

Drug Class Review on Overactive Bladder

Update #5: Preliminary Scan Report 1

February 2010

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

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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 # 4, March 2009 (searches through December 2008)

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 overactive bladder, do anticholinergic drugs differ in effectiveness?
 - a. Is there a difference in effectiveness between long-acting and short-acting formulations?
2. For adult patients with overactive bladder, do anticholinergic drugs differ in safety or adverse effects?
 - a. Is there a difference in safety or adverse effects between long-acting and short-acting formulations?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or comorbidities for which one anticholinergic drug is more effective or is associated with fewer adverse effects?
 - a. Are there differences in adverse event profiles in older patients between the drugs, particularly long-acting compared with short-acting, and newer drugs compared with the older drug oxybutynin?

Inclusion Criteria

Populations

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

Interventions

Included interventions are listed in Table 1.

Table 1. Included interventions

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

^a Not available in Canada.

Effectiveness outcomes

- Change in mean number of incontinence episodes per 24 hours
- Change in mean number of micturitions per 24 hours
- Change in mean number of pads per 24 hours
- Subjective patient assessments of symptoms (severity of ‘problems’ caused by bladder symptoms, severity of urgency, global evaluation of treatment)
- Quality of life

Safety outcomes

- Overall adverse effects
- Withdrawals due to overall adverse effects
- Serious adverse events reported
- Specific adverse events or withdrawals due to specific adverse events (dry mouth, effects on cognition, blurred vision, and cardiac conduction abnormalities)

Study Designs

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

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and December 2008 through February 2010 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 X2) 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

New Drugs

Oxybutynin chloride 10% transdermal gel (Gelnique®) – Approved 1/27/2009
Fesoterodine fumarate (Toviaz®) – Approved 10/31/2008

New Indications

None

New Safety Alerts

No new black box warnings or other series safety alerts were identified. Table 1 provides a summary of the new FDA Product Label changes.

Table 1. Summary of new FDA Product Label Changes

Drug name	FDA Product Label Section Modified	Date of Modification	Details
Darifenacin extended release	Adverse Reactions	December 2008	Information added on cardiovascular palpitations as a postmarketing experience
Tolterodine	Patient Package Insert	April 2009	<p>Addition in "What should I avoid while taking Detrol?" section</p> <ul style="list-style-type: none"> Medicines like Detrol can cause blurred vision or drowsiness. Use caution while driving or doing other dangerous activities until you know how Detrol affects you. <p>Addition in "What are possible side effects" section</p> <ul style="list-style-type: none"> Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088. Tell your doctor if you have any side effects that bother your or that do not go away.
Trospium chloride, including extended release dosage form	Precautions	June 2009	<p>June 2009</p> <p>Patients with Hepatic Impairment The term "<i>moderate</i>" added (moderate or severe hepatic)</p> <ul style="list-style-type: none"> Caution should be used when administering Sanctura in patients with moderate or severe hepatic dysfunction. Hepatic Insufficiency: There is no information

Drug name	FDA Product Label Section Modified	Date of Modification	Details
			regarding the effect of moderate to severe hepatic impairment
Ditropan, including extended release dosage form	Adverse Reactions	July 2009	Information added on memory impairment and QT interval prolongation reports from postmarketing surveillance

New Trials

Searches resulted in 77 citations. Of those, there are 13 new potentially relevant trials, including three head-to-head trials and ten placebo-controlled trials (see Appendix A, attached). Table 2 provides details of the treatment comparisons addressed in the new trials.

Table 2. Summary of new head-to-head trials

Author Year	Treatment comparisons
Head-to-Head Trials	
Chapple 2007	Fesoterodine vs tolterodine
Chapple 2008	Fesoterodine vs tolterodine
Choo 2008	Solifenacin vs tolterodine in 100% Korean population
Placebo-Controlled Trials	
Nitti 2007	Fesoterodine
Staskin 2009	Oxybutynin chloride 10% transdermal gel (Gelnique®)
Cardozo 2008	Solifenacin
Kaplan 2009	Solifenacin (add-on therapy in alpha-blocker treated men)
Karram 2009	Solifenacin
Toglia 2009	Solifenacin
Chapple 2009	Tolterodine ER (add-on therapy in alpha-blocker treated men)
Rogers 2008, Rogers 2009	Tolterodine ER (sexual functioning outcomes)
Herschorn 2008	Tolterodine ER
Van Kerrebroeck 2009	Tolterodine ER (quality of life)

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

Head-to-Head Trials

Chapple, C., P. Van Kerrebroeck, et al. (2007). "Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder.[Erratum appears in Eur Urol. 2008 Jun;53(6):1319]." 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 (> or =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., P. E. Van Kerrebroeck, et al. (2008). "Comparison of fesoterodine and tolterodine in patients with overactive bladder." BJU International **102**(9): 1128-32.

OBJECTIVE: To compare, in a post hoc analysis of a phase III trial, the maximum recommended doses of fesoterodine (8 mg) and tolterodine (4 mg) for improving overactive bladder (OAB) symptoms and health-related quality of life (HRQoL), as fesoterodine effectively reduces OAB symptoms vs placebo. **PATIENTS AND METHODS:** Eligible patients with frequency (> or =eight voids/24 h) and either urgency (> or =six episodes over 3 days) or urgency urinary incontinence (UUI; > or =three episodes over 3 days) were randomized to placebo, fesoterodine 4 or 8 mg, or tolterodine extended-release (ER) 4 mg for 12 weeks; fesoterodine 4 mg data were published elsewhere. Patients completed a 3-day bladder diary in which they recorded the time of each void, voided volume (VV), and the severity of urgency. A post hoc inferential analysis was conducted on the primary endpoint (voids/24 h), the two co-primary endpoints (UUI episodes/24 h and treatment response), several secondary endpoints (severe urgency plus UUI per 24 h, mean VV (MVV)/void, and continent days/week), HRQoL, using the King's Health Questionnaire (KHQ) and the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF), and self-reported bladder-related

problems. A subanalysis also assessed all endpoints for patients who were incontinent at baseline. Tolerability and safety were assessed by evaluating adverse events, residual urine volume, laboratory variables and treatment withdrawals. **RESULTS:** By week 12, patients with OAB in both active-treatment groups showed significant improvements in most bladder diary variables and treatment response rates compared with placebo. Fesoterodine 8 mg was statistically significantly better than tolterodine ER 4 mg for improving UUI episodes, severe urgency plus UUI, mean VV, and number of continent days/week. In addition, the fesoterodine and tolterodine ER groups showed significantly greater improvements in HRQoL than the placebo group, with positive changes in most domains of the KHQ and an improvement in ICIQ-SF score. The fesoterodine 8-mg group had statistically significant improvements over placebo in eight of nine KHQ domains. A major improvement in the severity of bladder-related problems was reported by 39% of the fesoterodine 8 mg and 34% of the tolterodine ER groups vs 25% of those on placebo ($P < \text{or} = 0.01$). Results for the subgroup of incontinent patients at baseline were similar to the overall results. Adverse events reported most commonly with active treatment included dry mouth, constipation, dry eye, dry throat, and nausea. **CONCLUSIONS:** Both fesoterodine and tolterodine ER significantly improved OAB symptoms and HRQoL, with statistically significant advantages for fesoterodine 8 mg compared with tolterodine ER on several important endpoints.

Choo, M. S., J. Z. Lee, et al. (2008). "Efficacy and safety of solifenacin succinate in Korean patients with overactive bladder: a randomised, prospective, double-blind, multicentre study." International Journal of Clinical Practice **62**(11): 1675-83.

PURPOSE: We assessed the efficacy and safety of solifenacin compared with tolterodine for treatment of overactive bladder (OAB) in Korean patients. **MATERIALS AND METHODS:** The study was randomised, double-blind, tolterodine-controlled trial in Korea. Patients had average frequency of ≥ 8 voids per 24 h and episodes of urgency or urgency incontinence ≥ 3 during 3-day voiding diary period. Patients were randomised to 12-week double-blind treatment with either tolterodine immediate release (IR) 2 mg twice daily (TOL4) or solifenacin 5 mg (SOL5) or 10 mg (SOL10) once daily. The outcome measure was mean change in daily micturition frequency, volume, daily frequency of urgency incontinence, urgency and nocturia from baseline to week 12. Quality of life was assessed using the King's Health Questionnaire. **RESULTS:** A total of 357 were randomised and 329 were evaluated for efficacy. All voiding parameters recorded in micturition diary improved after treatment in all three groups. Mean changes in volume voided were 19.30 ml (26.69%) in TOL4, 30.37 ml (25.89%) in SOL5 and 37.12 ml (33.36%) in SOL10 group ($p = 0.03$). Speed of onset of SOL10 efficacy on urgency incontinence was faster than that of SOL5 and TOL4. Quality of life improved in all three groups. Dry mouth was the most common adverse event; its incidence was the lowest in SOL5 group (7.63%, compared with 19.49% and 18.64% in SOL10 and TOL4 groups respectively). **CONCLUSIONS:** Solifenacin succinate 5 and 10 mg once daily improve OAB symptoms with acceptable tolerability levels compared with tolterodine IR 4 mg. Solifenacin 5 mg is a recommended starting dose in Korean patients with OAB.

Placebo-Controlled Trials

Cardozo, L., E. Hessdorfer, et al. (2008). "Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial." *BJU International* **102**(9): 1120-7.

OBJECTIVES: To examine the effects of the antimuscarinic agent solifenacin on urinary urgency, using a range of novel and established outcome measures, as urgency is the principal symptom of the overactive bladder syndrome (OAB). **PATIENTS AND METHODS:** The study (SUNRISE, solifenacin in the treatment of urgency symptoms of OAB in a rising dose, randomized, placebo-controlled, double-blind, efficacy trial) was a randomized, double-blind, 16-week, placebo-controlled, multicentre study of solifenacin 5/10 mg in 863 patients with symptoms of OAB for $>$ or $=$ 3 months. The primary efficacy variable was the change from baseline to endpoint in the number of episodes of severe urgency with or without urgency incontinence per 24 h, as measured using the Patient Perception of Intensity of Urgency Scale, grade 3 + 4. Secondary efficacy variables included patient-reported outcomes for bladder condition, urgency bother and treatment satisfaction. A 3-day voiding diary was used to record micturition frequency and episodes of urgency and incontinence. A 7-day diary was used to assess speed of onset of effect. **RESULTS:** Solifenacin 5/10 mg was significantly more effective than placebo in reducing the mean number of episodes of severe urgency with or without incontinence per 24 h from baseline to endpoint (-2.6 vs -1.8, $P < 0.001$). There were also statistically significant differences in favour of solifenacin 5/10 mg over placebo for all secondary variables measured at endpoint, including patient-reported outcomes. There was a significant improvement in urgency as early as day 3 of treatment. Treatment-emergent adverse events with solifenacin 5/10 mg were mainly mild or moderate in severity, and only led to discontinuation in 3.6% of patients. **CONCLUSION:** Solifenacin significantly reduced the number of urgency episodes and the extent of urgency bother, and was well tolerated; it was effective as early as day 3 of treatment.

Chapple, C., S. Herschorn, et al. (2009). "Tolterodine treatment improves storage symptoms suggestive of overactive bladder in men treated with alpha-blockers." *European Urology* **56**(3): 534-41.

BACKGROUND: Some men receiving alpha-blocker therapy for lower urinary tract symptoms report persistent storage symptoms suggestive of overactive bladder (OAB). **OBJECTIVE:** To evaluate the efficacy of tolterodine extended release (ER) in men on alpha-blocker therapy. **DESIGN, SETTING, AND PARTICIPANTS:** This double-blind trial included men aged $>$ or $=$ 40 yr with frequency, urgency, and at least moderate problems reported on the Patient Perception of Bladder Condition (PPBC), despite being on a stable dose of alpha-blocker for $>$ or $=$ 1 mo. **INTERVENTIONS:** Subjects were randomized to tolterodine ER 4 mg per day or placebo for 12 wk while continuing their prescribed alpha-blocker therapy. **MEASUREMENTS:** At baseline and week 12, subjects completed the PPBC, International Prostate Symptom Score (IPSS), Overactive Bladder Questionnaire (OAB-q), and 5-d bladder diaries using the five-point Urinary Sensation Scale (USS). Frequency-urgency sum was defined as the sum of USS ratings for all micturitions. **RESULTS AND LIMITATIONS:** PPBC improvement from baseline to week 12 was reported by 63.6% and 61.6% of subjects receiving tolterodine ER plus alpha-blocker and placebo plus alpha-blocker, respectively; this treatment difference,

which was the primary end point, was not statistically significant ($p > 0.6699$). At week 12, subjects receiving tolterodine ER plus alpha-blocker had significantly greater improvements versus placebo plus alpha-blocker in 24-h micturitions (-1.8 vs -1.2; $p = 0.0079$) and daytime micturitions (-1.3 vs -0.8; $p = 0.0123$); 24-h urgency episodes (-2.9 vs -1.8; $p = 0.0010$), daytime urgency episodes (-2.2 vs -1.4; $p = 0.0017$), and nocturnal urgency episodes (-0.5 vs -0.3; $p = 0.0378$); frequency-urgency sum (-7.8 vs -5.1; $p = 0.0065$); IPSS storage subscale (-2.6 vs -2.1; $p = 0.0370$); and OAB-q symptom bother scale (-17.9 vs -14.4; $p = 0.0086$) and coping domain (15.4 vs 12.4; $p = 0.0491$). Acute urinary retention requiring catheterization occurred in $< 1\%$ of either group. There were no clinically meaningful changes in postvoid residual volume or maximum urinary flow rate. **CONCLUSIONS:** Men with bothersome OAB symptoms despite continued alpha-blocker therapy showed significantly greater improvements in diary variables, IPSS Storage scores, and symptom bother when receiving additional tolterodine ER versus placebo plus alpha-blocker.

Herschorn, S., J. Heesakkers, et al. (2008). "Effects of tolterodine extended release on patient perception of bladder condition and overactive bladder symptoms*." Current Medical Research & Opinion **24**(12): 3513-21.

OBJECTIVE: To evaluate the efficacy of tolterodine extended release (ER) versus placebo at 1 and 12 weeks using questionnaires and diary measures. **Research design and methods:** Subjects with overactive bladder (OAB) were randomized to receive tolterodine ER (4 mg) or placebo for 12 weeks. This double-blind study is registered with ClinicalTrials.gov (identifier: NCT00143377). **MAIN OUTCOME MEASURES:** Subjects completed the Patient Perception of Bladder Condition (PPBC) and 3-day bladder diaries at baseline and weeks 1 and 12, and the Overactive Bladder Questionnaire (OAB-q) at baseline and week 12. PPBC score changes were analyzed using 2-category (improvement, no improvement), 3-category (improvement, no change, deterioration), and 4-category (≥ 2 -point improvement, 1-point improvement, no change, deterioration) stratifications. Categorical change in PPBC scores from baseline to week 12 was the primary endpoint. **RESULTS:** A total of 617 subjects were randomized (tolterodine ER, $n = 410$; placebo, $n = 207$). At week 1, a significantly higher percentage of subjects receiving tolterodine ER reported improvement on the PPBC compared with placebo ($p < 0.05$). Subjects receiving tolterodine ER also had a significantly greater reduction in all OAB symptoms versus placebo (all $p < 0.05$). At week 12, a higher percentage of tolterodine ER subjects reported PPBC improvement versus placebo subjects. This was significant in the 3- and 4-category analyses (both $p < 0.05$) but not in the 2-category analysis (the prespecified method of analysis; $p = 0.098$). Compared with the placebo group, the tolterodine ER group reported significantly greater week 12 improvements in all bladder diary variables (all $p < 0.01$) as well as in OAB-q Symptom Bother, total Health-Related Quality of Life, Coping, and Concern scores (all $p < 0.02$). **CONCLUSIONS:** Compared with placebo, subjects receiving tolterodine ER reported significantly greater improvements in nondiary patient-reported outcomes and OAB symptoms at week 12. Improvements in subjects' perception of their bladder-related problems and in OAB symptoms were observed as early as week 1. Further research is required to assess which aspects of subjects' bladder-related problems were improved. A large placebo effect may have prevented the prespecified 2-category analysis of PPBC

improvement from reaching statistical significance at week 12, which was the primary endpoint.

Kaplan, S. A., K. McCammon, et al. (2009). "Safety and tolerability of solifenacin add-on therapy to alpha-blocker treated men with residual urgency and frequency." Journal of Urology **182**(6): 2825-30.

PURPOSE: VICTOR was a 12-week, double-blind, placebo controlled trial assessing the safety and tolerability of solifenacin plus tamsulosin in men with residual overactive bladder symptoms after tamsulosin monotherapy. Efficacy of solifenacin plus tamsulosin vs placebo plus tamsulosin was also evaluated. **MATERIALS AND METHODS:** A total of 398 men 45 years old or older were randomized to 12 weeks of solifenacin plus tamsulosin or placebo plus tamsulosin once daily. The study population had 8 or more micturitions per 24 hours and 1 or more urgency episode per 24 hours after taking tamsulosin for 4 or more weeks, a total International Prostate Symptom Score of 13 or greater, a Patient Perception of Bladder Condition score of 3 or greater, a post-void residual of 200 ml or less and a peak flow rate of 5 ml per second or greater. Adverse events were monitored throughout the study. The primary efficacy end point was mean change from baseline to week 12 in micturitions per 24 hours. Secondary measures included mean change in urgency episodes per 24 hours, and changes in Patient Perception of Bladder Condition, Urgency Perception Scale and total International Prostate Symptom Scores. **RESULTS:** The most frequent adverse events in the solifenacin plus tamsulosin and placebo plus tamsulosin groups were dry mouth (7% and 3%, respectively) and dizziness (3% and 2%, respectively). Of the patients on solifenacin plus tamsulosin 7 (3%) reported retention and 3 required catheterization. No patients on placebo plus tamsulosin reported retention. Patients on solifenacin plus tamsulosin vs placebo plus tamsulosin showed larger reductions in frequency but not of statistical significance (-1.05 vs -0.67, $p = 0.135$). However, patients on solifenacin plus tamsulosin vs placebo plus tamsulosin did show statistically significant reductions in urgency (-2.18 vs -1.10, $p < 0.001$). Patient reported outcome measures showed no significant between group differences. **CONCLUSIONS:** Solifenacin plus tamsulosin was well tolerated. There was a low incidence of urinary retention requiring catheterization. At week 12 solifenacin plus tamsulosin decreased daily micturitions and urgency episodes. Only urgency reached statistical significance vs placebo plus tamsulosin.

Karram, M. M., M. R. Togliola, et al. (2009). "Treatment with solifenacin increases warning time and improves symptoms of overactive bladder: results from VENUS, a randomized, double-blind, placebo-controlled trial." Urology **73**(1): 14-8.

OBJECTIVES: In this double-blind, placebo-controlled trial, we assessed the efficacy and tolerability of solifenacin treatment for overactive bladder (OAB) with a focus on urgency-related endpoints. Changes in number of urgency episodes were evaluated as the primary endpoint; secondary endpoints included changes in conventional diary-based OAB symptoms. We also measured warning time (defined as the time from first sensation of urgency to voiding). **METHODS:** We randomized patients ($n = 739$) to once-daily solifenacin or placebo for 12 weeks. Solifenacin 5 mg or matching placebo was administered for 4 weeks; dose could be maintained or adjusted at weeks 4 and 8. Participants completed 3-day micturition diaries at multiple study visits; warning time was recorded at baseline and week 12. **RESULTS:** At study end, the mean number of

urgency episodes per 24 hours decreased by 3.91 (from 6.15 to 2.24) with solifenacin and by 2.73 (from 6.03 to 3.30) with placebo ($P < .0001$ between groups). Other diary-recorded symptoms (incontinence and micturition frequency) were also significantly more reduced with solifenacin compared with placebo. Median warning time increased 31.5 seconds (baseline, 67.8 seconds) with solifenacin, significantly longer ($P = .008$) than the median increase of 12.0 seconds (baseline, 65.0 seconds) observed with placebo. **CONCLUSIONS:** Solifenacin treatment significantly reduced episodes of urgency and other key symptoms of OAB. Solifenacin is the first antimuscarinic to demonstrate significant warning time improvement at approved dosing, as shown in a large OAB study population. This is the largest OAB clinical trial yet conducted to evaluate warning time and diary variables in the same study population.

Nitti, V. W., R. Dmochowski, et al. (2007). "Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome." *Journal of Urology* **178**(6): 2488-94.

PURPOSE: We evaluated the efficacy, tolerability and safety of the new antimuscarinic agent fesoterodine relative to placebo for overactive bladder syndrome. **MATERIALS AND METHODS:** This was a randomized, double-blind, placebo controlled, multicenter trial performed in the United States. Overall 836 subjects with urinary frequency, urinary urgency or urgency urinary incontinence were randomized to placebo (274), 4 mg fesoterodine (283) or 8 mg fesoterodine (279) once daily for 12 weeks. The primary efficacy end point was the change in the number of micturitions per 24 hours. Co-primary end points were the change in the number of urgency urinary incontinence episodes per 24 hours and the treatment response. Secondary efficacy end points were other bladder diary variables, such as the change in mean voided volume per micturition, number of continent days and number of urgency episodes per 24 hours. Tolerability and safety were assessed by evaluating adverse events, electrocardiograms, post-void residual urine volume, laboratory parameters and treatment withdrawals. **RESULTS:** Treatment with 4 or 8 mg fesoterodine resulted in statistically significant and clinically relevant improvements from baseline to end of treatment for the primary and co-primary end points compared with placebo ($p < 0.05$). Results for most secondary end points, including mean voided volume per micturition, number of continent days and number of urgency episodes per 24 hours, were also significantly improved vs placebo. The adverse events reported more frequently with fesoterodine than with placebo were dry mouth, constipation and urinary tract infection. **CONCLUSIONS:** The 2 doses of fesoterodine were well tolerated and they statistically significantly improved overactive bladder symptoms.

Rogers, R., G. Bachmann, et al. (2008). "Efficacy of tolterodine on overactive bladder symptoms and sexual and emotional quality of life in sexually active women." *International Urogynecology Journal* **19**(11): 1551-7.

We evaluated overactive bladder (OAB) symptoms and sexual and emotional health in sexually active women with OAB/urgency urinary incontinence (UI) treated with tolterodine extended release (ER). Sexually active women with OAB symptoms were randomized to placebo or tolterodine ER. Five-day bladder diaries, Sexual Quality of Life Questionnaire-Female (SQOL-F), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ), and Hospital Anxiety and Depression Scale (HAD) were completed at baseline and week 12. Tolterodine ER ($n = 201$; mean \pm SD age, 49 \pm 12

years) reduced UUI episodes ($P = 0.0029$), total ($P = 0.0006$) and OAB ($P < 0.0001$) micturitions, and pad use per 24 h ($P = 0.0024$), and was associated with improvements in SQOL-F ($P = 0.004$), PISQ total ($P = 0.009$), and HAD Anxiety ($P = 0.03$) scores versus placebo ($n = 210$; mean \pm SD age, 47 \pm 12 years). OAB symptoms improved with tolterodine ER as did the scores of sexual health and anxiety measures in sexually active women with OAB.

Rogers, R. G., G. Bachmann, et al. (2009). "Effects of tolterodine ER on patient-reported outcomes in sexually active women with overactive bladder and urgency urinary incontinence." Current Medical Research & Opinion **25**(9): 2159-65.

OBJECTIVE: To assess the effects of tolterodine extended release (ER) on patient-reported outcomes (PROs) in sexually active women with overactive bladder (OAB) and urgency urinary incontinence (UUI). **RESEARCH DESIGN AND METHODS:** This multicenter, double-blind, placebo controlled trial included 411 women aged ≥ 18 years reporting OAB symptoms for ≥ 3 months; ≥ 8 micturitions per 24 hours (including ≥ 0.6 UUI episodes and ≥ 3 OAB micturitions) in 5-day bladder diaries at baseline, and being in a sexually active relationship for ≥ 6 months. Subjects randomized to placebo or tolterodine ER completed validated OAB- or incontinence-specific questionnaires, including the Patient Perception of Bladder Condition (PPBC), Overactive Bladder Questionnaire (OAB-q), Urgency Perception Scale (UPS), and the Incontinence Impact Questionnaire (IIQ) at baseline and week 12, as well as the Perception of Treatment Benefit and Treatment Satisfaction questions at week 12. This study is registered with ClinicalTrials.gov (identifier: NCT00143481). **RESULTS:** The mean age of enrolled women was approximately 48 years. Compared with placebo, the tolterodine ER group reported significant baseline to week 12 improvements in PPBC responses ($p = 0.0048$); OAB-q Symptom Bother, total Health-Related Quality of Life (HRQL), and HRQL domain scores (all $p < 0.05$); IIQ Emotional Health domain scores ($p < 0.05$); proportions of subjects reporting treatment benefit (79 vs. 54%; $p < 0.0001$) and satisfaction (78 vs. 59%; $p < 0.0001$). Improvements on the UPS were not significantly different. **CONCLUSIONS:** Tolterodine ER treatment was associated with improvements in multiple OAB- and incontinence-specific PROs in a sexually active, relatively young, and racially diverse population of women. The findings provide clinicians with new insights into the impact of OAB and its treatment on HRQL in this population, which has been underrepresented in previous OAB studies. Study limitations include a potential underestimation of the impact of OAB symptoms resulting from the exclusion of women who may not be sexually active because of their urinary symptoms.

Staskin, D. R., R. R. Dmochowski, et al. (2009). "Efficacy and safety of oxybutynin chloride topical gel for overactive bladder: a randomized, double-blind, placebo controlled, multicenter study." Journal of Urology **181**(4): 1764-72.

PURPOSE: We assessed the efficacy and safety of oxybutynin chloride topical gel vs placebo in adults with overactive bladder. **MATERIALS AND METHODS:** Men and women 18 years or older with urge predominant urinary incontinence were enrolled in randomized, parallel group, double-blind, placebo controlled Study OG05009 done at 76 clinics in the United States. Eligible patients were assigned to receive 1 gm oxybutynin chloride topical gel (10% weight per weight ethanol based formulation of oxybutynin) or

matching placebo once daily for 12 weeks. Efficacy was assessed using data from 3-day urinary diaries and the primary outcome was the change from baseline in the number of urge incontinence episodes. Safety was monitored through adverse event reporting. Efficacy results in the oxybutynin chloride topical gel and placebo groups were compared by ANCOVA with last observations carried forward. RESULTS: A total of 789 randomized patients, including 704 women (89.2%), with a mean age of 59 years were assigned to treatment with oxybutynin chloride topical gel (389) or placebo (400). The mean number of urge incontinence episodes decreased significantly more in patients treated with oxybutynin chloride topical gel than in those given placebo (-3.0 vs -2.5 per day, $p < 0.0001$). Mean urinary frequency decreased (-2.7 per day, $p = 0.0017$) and voided volume increased (21.0 ml, $p = 0.0018$) significantly more in the oxybutynin chloride group than in the placebo group (-2.0 per day and 3.8 ml, respectively). Treatment related dry mouth was more frequent in the oxybutynin chloride group than in the placebo group (27 of 389 patients or 6.9% vs 11 of 400 or 2.8%). Application site reactions were infrequently observed in the oxybutynin chloride and placebo groups (21 of 389 patients or 5.4% and 4 of 400 or 1.0%, respectively). No serious treatment related adverse events occurred. CONCLUSIONS: Oxybutynin chloride topical gel was efficacious in improving overactive bladder symptoms and was well tolerated in adult patients.

Toglia, M. R., S. R. Serels, et al. (2009). "Solifenacin for overactive bladder: patient-reported outcomes from a large placebo-controlled trial." *Postgraduate Medicine* **121**(5): 151-8.

OBJECTIVE: Overactive bladder (OAB) is a prevalent, chronic condition that can negatively affect health-related quality of life (HRQL). Treatment goals are to improve symptoms and HRQL. We assessed the efficacy of solifenacin in OAB patients using several patient-reported outcome (PRO) measures, with a focus on urgency severity. Results for the primary endpoint, reductions in daily urgency episodes, and other bladder-diary variables have been recently reported. MATERIALS AND METHODS: In this 12-week multicenter trial, 739 patients (aged ≥ 18 years) were randomized to flexibly dosed solifenacin (5/10 mg) or placebo. Prespecified secondary PRO measures included the Indevus Urgency Severity Scale (IUSS), Urgency Perception Scale (UPS), Patient Perception of Bladder Condition (PPBC), and Overactive Bladder Questionnaire (OAB-q). Appropriate statistical tests compared treatment-group differences in continuous and categorical data. RESULTS: In the full analysis set, patients who received solifenacin ($n = 357$) versus placebo ($n = 350$) showed significant improvements on the IUSS and UPS; treatment-group differences were 0.4 ($P < 0.0001$) and 0.2 ($P = 0.0018$), respectively. On the PPBC, significantly more patients taking solifenacin (66%) than placebo (48%) perceived fewer bladder-related problems ($P < 0.0001$) by week 12. On the OAB-q, solifenacin was superior to placebo for the Symptom Bother and total HRQL scales and for 3 of the 4 HRQL domains at study end ($P \leq 0.01$). Overall, these findings were consistent with those reported previously for bladder-diary-documented urgency and other OAB symptoms. CONCLUSION: Flexibly dosed, once-daily solifenacin was associated with statistically significant and clinically meaningful improvements in urgency and other symptom-specific bother and HRQL compared with placebo.

Van Kerrebroeck, P. E. V., C. J. Kelleher, et al. (2009). "Correlations among improvements in urgency urinary incontinence, health-related quality of life, and perception of bladder-related

problems in incontinent subjects with overactive bladder treated with tolterodine or placebo." Health & Quality of Life Outcomes 7: 13.

BACKGROUND: Previous studies demonstrate that tolterodine extended release (ER) significantly improves urgency urinary incontinence (UUI) episodes. Instruments that measure patient-reported outcomes (PROs) provide additional information that is valuable for assessing whether clinical improvements are meaningful to the patient. This study determined the correlation of changes in bladder diary variables and other PROs in subjects with overactive bladder (OAB). **METHODS:** Subjects with OAB, urinary frequency, and UUI were treated with 4 mg once-daily tolterodine ER or placebo for 12 weeks. Subjects completed 7-day bladder diaries, the Patient Perception of Bladder Condition (PPBC), and the King's Health Questionnaire (KHQ) at baseline and week 12. Only subjects who reported at least some minor bladder-related problems at baseline (PPBC score \geq 3) were included in this analysis. **RESULTS:** Reductions in UUI episodes per week were significantly greater in the tolterodine ER group ($n = 500$) compared with the placebo group ($n = 487$) at week 12 (-71% vs -33%, $P < 0.0001$). A significantly greater percentage of subjects in the tolterodine ER group reported improvement on the PPBC versus placebo (58% vs 45%, $P < 0.0001$), and 7 of 10 KHQ domains were significantly improved versus placebo (all $P < 0.05$). Significant correlations were found for median percentage changes in UUI episodes with changes in PPBC scores ($r = 0.35, P < 0.0001$) and the 7 improved KHQ domains ($r = 0.16-0.32, P < \text{or} = 0.0011$). Changes in PPBC scores and all KHQ domains were significantly correlated ($r = 0.13-0.38, P < \text{or} = 0.009$) in the tolterodine ER group. Correlations among endpoints in the placebo group were similar to those observed in the tolterodine ER group. **CONCLUSION:** Improvement in UUI episodes after 12 weeks of treatment with tolterodine ER or placebo was correlated with improvements in patients' perception of their bladder-related problems and health-related quality of life. Correlations were moderate in magnitude but statistically significant, suggesting that PROs are important and relevant measures for evaluating OAB treatment.