean result for solifenacin 5 mg amounted to a 51% additional improvement over that of tolterodine ER 4 mg. For patients choosing to remain on these treatments improvements in favour of solifenacin were maintained at study end (12-weeks). Treatments were well tolerated. **CONCLUSIONS:** Within 4 weeks solifenacin 5mg was statistically significantly better than tolterodine ER 4 mg in improving incontinence and reducing incontinence pad use. Differences in efficacy in favour of solifenacin 5 mg were maintained from 4 weeks for the duration of the study for patients choosing to remain on their starting dose.

Dmochowski, R., P. Abrams, et al. (2007). "Efficacy and tolerability of tolterodine extended release in male and female patients with overactive bladder." *European Urology* 51(4): 1054-64; discussion 1064.

OBJECTIVES: To evaluate the efficacy and tolerability of tolterodine extended release (ER) in men and women with overactive bladder (OAB). **METHODS:** We analyzed data from two 12-wk, placebo-controlled trials of tolterodine ER (4mg QD). Patients completed 7-d bladder diaries and rated the urgency sensation associated with each micturition on a 5-point urgency rating scale. Micturitions were categorized by urgency rating: total (1-5), non-OAB (1-2), OAB (3-5), or severe OAB (4-5). Changes in micturitions during 24-h, daytime, and nocturnal intervals were assessed. **RESULTS:** At baseline, 73% (547 of 745) of men and 57% (539 of 953) of women were continent. By week 12, tolterodine ER (n=848) reduced OAB and severe OAB micturitions during 24-h, daytime, and nocturnal intervals in both sexes compared with placebo (n=850). Adverse event rates were low and similar across treatment and gender. **CONCLUSIONS:** In men and women with OAB, tolterodine ER reduced OAB and severe OAB micturitions, and was well tolerated.

Dmochowski, R., K. Kreder, et al. (2007). "The clinical efficacy of tolterodine extended-release is maintained for 24 h in patients with overactive bladder." *BJU International* 100(1): 107-10.

OBJECTIVE: To assess the 24-h efficacy of tolterodine extended-release (ER) in patients with overactive bladder (OAB) and urgency urinary incontinence (UUI). **PATIENTS AND METHODS:** We conducted a post hoc analysis of a 12-week, placebo-controlled trial of tolterodine-ER in patients with frequency ($>$ or $=8$ voids/24 h) and UUI ($>$ or $=5$ episodes/week) for $>$ or $=6$ months. Seven-day bladder diaries were used to record diary endpoints; 24-h diary data were stratified by 6-h periods beginning at midnight. **RESULTS:** Compared with placebo (508 patients), tolterodine-ER (507 patients) significantly and consistently increased volume voided per void and reduced UUI episodes and micturition frequency during each interval. **CONCLUSIONS:** These results indicate that tolterodine-ER maintained clinical efficacy over 24 h and should be effective for OAB symptoms without regard to whether symptoms occur during the day or at night.

Robinson, D., L. Cardozo, et al. (2007). "A randomized double-blind placebo-controlled multicentre study to explore the efficacy and safety of tamsulosin and tolterodine in women with overactive bladder syndrome." *BJU International* 100(4): 840-5.

OBJECTIVES: To evaluate the efficacy of tamsulosin oral-controlled absorption system (OCAS) vs placebo in overactive bladder (OAB), to evaluate the safety and tolerability of once-daily dosing with tamsulosin OCAS, and to compare the efficacy and safety with tolterodine extended-release (ER). **PATIENTS AND METHODS:** A parallel-group, multicentre, multinational study was conducted with a single-blind placebo run-in period of 2 weeks, followed by a randomized, double-blind, double-dummy active and placebo-controlled treatment period of 6 weeks; women (aged 18-70 years) with symptoms of OAB for ≥ 3 months were recruited. Women were randomized to receive one of four doses of tamsulosin OCAS (0.25, 0.5, 1.0 or 1.5 mg), 4 mg of tolterodine ER, or placebo once daily for 6 weeks. The primary efficacy variable was the change in the mean number of voids/24 h. Secondary efficacy variables included change from baseline in: mean volume voided per void, mean number of incontinence episodes/24 h, mean number of urgency episodes/24 h and in quality of life (QoL), as assessed using the Kings Health Questionnaire (KHQ). **RESULTS:** Overall, 364 women were randomized; the primary efficacy analysis showed that the difference from placebo in the mean number of voids/24 h was not statistically significant for tamsulosin OCAS 1.5 mg ($P = 0.189$). There was no statistically significant difference for tolterodine ER 4 mg vs placebo in the mean number of voids/24 h ($P = 0.353$). Similarly, for the secondary outcome variables there was no statistically significant difference between tamsulosin and placebo. Although women taking tolterodine ER 4 mg had a consistently greater increase in mean voided volume/void and consistent decreases in incontinence episodes/24 h, urgency episodes/24 h and episodes of nocturia/24 h, this was not statistically significant. There was no significant improvement in QoL scores across the treatment groups. Tamsulosin OCAS was well tolerated and the proportion of women discontinuing because of adverse events was low (4.7%). **CONCLUSION:** Tamsulosin is not effective for treating OAB in women and the evidence from this study does not support its use on an empirical basis.

Staskin, D., P. Sand, et al. (2007). "Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial." *Journal of Urology* 178(3 Pt 1): 978-83; discussion 983-4.

PURPOSE: An extended release formulation of trospium chloride was recently developed for the once daily treatment of overactive bladder. We investigated the safety, efficacy and tolerability of 60 mg trospium chloride once daily. **MATERIALS AND METHODS:** Subjects with overactive bladder were randomized 1:1 to receive 60 mg trospium chloride once daily or placebo in this 12-week multicenter, parallel, double-blind, placebo controlled trial. Primary end points were calculated changes in diary recorded daily urinary frequency and daily urgency urinary incontinence episodes. Secondary end points were urgency severity, volume voided per void and the number of urgency voids per day. Safety was assessed by clinical examination, adverse event monitoring, clinical laboratory values and resting electrocardiograms. **RESULTS:** Overall 601 subjects were prescribed trospium once daily (298) or placebo (303). Trospium once daily treatment resulted in significant improvements over placebo in all primary and key secondary efficacy outcomes at weeks 1 through 12. The most common adverse events were dry mouth (trospium 8.7% vs placebo 3%) and constipation (trospium 9.4% vs placebo 1.3%). Central nervous system adverse events were rare (headache with trospium 1.0% vs placebo 2.6%). No clinically meaningful changes in laboratory, physical examination or electrocardiogram parameters were noted. **CONCLUSIONS:** Trospium once daily provided significant improvements in overactive bladder symptoms (frequency, urgency urinary incontinence and urgency). Efficacy was similar to that seen previously with trospium chloride twice daily, while class effect anticholinergic adverse events occurred at comparatively low levels. Dry mouth was elicited at the lowest reported rate in the oral antimuscarinic drug class.

Yamaguchi, O., E. Marui, et al. (2007). "Randomized, double-blind, placebo- and propiverine-controlled trial of the once-daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder." *BJU International* 100(3): 579-87.

OBJECTIVES: To compare solifenacin succinate (5 and 10 mg once-daily) to placebo and propiverine hydrochloride (20 mg once-daily), respectively, in Japanese patients with overactive bladder syndrome (OAB). **PATIENTS AND METHODS:** A multicentre, 12-week, double-blind phase III trial randomized men and women aged \geq 20 years with OAB to solifenacin 5 or 10 mg, propiverine 20 mg, or placebo. Changes at endpoint in number of voids/24 h, urgency, incontinence, urgency incontinence and nocturia episodes, volume voided/void, restoration of continence and quality of life (QoL) were examined. **RESULTS:** Of 1593 patients randomized, 1584 were treated; at the endpoint there were greater reductions in mean (sd) voids/24 h with solifenacin 5 mg, at -1.93 (1.97), and 10 mg, at -2.19 (2.09), and propiverine 20 mg, at -1.87 (2.70), than with placebo, at -0.94 (2.29) ($P < 0.001$ for all). Solifenacin (5 and 10 mg) was superior to placebo, and no worse than propiverine 20 mg, for this variable. There were significantly fewer mean (sd) urgency, incontinence and urgency incontinence episodes with solifenacin and propiverine than with placebo, with respective changes on placebo of -1.28 (2.90), -0.72 (1.95) and -0.69 (2.00); solifenacin 5 mg, -2.41 (2.88), -1.59 (2.12) and -1.45 (1.89) ($P < 0.001$ for all), and 10 mg, -2.78 (2.82), -1.60 (1.81) and -1.52 (1.77) ($P < 0.001$ for all), and propiverine 20 mg, -2.30 (3.08), -1.25 (2.79) and -1.19 (2.20) ($P < 0.001$, = 0.002 and = 0.002 respectively). All active treatments vs placebo improved the volume voided ($P < 0.001$ for all) and QoL; solifenacin 10 mg reduced nocturia episodes ($P = 0.021$) and significantly improved urgency episodes ($P = 0.012$) and volume voided ($P = 0.009$) vs propiverine 20 mg, and solifenacin 5 mg caused less

dry mouth ($P = 0.003$). Solifenacin 10 mg caused more dry mouth ($P = 0.012$) and occurrences of constipation ($P = 0.004$) than propiverine 20 mg, but discontinuation rates between both treatment groups were similar. Continence was restored at endpoint in more than half of the patients on active treatment. **CONCLUSION:** Solifenacin 5 and 10 mg once daily significantly improved the symptoms of OAB compared with placebo. Solifenacin therapy at 5 mg once daily is well-tolerated; 10 mg can be given if additional efficacy is required.