

# Drug Class Review on Overactive Bladder



## Update #4: Preliminary Scan Report

March 2007

**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 #3 Final Report was completed in December of 2005.

**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)	Oral tablet	Buscopan

Active ingredients	Form	Brand name
butylbromide		
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 MEDLINE (June 2005 to March 2007). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

### **Study Selection**

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

## RESULTS

### Overview

We identified 97 potentially relevant citations. Of those, there are 20 new potentially relevant controlled clinical trials (Appendix A).

### New Drugs

None

### New Indications

None

### New Safety Alerts

<b>Drug</b>	<b>Source</b>	<b>Date of change</b>	<b>Type of change</b>	<b>Details</b>
Tolterodine	FDA	3/06	Label Change: Precautions	Patients with Congenital or Acquired QT Prolongation
Oxybutynin	FDA	7/06	Label Change: Precautions and Adverse Reactions	Dizziness
Trospium	FDA	12/06	Label Change: Adverse Reactions	Rash

## APPENDIX A

Anderson, R. U., S. MacDiarmid, et al. (2006). "Effectiveness and tolerability of extended-release oxybutynin vs extended-release tolterodine in women with or without prior anticholinergic treatment for overactive bladder." International Urogynecology Journal **17**(5): 502-11.

The efficacy and the tolerability of extended-release oxybutynin chloride, 10 mg daily, and extended-release tolterodine tartrate, 4 mg daily, in women with or without prior anticholinergic treatment for overactive bladder (OAB) were compared in a post-hoc analysis of data from the Overactive Bladder: Performance of Extended Release Agents (OPERA) trial. The patient population and study methods have been described previously (Diokno et al., for the OPERA Study Group, Mayo Clin Proc 78:687-695, 2003). Among the group with anticholinergic experience, extended-release oxybutynin was significantly more effective than extended-release tolterodine in reducing micturition frequency at last observation ( $p=0.052$ ). Complete freedom from urge incontinence was reported by significantly more patients taking oxybutynin than tolterodine at last observation (23.6 vs 15.1%,  $p=0.038$ ). In addition, among patients completing a full 12 weeks of oxybutynin treatment, significantly greater reductions were observed compared with those taking tolterodine on the primary efficacy variable, number of urge incontinence episodes ( $p=0.049$ ), and the combined total of urge and non-urge episodes ( $p=0.012$ ), although the differences between treatment groups were not significant at last observation. In the anticholinergic-naïve group, efficacy and tolerability outcomes were similar across treatments, except that oxybutynin was associated with a significantly lower frequency of micturition at last observation ( $p=0.035$ ). No efficacy differences favoring tolterodine were observed, and tolerability of the treatments was comparable. Dry mouth (mostly mild to moderate in severity) was reported significantly more often among participants taking extended-release oxybutynin than extended-release tolterodine (32.2 vs 19.2%,  $p=0.004$ ), but only among those with previous anticholinergic experience. Discontinuation rates were comparably low across groups. The results demonstrate the appropriateness of initiating treatment for OAB with extended-release oxybutynin, particularly in women presenting with incontinence.

Armstrong, R. B., K. M. Luber, et al. (2005). "Comparison of dry mouth in women treated with extended-release formulations of oxybutynin or tolterodine for overactive bladder." International Urology & Nephrology **37**(2): 247-52.

The incidence, severity and tolerability of dry mouth was compared in 790 women with overactive bladder who were treated with extended-release oxybutynin chloride 10 mg/day or extended-release tolterodine tartrate 4 mg/day for 12 weeks in a multicenter, double-blind, parallel-group study. Dry mouth was the most common adverse event associated with treatment, with an incidence rate of 28.1% in the oxybutynin group and 21.6% in the tolterodine group ( $P = 0.039$ ). The majority of dry mouth events were mild in both treatment groups. Severe dry mouth occurred in 1.5% and 0.5% of patients in the oxybutynin and tolterodine groups, respectively ( $P = 0.173$ ). Seven patients on extended-release oxybutynin and 4 patients on extended-release tolterodine discontinued treatment due to dry mouth ( $P = 0.380$ ). The results of this analysis showed that dry mouth was common with both treatments, but most events were mild; there was no difference in the rate of severe dry mouth or in the rate of withdrawal due to dry mouth.

Chapple, C. R., R. Martinez-Garcia, et al. (2005). "A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial.[see comment]." European Urology **48**(3): 464-70.

OBJECTIVE: To compare two new generation antimuscarinics at their recommended doses for treatment of overactive bladder syndrome (OAB). METHODS: A prospective, double blind, double-dummy, two-arm, parallel-group, 12-week study was conducted to compare the efficacy and safety of solifenacin 5 or 10 mg and tolterodine extended release (ER) 4 mg once daily in

OAB patients. After 4 weeks of treatment patients had the option to request a dose increase but were dummied throughout as approved product labelling only allowed an increase for those on solifenacin. RESULTS: Solifenacin, with a flexible dosing regimen, showed greater efficacy to tolterodine in decreasing urgency episodes, incontinence, urge incontinence and pad usage and increasing the volume voided per micturition. More solifenacin treated patients became continent and reported improvements in perception of bladder condition assessments. The majority of side effects were mild to moderate in nature, and discontinuations were comparable and low in both groups. CONCLUSIONS: Solifenacin, with a flexible dosing regimen, was found to be superior to tolterodine ER with respect to the majority of the efficacy variables.

Fader, M., S. Glickman, et al. (2007). "Intravesical atropine compared to oral oxybutynin for neurogenic detrusor overactivity: a double-blind, randomized crossover trial." Journal of Urology **177**(1): 208-13; discussion 213.

PURPOSE: We tested the efficacy and side effect profiles of intravesical atropine compared to oxybutynin immediate release when used by individuals with multiple sclerosis. MATERIALS AND METHODS: We performed a study to determine the most effective dose of atropine. Eight participants used increasing doses of intravesical atropine during a 12-day period. Bladder diary data showed that the instillation of 6 mg atropine 4 times daily was most effective for increasing bladder capacity (voided/catheter volumes). We then did a randomized, double-blind crossover trial. Participants received 14 days of treatment with oral oxybutynin or with intravesical atropine, followed by 14 days of alternative treatment. Participants recorded a bladder diary and rated side effects and quality of life. The primary outcome variable was bladder capacity. RESULTS: A total of 57 participants with multiple sclerosis completed the study. Average change in bladder capacity was higher in the atropine arm. The mean +/- SD oxybutynin change was 55.5 +/- 67.2 ml, the mean atropine change was 79.6 +/- 89.6 ml and the mean difference between arms was 24.1 ml (95% CI -0.4, 49.7; p = 0.053). Changes in incontinence events and voiding frequency were not statistically different between the arms. Changes in total side effect and dry mouth scores were significantly better in the atropine treatment arm. CONCLUSIONS: Intravesical atropine was as effective as oxybutynin immediate release for increasing bladder capacity and it was probably better with less antimuscarinic side effects. We recommend that intravesical atropine should be made available to patients with neurogenic detrusor overactivity and voiding problems requiring intermittent catheterization as an alternative to oral therapy, which often has troublesome side effects.

Hill, S., V. Khullar, et al. (2006). "Dose response with darifenacin, a novel once-daily M3 selective receptor antagonist for the treatment of overactive bladder: results of a fixed dose study." International Urogynecology Journal **17**(3): 239-47.

This study evaluated the efficacy, tolerability, and safety of darifenacin, an M3 selective receptor antagonist (M3 SRA), in patients with overactive bladder (OAB). In a multicenter, double-blind, placebo-controlled dose-ranging study, 439 adult OAB patients (85.4% female) were randomized to darifenacin controlled-release tablets 7.5 mg (n = 108), 15 mg (n = 107) or 30 mg (n = 115) qd, or placebo (n = 109) for 12 weeks. Darifenacin significantly reduced the median number of incontinence episodes/week (-68.7, -76.5, and -77.3% from baseline at 7.5, 15, and 30 mg, respectively, vs -46% with placebo, all p < 0.01) and dose relatedly improved micturition frequency, frequency and severity of urgency, nocturia, and bladder capacity. Darifenacin was well tolerated. Adverse events were commonly mild to moderate dry mouth and constipation. There were no safety concerns. Darifenacin is effective and well tolerated in the treatment of OAB, with 7.5 and 15 mg doses offering flexibility of dosing for optimal treatment outcome.

Horstmann, M., T. Schaefer, et al. (2006). "Neurogenic bladder treatment by doubling the recommended antimuscarinic dosage." Neurourology & Urodynamics **25**(5): 441-5.

**INTRODUCTION AND OBJECTIVES:** The dosage of the antimuscarinic drugs: Tolterodine ER or Trosipium was increased to a higher-than-recommended dosage in patients where the manufacturer's recommended dosage had failed. All patients were suffering from neurogenic detrusor overactivity incontinence. Tolerability and success were evaluated in the present study. **MATERIALS AND METHODS:** Twenty-one patients with neurogenic detrusor overactivity were evaluated: 17 with spinal cord injury, 3 with multiple sclerosis, and 1 with a meningocele. All patients catheterized themselves or were catheterized. If neurogenic detrusor overactivity continued and the medication was well tolerated, the dosage was doubled to either 8 mg of Tolterodine ER [2 x 4 mg (n = 11)] or 90 mg of Trosipium [3 x 30 mg (n = 10)]. The follow-up was monitored by a bladder diary and urodynamic evaluation. **RESULTS:** Sixteen patients significantly decreased their incontinence episodes from 8-12 episodes before to 0-2 episodes during the doubled treatment. The reflex volume increased from 202 +/- 68 to 332 +/- 50 ml (P < 0.001). Cystometric capacity enlarged from 290 +/- 56 to 453 +/- 63 ml (P < 0.001). One patient had to stop the medication because of intolerable side effects and five patients did not experience satisfactory benefit. **CONCLUSION:** The increased dosage of Tolterodine or Trosipium is an effective treatment in patients with neurogenic bladder.

Junemann, K.-P., M. Halaska, et al. (2005). "Propiverine versus tolterodine: efficacy and tolerability in patients with overactive bladder." *European Urology* **48**(3): 478-82.

**OBJECTIVES:** Propiverine and tolterodine were compared with respect to efficacy, tolerability and impact on the quality of life in the treatment of patients with idiopathic detrusor overactivity. **METHODS:** In a randomised, double-blind, multicentre clinical trial, patients with idiopathic detrusor overactivity were treated with 15 mg propiverine twice daily or 2mg tolterodine twice daily over a period of 28 days. The maximum cystometric capacity was determined at baseline and after 4 weeks of therapy. The difference of both values was used as the primary endpoint. Secondary endpoints were voided volume per micturition, evaluation of efficacy (by the investigator), tolerability, post void residual urine, and quality of life. **RESULTS:** The mean maximum cystometric capacity increased significantly (p < 0.01) in both groups. The volume at first urge and the frequency/volume chart parameters also showed relevant improvements during treatment. 42/100 patients in the propiverine group and 43/102 in the tolterodine group experienced adverse events. The most common adverse event, dry mouth, occurred in 20 patients in the propiverine group and in 19 patients in the tolterodine group. The scores for the **quality of life** improved comparably in both groups. **CONCLUSION:** The study demonstrates comparable efficacy, tolerability, and improvement in the quality of life of 15 mg propiverine twice-daily and 2mg tolterodine twice-daily in the treatment of the symptoms of idiopathic detrusor overactivity.

Kaplan, S. A., C. G. Roehrborn, et al. (2006). "Tolterodine extended release improves overactive bladder symptoms in men with overactive bladder and nocturia." *Urology* **68**(2): 328-32.

**OBJECTIVES:** To evaluate the efficacy and safety of nighttime dosing with tolterodine extended release (TER) in men with overactive bladder (OAB) and nocturia. **METHODS:** This was a post hoc analysis of data from two 12-week, double-blind, placebo-controlled trials of nighttime (<4 hours before bedtime) TER (4 mg daily) dosing. Men with a mean micturition frequency of eight or more times in 24 hours, including a mean of 2.5 or more nocturia episodes/night, were included. For each micturition, patients used 7-day diaries to record urinary urgency on a 5-point urgency rating scale (1, none; 2, mild; 3, moderate; 4, severe; 5, urgency urinary incontinence). Micturitions were analyzed post hoc by urgency rating categories: total (1 to 5), non-OAB (1 to 2), OAB (3 to 5), and severe OAB (4 to 5). Adverse events were recorded throughout the study. **RESULTS:** A total of 745 men (mean age 64 years) were randomized to placebo (n = 374) or TER (n = 371). Of the 745 men, 73% reported no incontinence episodes in a 7-day diary at baseline. At week 12, the weekly values for nighttime severe OAB micturitions and 24-hour and daytime total, OAB, and severe OAB micturitions were significantly reduced in the TER group

versus the placebo group. The TER-treated men also reported a significant reduction in the mean urgency rating versus placebo. Adverse events associated with TER were low and comparable to those in the placebo group, with the exception of dry mouth (11% versus 4%). Withdrawals because of adverse events were infrequent (3% TER, 4% placebo). Five men were withdrawn for symptoms suggestive of urinary retention (3 TER, 2 placebo). CONCLUSIONS: Nighttime TER dosing reduced urgency-related micturitions and was well tolerated in men with OAB and nocturia.

Kaplan, S. A., C. G. Roehrborn, et al. (2006). "Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial." *JAMA* **296**(19): 2319-28.

CONTEXT: Men with overactive bladder and other lower urinary tract symptoms may not respond to monotherapy with antimuscarinic agents or alpha-receptor antagonists. OBJECTIVE: To evaluate the efficacy and safety of tolterodine extended release (ER), tamsulosin, or both in men who met research criteria for both overactive bladder and benign prostatic hyperplasia. DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, placebo-controlled trial conducted at 95 urology clinics in the United States involving men 40 years or older who had a total International Prostate Symptom Score of 12 or higher and, an International Prostate Symptom Score quality-of-life (QOL) item score of 3 or higher, a self-rated bladder condition of at least moderate bother, and a bladder diary documenting micturition frequency ( $\geq 8$  micturitions per 24 hours) and urgency ( $\geq 3$  episodes per 24 hours), with or without urgency urinary incontinence. Patients were recruited between November 2004 and February 2006, and the study was completed May 2006. INTERVENTIONS: Patients were randomly assigned to receive placebo (n = 222), 4 mg of tolterodine ER (n = 217), 0.4 mg of tamsulosin (n = 215), or both tolterodine ER plus tamsulosin (n = 225) for 12 weeks. MAIN OUTCOME MEASURES: Patient perception of treatment benefit, bladder diary variables, International Prostate Symptom Scores, and safety and tolerability were assessed. RESULTS: A total of 172 men (80%) receiving tolterodine ER plus tamsulosin reported treatment benefit by week 12 compared with 132 patients (62%) receiving placebo (P<.001), 146 (71%) receiving tamsulosin (P=.06 vs placebo), or 135 (65%) receiving tolterodine ER (P=.48 vs placebo). Patients receiving tolterodine ER plus tamsulosin compared with placebo experienced significant reductions in urgency urinary incontinence (-0.88 vs -0.31, P=.005), urgency episodes without incontinence (-3.33 vs -2.54, P=.03), micturitions per 24 hours (-2.54 vs -1.41, P<.001), and micturitions per night (-0.59 vs -0.39, P.02). Patients receiving tolterodine ER plus tamsulosin demonstrated significant improvements on the total International Prostate Symptom Score (-8.02 vs placebo, -6.19, P=.003) and QOL item (-1.61 vs -1.17, P=.003). All interventions were well tolerated. The incidence of acute urinary retention requiring catheterization was low (tolterodine ER plus tamsulosin, 0.4%; tolterodine ER, 0.5%; tamsulosin, 0%; and placebo, 0%). CONCLUSIONS: These results suggest that treatment with tolterodine ER plus tamsulosin for 12 weeks provides benefit for men with moderate to severe lower urinary tract symptoms including overactive bladder. Clinical Trials Registration [clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00147654.

Karademir, K., K. Baykal, et al. (2005). "A peripheral neuromodulation technique for curing detrusor overactivity: Stoller afferent neurostimulation." *Scandinavian Journal of Urology & Nephrology* **39**(3): 230-3.

OBJECTIVE: To perform Stoller afferent neurostimulation (SANS) with and without a low-dose anticholinergic (oxybutynin hydrochloride) in patients with detrusor overactivity and compare the results obtained with the two therapeutic approaches. MATERIAL AND METHODS: A total of 43 patients with symptoms of detrusor overactivity (frequency, urgency, urge incontinence) underwent urodynamic studies (UDS). Those in whom UDS revealed phasic detrusor overactivity were evaluated using a quality of life questionnaire and voiding diaries. Patients were randomized

into two groups: Group 1 received SANS alone; Group 2 received SANS combined with a low-dose anticholinergic (5 mg of oral oxybutynin hydrochloride). Both groups were re-evaluated following 8 weeks of therapy. RESULTS: There were 21 patients in Group 1 and 22 in Group 2. The treatment response rate was 61.6% and 83.2% in Groups 1 and 2, respectively. In both groups, the best symptomatic improvements were obtained in patients with urge incontinence. The percentage decreases in the mean number of symptoms of frequency and urgency were 36.7% and 46.1%, respectively in Group 1 and 44.2% and 61.1%, respectively in Group 2. However, there were no statistically significant differences in the effects on frequency and urgency between the two groups. The anticholinergic drug was well tolerated by all patients in Group 2. One patient reported local tenderness, and a small hematoma developed in another following SANS therapy. CONCLUSION: SANS is an easy and inexpensive therapeutic method with low morbidity in patients with an overactive bladder. Combination with a low-dose anticholinergic increases the success rate without causing any significant side-effects.

Kelleher, C., L. Cardozo, et al. (2006). "Solifenacin: as effective in mixed urinary incontinence as in urge urinary incontinence." *International Urogynecology Journal* **17**(4): 382-8.

Patients with mixed urinary incontinence (MUI) are frequently treated with antimuscarinic therapy, despite little data being previously published for this patient group. We present a subgroup analysis of patients with overactive bladder syndrome, assessing the efficacy of once-daily solifenacin succinate in patients with MUI (n = 1041) or urge urinary incontinence (UII; n = 1648) only. A greater proportion of patients receiving solifenacin achieved resolution of incontinence in both the MUI and UII groups (MUI: 5 mg = 43%, 10 mg = 49%; UII: 5 mg = 55%, 10 mg = 54%) compared with patients receiving placebo (MUI 33%, UII 35%). Baseline to endpoint improvements in all other symptoms were statistically significant vs placebo for both solifenacin doses in both cohorts. The incidence of adverse events was comparable between the MUI and UII cohorts. This analysis shows that once-daily solifenacin was as effective and well tolerated in patients with MUI as in patients with UII.

Nitti, V. W., R. Dmochowski, et al. (2006). "Efficacy and tolerability of tolterodine extended-release in continent patients with overactive bladder and nocturia." *BJU International* **97**(6): 1262-6.

OBJECTIVE: To evaluate the clinical efficacy and tolerability of tolterodine extended-release (ER) in continent patients with overactive bladder (OAB) and nocturia. PATIENTS AND METHODS: A post hoc analysis was conducted of data from a 12-week, double-blind study of 850 patients randomized to tolterodine ER (4 mg once daily) or placebo, taken within 4 h of going to bed. Patients with a mean of  $\geq 8$  voids/24 h were enrolled, including a mean of  $\geq 2.5$  voids/night. Patients completed 7-day voiding diaries, and for each void an urgency rating was assessed using a 5-point scale (1, none; 5, urgency incontinence); 24-h voids were categorized by urgency rating: total (1-5), non-OAB (1-2), OAB (3-4), and severe OAB (4-5) voids. All adverse events were recorded. RESULTS: The post hoc analysis included 513 patients (243 placebo; 270 tolterodine ER; 58% men) who were continent at baseline; 47% of 24-h voids were classed as non-OAB, and 12% as severe OAB. After 12 weeks of treatment, tolterodine ER significantly reduced mean urgency rating and 24-h OAB, severe OAB, and total voids vs placebo. Tolterodine ER did not affect normal, non-OAB voids, and there were no significant adverse events related to voiding. Other than dry mouth (tolterodine ER, 9% vs placebo, 2%), all the adverse events were reported in  $<3\%$  of patients;  $<2\%$  of patients receiving tolterodine ER withdrew because of adverse events. CONCLUSIONS: In continent patients with OAB, tolterodine ER significantly improved urgency rating and reduced 24-h OAB, severe OAB, and total voids, suggesting that it is an effective and well-tolerated treatment option for this subpopulation. More studies are needed to better understand the clinical efficacy of tolterodine ER in this under evaluated group of OAB patients without incontinence.

Rackley, R., J. P. Weiss, et al. (2006). "Nighttime dosing with tolterodine reduces overactive bladder-related nocturnal micturitions in patients with overactive bladder and nocturia." *Urology* **67**(4): 731-6; discussion 736.

**OBJECTIVES:** To evaluate the efficacy and tolerability of nighttime tolterodine dosing on urgency-related micturitions in patients with overactive bladder (OAB) and nocturia.

**METHODS:** This was a 12-week randomized controlled study of 850 patients given 4 mg tolterodine extended release (TER) or placebo once daily 4 hours or less before bed. Patients with eight or more micturitions/24 hours and a mean of 2.5 episodes/night or more were included. Changes in the number of nighttime and 24-hour micturitions were analyzed by urgency rating per micturition. The urgency per micturition was recorded in 7-day diaries using a 5-point rating scale (score 1 to 5). Each micturition was classified according to the following urgency rating categories: total (1 to 5), non-OAB (1 to 2), or OAB (3 to 5). OAB-related micturitions were further classified as nonsevere (score 3) and severe (score 4 to 5). **RESULTS:** TER reduced the total number of nocturnal micturitions, but, compared with placebo, this difference was not statistically significant. However, TER did significantly reduce OAB-related and severe OAB-related nocturnal micturitions compared with placebo. TER had no effect on non-OAB micturitions. TER significantly reduced the total, OAB, and severe OAB micturitions during 24-hour and daytime intervals compared with placebo. Significantly more TER-treated than placebo-treated patients reported a treatment benefit and willingness to continue treatment. Adverse events associated with nighttime dosing of TER versus placebo were few. **CONCLUSIONS:** TER significantly reduced OAB-related micturitions during 24-hour, daytime, and nighttime intervals. TER did not affect normal (non-OAB) micturitions. Nighttime dosing with TER was associated with few adverse events and adverse event-related withdrawals. The 24-hour efficacy of TER was maintained with nighttime dosing.

Roehrborn, C. G., P. Abrams, et al. (2006). "Efficacy and tolerability of tolterodine extended-release in men with overactive bladder and urgency urinary incontinence." *BJU International* **97**(5): 1003-6.

A group of authors from the USA evaluated the efficacy and tolerability of tolterodine extended-release on objective and subjective endpoints in men with an overactive bladder. They found that it significantly reduced incontinent episodes and improved patient perception of treatment benefit in men with an overactive bladder **OBJECTIVE:** To evaluate the efficacy and tolerability of tolterodine extended-release (ER) on objective and subjective endpoints in men with overactive bladder (OAB) and urgency urinary incontinence (UI). **PATIENTS AND METHODS** This was a post hoc analysis of data collected from men with OAB enrolled in a 12-week, double-blind, placebo-controlled trial of tolterodine ER (4 mg once daily; tolterodine ER registration trial) and included men with urinary frequency (> or =8 micturitions/24 h) and urgency UI (> or =5 episodes/week). UI episodes were assessed using 7-day bladder diaries. Patient perception of treatment benefit was evaluated after 12 weeks. Adverse events (AEs) were recorded throughout the study. **RESULTS:** In all, 163 men with OAB (placebo, 86; tolterodine ER, 77; mean age 65 years) were evaluated. Baseline demographics and clinical characteristics were similar for the two treatment groups. Compared with placebo, tolterodine ER significantly reduced weekly UI episodes (median % change, -71% vs -40%,  $P < 0.05$ ; mean numeric change, -11.9 vs -5.9,  $P = 0.02$ ). Men receiving tolterodine ER had fewer micturitions/24 h, but this was not a significant difference from placebo (median % change, -12% vs -4%,  $P = 0.22$ ). Significantly more men treated with tolterodine-ER (63%) than placebo-treated men (46%) reported a benefit of treatment after 12 weeks ( $P = 0.04$ ). The most commonly reported AEs associated with tolterodine-ER vs placebo were dry mouth (16% vs 7%), constipation (4% vs 9%), dyspepsia (4% vs 1%), dizziness (5% vs 1%), and somnolence (3% vs 1%). One of the men receiving tolterodine ER had symptoms suggestive of urinary retention that led to his withdrawal from the study. None of the men had acute urinary retention requiring catheterization. **CONCLUSION:** In men with OAB and

urgency UI, tolterodine ER was well tolerated and significantly reduced episodes of urgency UI, and improved patient perception of treatment benefit.

Rudy, D., K. Cline, et al. (2006). "Multicenter phase III trial studying trospium chloride in patients with overactive bladder." *Urology* **67**(2): 275-80.

**OBJECTIVES:** To study the efficacy and safety of trospium chloride in treating overactive bladder. Trospium chloride is an anticholinergic agent with predominantly peripheral nonselective antimuscarinic activity and thus has potential therapeutic value in treating patients with overactive bladder. **METHODS:** Patients with overactive bladder were randomized on a 1:1 basis to either placebo or trospium chloride 20 mg twice daily in this 12-week, multicenter, parallel, double-blind, placebo-controlled study. The primary endpoint was the change in the average number of toilet voids per 24 hours. The secondary efficacy variables were changes in the average void urgency severity, volume per toilet void, urge frequency, number of daily urge urinary incontinence episodes, and daytime sleepiness. **RESULTS:** A total of 658 patients were randomized at 52 sites. Trospium chloride significantly decreased the average number of daily toilet voids, average urgency severity, urge frequency, and urge urinary incontinence episodes and increased the average volume per void at weeks 1, 4, and 12. All effects occurred by the end of week 1 and all improved and were sustained throughout the 12-week study. Adverse events included dry mouth and constipation. **CONCLUSIONS:** Trospium chloride had significant and sustained effectiveness beginning at the end of week 1 and continuing through 12 weeks of treatment. Trospium chloride was also safe and generally well tolerated.

Rudy, D., K. Cline, et al. (2006). "Time to onset of improvement in symptoms of overactive bladder using antimuscarinic treatment." *BJU International* **97**(3): 540-6.

**OBJECTIVE:** To evaluate the time to onset of statistically significant and clinically meaningful effects of trospium chloride in patients with an overactive bladder (OAB). **PATIENTS AND METHODS:** Data from a recent Phase III clinical study of trospium chloride were obtained, in which 658 patients with OAB were randomized (1 : 1) to placebo or trospium chloride 20 mg twice daily for 12 weeks. Original study safety endpoints consisting of adverse events, vital signs, electrocardiograms, and laboratory changes were collected, while original efficacy endpoints included number of toilet voids/day, urgency severity per toilet void, urge urinary incontinence (UUI), and volume voided per toilet void at weeks 1, 4, and 12. Results were also analysed using the OAB Symptom Composite Score (OAB-SCS). The efficacy analysis focused on changes from baseline in these endpoints from 1 to 7 days of treatment to establish the earliest point at which there was statistical significance or clinical efficacy. **RESULTS:** There were statistically significant improvements in efficacy over placebo in endpoints (toilet voids, urgency severity/void, UUI episodes, OAB-SCS) within a few days of treatment, with improvements in symptoms continuing to 7 days of treatment. There were clinically meaningful improvements in most endpoints by the end of the first week. **CONCLUSIONS:** The time to onset of the clinical effect should be studied more extensively to identify when patients might expect a clinically meaningful improvement in their OAB-related symptoms.

Song, C., J. T. Park, et al. (2006). "Effects of bladder training and/or tolterodine in female patients with overactive bladder syndrome: a prospective, randomized study." *Journal of Korean Medical Science* **21**(6): 1060-3.

We compared the effects of bladder training and/or tolterodine as first line treatment in female patients with overactive bladder (OAB). One hundred and thirty-nine female patients with OAB were randomized to treatment with bladder training (BT), tolterodine (To, 2 mg twice daily) or both (Co) for 12 weeks. Treatment efficacy was measured by micturition diary, urgency scores and patients' subjective assessment of their bladder condition. Mean frequency and nocturia significantly decreased in all treatment groups, declining 25.9% and 56.1%, respectively, in the

BT group; 30.2% and 65.4%, respectively, in the To group; and 33.5% and 66.3%, respectively in the Co group ( $p < 0.05$  for each). The decrease in frequency was significantly greater in the Co group than in the BT group ( $p < 0.05$ ). Mean urgency score decreased by 44.8%, 62.2% and 60.2% in the BT, To, and Co groups, respectively, and the improvement was significantly greater in the To and Co groups than in the BT group ( $p < 0.05$  for each). Although BT, To and their combination were all effective in controlling OAB symptoms, combination therapy was more effective than either method alone. Tolterodine alone may be instituted as a first-line therapy, but may be more effective when combined with bladder training.

Wang, A. C., S.-Y. Chih, et al. (2006). "Comparison of electric stimulation and oxybutynin chloride in management of overactive bladder with special reference to urinary urgency: a randomized placebo-controlled trial." *Urology* **68**(5): 999-1004.

**OBJECTIVES:** To compare the efficacy of electric stimulation (ES), oxybutynin, and placebo in managing the symptom complex of overactive bladder (OAB), particularly urgency. **METHODS:** A randomized placebo-controlled trial was conducted for 68 patients with OAB, placing emphasis on urinary urgency. The interventions for the 12-week treatment period, conducted by the physiotherapist, who was unaware of the progress and outcome, included a vaginal ES program using biphasic symmetric, pulsed current with a 10-Hz frequency, 400-micros pulse width, 10/5 duty cycle, and varying intensity; and oxybutynin (2.5 mg) or placebo three times per day. Identical preintervention and postintervention assessments included the measurement of warning time, urodynamics, voiding diaries, and King's Health Questionnaire. **RESULTS:** Of the 68 women who completed this study, 24 were in the ES, 23 in the oxybutynin, and 21 in the placebo group. The between-group comparison showed that significant improvements in daily voided volume, pad count, number of urgency and nocturia episodes, and the domain 2 score and total score of the King's Health Questionnaire existed between the ES and the other groups (all  $P < \text{or} = 0.050$ ). The changes in warning time, maximal voided volume, number of urgency episodes, and frequency were significantly improved between oxybutynin and placebo (all  $P < 0.013$ ). Additionally, a comparison of the voided volume in uroflowmetry between the ES and placebo groups revealed a greater difference after treatment ( $P = 0.013$ ). The reduction rate of OAB was 58.4% for the ES, 39.1% for the oxybutynin, and 9.5% for the placebo group ( $P = 0.036$ ). **CONCLUSIONS:** ES had the greatest subjective outcome for OAB and was the most effective of the three treatments. Oxybutynin was more effective than placebo.

Zinner, N., J. Susset, et al. (2006). "Efficacy, tolerability and safety of darifenacin, an M(3) selective receptor antagonist: an investigation of warning time in patients with OAB.[erratum appears in Int J Clin Pract. 2006 Jul;60(7):890]." *International Journal of Clinical Practice* **60**(1): 119-26.

This double-blind, randomised placebo-controlled, multicentre study evaluated the efficacy, tolerability and safety of 12 weeks' treatment with controlled release darifenacin 15 mg once daily (qd), in 445 patients with overactive bladder (OAB). The primary endpoint was warning time (time from first sensation of urgency to voiding), and secondary endpoints included urge incontinence episodes and volume voided. Darifenacin treatment resulted in numerical increases in warning time, but these were not significant compared with placebo -- highlighting difficulties in assessing this parameter. Significant improvements were seen with darifenacin vs. placebo in urge incontinence episodes/week, volume voided and quality of life (QoL). Darifenacin was associated with increases in urgency-free time (UFT; time between any void to the next urgency event) vs. placebo. Treatment was well tolerated; the most commonly reported adverse events were the typical antimuscarinic effects of dry mouth and constipation, both infrequently leading to discontinuation. This study demonstrated the difficulty in measuring warning time, due in part to its subjective nature; the authors believe further investigation is warranted to allow urgency to be better defined. Further investigation of UFT is required to determine its role in evaluating

urgency. The study confirmed that darifenacin 15 mg qd is an effective and well-tolerated treatment for OAB, which improves QoL.

Zinner, N., J. Tuttle, et al. (2005). "Efficacy and tolerability of darifenacin, a muscarinic M3 selective receptor antagonist (M3 SRA), compared with oxybutynin in the treatment of patients with overactive bladder." *World Journal of Urology* **23**(4): 248-52.

A randomized, double-blind, placebo-controlled, four-way crossover, safety study of darifenacin versus oxybutynin was carried out on 76 patients with overactive bladder (OAB). Adults with OAB received 2 weeks each of darifenacin 15 and 30 mg once daily (q.d.), oxybutynin 5 mg three times daily (t.i.d.) and placebo, in random sequence at 10-day intervals. Darifenacin and oxybutynin significantly reduced incontinence episodes, and the number/severity of urgency episodes (all  $P < 0.05$  versus placebo). Improvements in OAB symptoms with darifenacin were dose-dependent. Dry mouth was less common with darifenacin 15 mg than oxybutynin (13% and 36%;  $P < 0.05$ ), while constipation was comparable (10% and 8%, respectively). Corresponding rates for darifenacin 30 mg were 34% and 21%, respectively. Patients only reported blurred vision or dizziness with oxybutynin (3% and 2%, respectively). Darifenacin (15 mg q.d.) provides comparable efficacy with improved tolerability versus oxybutynin (5 mg t.i.d.) in the treatment of patients with OAB.