

# Drug Class Review

## Overactive Bladder Drugs

Preliminary Scan Report #2

March 2015

Last Report: Summary Review, June 2013

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. 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 to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. 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 U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

### Date of Previous Report

Summary Review: June 2013 (searches through May 2013)

### Date of Previous Scans

Scan #1: February 2014

### 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:

1. What is the evidence on the efficacy and effectiveness of the overactive bladder drugs in adults?
2. What is the evidence on the harms of overactive bladder drugs in adults?
3. What is the evidence on whether there are subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one overactive bladder drug is more effective or associated with fewer harms?

## **Inclusion Criteria**

### **Populations**

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

### **Drugs**

Darifenacin, fesoterodine fumarate, flavoxate hydrochloride, mirabegron, oxybutynin chloride, solifenacin succinate, tolterodine tartrate, and trospium chloride.

### **Comparators**

The primary comparison is one of the included overactive bladder drugs with another included overactive bladder drug.

### **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, and global evaluation of treatment)

### **Harms 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 (from previous report)**

For effectiveness:

- Controlled clinical trials
- Recent, good quality systematic reviews
- Comparative observational studies of at least 1 year’s duration and reporting functional outcomes

For harms:

- Controlled clinical trials
- Comparative observational studies (cohort or case-control) with a well-defined neuropathic pain population
- Non-comparative observational studies only if the duration is 1 year or longer, and if serious harms are reported; a serious harm is one that results in long-term health effects or mortality

## METHODS FOR SCAN

### Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations February 2014 through February 2015 using terms for included drugs. We limited results to randomized controlled trials and controlled clinical trials conducted in humans and published in English. We also searched the FDA website (<http://www.fda.gov/medwatch/safety.htm> and <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>) for identification of new drugs, new populations, and new serious harms. To identify new drugs, we also searched CenterWatch (<http://www.centerwatch.com>), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>) (<http://www.effectivehealthcare.ahrq.gov/>), the Canadian Agency for Drugs and Technology in Health (<http://www.cadth.ca/>), the VA Evidence-based Synthesis Program (<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>), and University of York Centre for Reviews and Dissemination (<http://www.york.ac.uk/inst/crd/crdreports.htm> - “Our Publications” and “Our Databases”). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

### Study Selection

We included only potentially relevant randomized controlled trials, controlled clinical trials, and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## RESULTS

### New Drugs

#### ***Identified in this Preliminary Update Scan***

None.

#### ***Identified in previous Preliminary Update Scan***

None.

### New Uses

#### ***Identified in this Preliminary Update Scan***

None.

#### ***Identified in previous Preliminary Update Scan***

None.

## **New Serious Harms**

### ***Identified in this Preliminary Update Scan***

None.

### ***Identified in previous Preliminary Update Scan***

None.

## **New Comparative Effectiveness Reviews**

### ***Identified in this Preliminary Update Scan***

None.

### ***Identified in previous Preliminary Update Scan***

No new comparative effectiveness reviews were identified through searches of the AHRQ, CADTH, VA, and CRD websites.

## **Randomized Controlled Trials**

### ***Identified in this Preliminary Update Scan***

Medline searches for this scan resulted in 11 citations. Of those, 4 were potentially relevant new trials, all of which were placebo-controlled trials of mirabegron each with a tolterodine active-controlled arm. One trial was a phase II proof-of-concept study, one trial was a phase II dose-ranging study, one trial was a post-hoc analysis of a previously conducted European-Australian phase III trial (NCT00689104) in patients with and without prior antimuscarinic therapy for overactive bladder, and the last trial was a phase III study in Japanese patients. All trials studied the change in mean number of micturitions per 24 hours.

### ***Identified in previous Preliminary Update Scan***

Eleven potentially relevant new trials were identified in the previous preliminary update scan. An additional 13 trials were previously reported in the Summary Review as published since the search dates of the included systematic reviews. Together, with the 4 trials identified in the current preliminary update scan, we have identified a total of 28 new trials (9 head-to-head trials and 19 placebo-controlled trials). Characteristics of head-to-head studies are included in Table 1 and abstracts are available in Appendix A. Placebo-controlled studies are listed by drug of study, below, and abstracts are available upon request. Existing new head-to-head evidence compares: solifenacin with darifenacin; mirabegron, fesoterodine, solifenacin and trospium with tolterodine; and trospium, solifenacin, and tolterodine with oxybutynin.

**Table 1. New head-to-head trials of overactive bladder drugs (N=9)**

| Author, Year         | N     | Drug A                          | Drug B              | Population Details  |
|----------------------|-------|---------------------------------|---------------------|---|
| But, 2012            | 77    | Solifenacin 5 mg                | Darifenacin 7.5 mg  | Open label, all women, Slovenian patients                                       |
| Chapple, 2013        | 2,444 | Mirabegron 50 or 100 mg         | ER Tolterodine 4 mg | Patients with OAB symptoms for at least 3 months                                |
| Corcos, 2011         | 1,013 | Fesoterodine 4 mg               | ER Tolterodine 4 mg | Patients with OAB symptoms for at least 3 months                                |
| Dede, 2013           | 90    | Tolterodine<br>Trospium         | Oxybutynin          | Women with urge urinary incontinence  |
| Herschorn, 2011      | 132   | Solifenacin 5 mg                | IR Oxybutynin 15 mg | Patients with OAB symptoms for at least 3 months                                |
| Hsiao, 2011          | 48    | Solifenacin 5 mg                | ER Tolterodine 4 mg | Women, post-marketing study   |
| Kaplan, 2011         | 2,417 | Fesoterodine 8 mg               | ER Tolterodine 4 mg | Subjects with >1 urgency incontinence episode and ≥ 8 micturitions per 24 hours |
| Konstantinidis, 2013 | 47    | Fesoterodine plus<br>Tamsulosin | Tamsulosin          | Men > 50 with lower urinary tract symptoms                                      |
| Khullar, 2013        | 1,978 | Mirabegron 50 or 100 mg         | ER Tolterodine 4 mg | Patients with OAB symptoms for at least 3 months                                |

**New placebo-controlled trials of overactive bladder drugs (N=19)****Fesoterodine**

- Kaplan, 2012
- Staskin, 2011
- Wagg, 2013
- Weiss, 2013

**Mirabegron**

- Chapple, 2013a
- Chapple, 2013b
- Herschorn, 2013
- Khullar, 2013
- Nitti, 2013a
- Nitti, 2013b
- Yamaguchi, 2014

**Oxybutynin**

- Sand, 2012

**Solifenacin**

- Cardozo, 2013
- Oreskovic, 2012
- Yokoyama, 2011

**Solifenacin + Tamsulosin**

- Kaplan, 2013a
- Kaplan, 2013b
- Yamaguchi, 2011

**Tolterodine SR + Doxazosin**

- Lee, 2011

\*Shading indicates trials identified in the current preliminary update scan.

**SUMMARY**

Cumulatively, we have identified no new drugs, new uses, new serious harms, and new comprehensive comparative effectiveness reviews of overactive bladder drugs since the Summary Review. We have identified a total of 28 new trials, including 9 head-to-head trials. With the exception of one small trial in women (N=77), which compared darifenacin with solifenacin, the new trials compared the newer overactive bladder drugs with tolterodine, oxybutynin and/or placebo.

## APPENDIX A. ABSTRACTS OF POTENTIALLY RELEVANT NEW TRIALS OF OVERACTIVE BLADDER DRUGS

### Head-to-head trials (N=9)

But, I., M. S. Goldstajn, et al. (2012). "Comparison of two selective muscarinic receptor antagonists (solifenacin and darifenacin) in women with overactive bladder--the SOLIDAR study." *Collegium Antropologicum* **36**(4): 1347-1353.

Overactive bladder (OAB) is a common, often debilitating, condition defined as urgency and urge incontinence, usually with frequency and nocturia. The use of muscarinic receptor antagonists are the mainstay of treatment, but their non-selectivity can result in unacceptable adverse effects that limit their usefulness. The purpose of this study was to evaluate 2 of the newer antimuscarinic agents, solifenacin and darifenacin, which demonstrate greater selectivity, in order to compare their tolerance and effectiveness. This was a multicentre, prospective, randomised, comparative (1:1) open-label study conducted in 4 centres comprising Slovenian gynaecologists and urologists. A total of 77 female patients with OAB were enrolled who received either solifenacin 5 mg or darifenacin 7.5 mg once daily. Study measurements consisted of changes in OAB symptoms and quality of life (QOL) evaluations after 1 and 3 months of treatment. Both treatment groups showing a reduction in all OAB symptoms but with no notable difference being seen between the 2 groups. Solifenacin though showed statistically greater improvements in QOL, better overall treatment satisfaction, and a decreased incidence of dry mouth after 3 months of treatment compared to the darifenacin group. This study demonstrates interesting initial results and indicates that these 2 drugs have a different profile that may confer an advantage to patients, but further methodologically rigorous studies comparing the use of solifenacin and darifenacin in OAB are required to establish the differences between these drugs over longer periods of treatment.

Chapple CR. Kaplan SA. Mitcheson D. Klecka J. Cummings J. Drogendijk T. Dorrepaal C. Martin N. *European Urology*. 63(2):296-305, 2013 Feb. "Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a beta(3)-adrenoceptor agonist, in overactive bladder. "

**BACKGROUND:** Despite several antimuscarinic treatment options for overactive bladder (OAB), there is still a need for distinct treatment approaches to manage this condition. Mirabegron, a beta(3)-adrenoceptor agonist, has demonstrated efficacy and tolerability for up to 12 wk in phase 3 trials.

**OBJECTIVE:** To assess the 12-mo safety and efficacy of mirabegron.

**DESIGN, SETTING, AND PARTICIPANTS:** Patients > 18 yr of age with OAB symptoms for > 3 mo.

**INTERVENTIONS:** After a 2-wk single-blind placebo run-in, patients with eight or more micturitions per 24h and three or more urgency episodes in a 3-d micturition diary were randomized 1:1:1 to once-daily mirabegron 50mg, mirabegron 100mg, or tolterodine extended release (ER) 4 mg for 12 mo.

**OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS:** Primary variable: incidence and severity of treatment-emergent AEs (TEAEs). Secondary variables: change from baseline at months 1, 3, 6, 9, and 12 in key OAB symptoms.

**RESULTS AND LIMITATIONS:** A total of 812, 820, and 812 patients received mirabegron 50mg, mirabegron 100mg, and tolterodine ER 4 mg, respectively. Baseline demographic and OAB characteristics were similar across groups. TEAEs were reported in 59.7%, 61.3%, and 62.6% of patients, respectively; most were mild or moderate. Serious TEAEs were reported in 5.2%, 6.2%, and 5.4% of patients, respectively. The most common TEAEs were similar across groups. Dry mouth was reported by 2.8%, 2.3%, and 8.6% of patients, respectively. Adjusted mean changes from baseline to final visit in morning systolic blood pressure were 0.2, 0.4, and -0.5mm Hg for mirabegron 50mg, 100mg, and tolterodine ER 4 mg, respectively. Mirabegron and the active control, tolterodine, improved key OAB symptoms from the first measured time point of 4 wk, and efficacy was maintained throughout the 12-mo treatment period. The study was not placebo controlled, which was a limitation.

**CONCLUSIONS:** The safety and tolerability of mirabegron was established over 1 yr, with sustained efficacy observed over this treatment period.

Corcos, J., J. C. Angulo, et al. (2011). "Effect of fesoterodine 4 mg on bladder diary and patient-reported outcomes during the first week of treatment in subjects with overactive bladder." *Current Medical Research & Opinion* **27**(5): 1059-1065.

**OBJECTIVE:** To assess the onset of efficacy of fesoterodine 4 mg compared with placebo in subjects with overactive bladder (OAB) symptoms.

**RESEARCH DESIGN AND METHODS:** Subjects who reported OAB symptoms for  $\geq$  3 months and recorded  $\geq$  8 micturitions and  $\geq$  1 urgency urinary incontinence (UUI) episode per 24 hours in 3-day baseline diaries were randomized to fesoterodine 4 mg, tolterodine extended release (ER) 4 mg, or placebo. This is an analysis of first week data from a 12-week, double-blind trial. ClinicalTrials.gov unique ID: NCT00444925.

**MAIN OUTCOME MEASURES:** Baseline to week 1 changes in 3-day bladder diary variables, Patient Perception of Bladder Condition (PPBC), and Urgency Perception Scale (UPS) scores reported by subjects receiving fesoterodine 4mg or placebo.

**RESULTS:** By week 1, fesoterodine 4 mg (n = 679) was associated with significantly greater improvements compared with placebo (n = 334) in micturitions, urgency, severe urgency and UUI episodes, frequency-urgency sum, and MVV per 24 hours and 3-day diary-dry rate (all  $p < 0.05$ ), but not nocturnal micturitions per 24 hours ( $p = 0.273$ ). These differences were significant as early as day 5 of treatment (i.e., day 1 of the 3-day diary) for all diary endpoints except nocturnal micturitions and MVV. Changes in PPBC scores were significantly more favorable with fesoterodine 4mg versus placebo ( $p = 0.0143$ ); changes in UPS scores were not significantly different ( $p = 0.077$ ).

**CONCLUSION:** The results provide evidence that patients receiving fesoterodine 4 mg for their OAB symptoms may expect to experience a response as early as 1 week after initiating treatment. One limitation is that, although 65% of subjects had received treatment with antimuscarinics before the study, whether subjects were dissatisfied with previous treatment and reasons for dissatisfaction were not collected. This might affect the magnitude of outcome improvements. Also, it is not known whether the UPS is sensitive enough to detect treatment differences as early as week 1.

Dede H. Dolen I. Dede FS. Sivaslioglu AA. What is the success of drug treatment in urge urinary incontinence? What should be measured? *Archives of Gynecology & Obstetrics*. 287(3):511-8, 2013 Mar.

**PURPOSE:** The aim of this study is to evaluate the efficacy and the tolerability of three classic antimuscarinic drugs used in the treatment of over active bladder syndrome using clinical data and quality of life tests, and to evaluate the parameters affecting the success of these drugs.

**METHODS:** A total of 90 patients with urge urinary incontinence were randomly allocated into three groups either to receive tolterodine (group A), trospium chloride (group B) or oxybutynin (group C). Urogenital distress inventory short form (UDI-6) and Incontinence impact questionnaire short form (IIQ-7) of the Turkish Urogynecology and Pelvic Reconstructive Surgery Association were performed to each patient before and after treatment to evaluate the effectiveness and tolerability of the antimuscarinic drugs. Adverse events were also recorded during treatment.

**RESULTS:** Improved urodynamic test values were recorded after 6 weeks of treatment in each group. Similarly, statistically significant differences were observed in UDI-6 and IIQ-7 test scores before and after treatment. Complete cure was achieved in 86 % of patients in group A; however, complete cure rates were 67 and 80 % in group B and C, respectively. Although, patients reported comparable tolerability against trospium chloride (77 %) and tolterodine (80 %), only 23 % of patients using oxybutynin considered the drug as tolerable. The most common side effect was dry mouth, followed by insomnia. Both dry mouth and insomnia was highest in group C (50 %). One patient (0.3 %) in group B and two patients (0.7 %) in group C reported that they did not want to continue to use the drug.

**CONCLUSION:** Antimuscarinic medications are very successful in the treatment of urge urinary incontinence; however, the success of treatment is not only limited to clinical improvement. Patients do not regard a drug as successful unless it is tolerable, easy to adapt to the daily life and improve the quality of life even it has very successful clinical outcomes.

Herschorn, S., P. Pommerville, et al. (2011). "Tolerability of solifenacin and oxybutynin immediate release in older (> 65 years) and younger (<= 65 years) patients with overactive bladder: sub-analysis from a Canadian, randomized, double-blind study." *Current Medical Research & Opinion* **27**(2): 375-382.

**OBJECTIVE:** Overactive bladder (OAB) is a common condition whose prevalence increases with age. Antimuscarinic agents are the pharmacologic treatment of choice, but adverse events such as dry mouth may lead to early discontinuation. The purpose of this analysis was to compare the incidence and severity of dry mouth and other adverse events with solifenacin 5 mg/day and oxybutynin immediate release (IR) 15 mg/day in patients <= 65 years and >65 years in the Canadian VECTOR study (VEsicare in Comparison To Oxybutynin for oveRactive bladder patients).

**RESEARCH DESIGN AND METHODS:** VECTOR was a randomized, multicentre, prospective, double-blind, double-dummy study in 132 subjects with >= 1 urgency episode per 24 h, with or without urgency incontinence, and >= 8 micturitions per 24 h for >= 3 months. After a 2-week washout, patients received solifenacin 5 mg once daily or oxybutynin IR 5 mg tid for 8 weeks. For the current post-hoc analysis, adverse events were evaluated in subgroups of patients <= 65 years and >65 years, using a full logistic regression model, multinomial logit regression model and reduced model.

**RESULTS:** The incidence and severity of dry mouth and other adverse events with solifenacin were similar between younger and older patients. In both age subgroups,

solifenacin 5 mg/day was associated with fewer episodes and lower severity of dry mouth, and a lower discontinuation rate, compared with oxybutynin IR 15 mg/day. CONCLUSIONS: Solifenacin 5 mg/day was better tolerated than oxybutynin IR 15 mg/day in younger ( $\leq 65$  years) and older ( $> 65$  years) subgroups. Solifenacin was equally well tolerated in both age subgroups. Limitations of the analysis were that the study was not preplanned to perform post-hoc subgroup analysis, patients knew that dry mouth was a primary outcome, and the study used fixed doses of each drug.

Hsiao, S.-M., T.-C. Chang, et al. (2011). "Comparisons of urodynamic effects, therapeutic efficacy and safety of solifenacin versus tolterodine for female overactive bladder syndrome." *Journal of Obstetrics & Gynaecology Research* **37**(8): 1084-1091.

AIM: To evaluate the urodynamic effects, therapeutic efficacy and safety of solifenacin versus tolterodine treatment for women with overactive bladder syndrome. METHODS: Patients were randomized to receive either solifenacin 5 mg or tolterodine ER 4 mg once a day for 12 weeks at each four-week visit in a post-marketing study. Only women (solifenacin [n = 26] vs. tolterodine [n = 22]) were included in this subgroup analysis. Adverse events and changes of urodynamic values and clinical data were compared between the solifenacin and tolterodine groups.

RESULTS: The volume voided per micturition increased in the solifenacin group (n = 21) (P = 0.04). The strong desire to void and pad-test result improved in the tolterodine group (n = 21; P = 0.02 and 0.03, respectively). There were no between-group differences in changes of any urodynamic data, voiding diary values or adverse events after treatment; however, changes of heart rate differed between the two groups (P = 0.0004), especially at visit 2 (solifenacin vs. tolterodine, -4.3 vs. 3.8, P = 0.02) and visit 3 (-3.2 vs. 4.8, P = 0.03).

CONCLUSIONS: Both solifenacin and tolterodine had similar urodynamic effects, therapeutic efficacy and adverse events in treating women with overactive bladder syndrome; however, tolterodine had a greater effect in increasing heart rate than solifenacin. 2011 The Authors. *Journal of Obstetrics and Gynaecology Research* 2011 Japan Society of Obstetrics and Gynecology.

Kaplan, S. A., T. Schneider, et al. (2011). "Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: a prospective, head-to-head, placebo-controlled trial." *BJU International* **107**(9): 1432-1440.

OBJECTIVE: \* To show the superior efficacy of fesoterodine over tolterodine extended release (ER) in a placebo-controlled overactive bladder (OAB) trial with predefined treatment comparisons for both diary measures and patient-reported outcomes.

MATERIALS AND METHODS: \* In this 12-week, double-blind, double-dummy trial, subjects reporting  $>1$  urgency urinary incontinence (UUI) episode and  $\geq 8$  micturitions per 24 h at baseline were randomized to fesoterodine (4 mg for 1 week, 8 mg for 11 weeks), tolterodine ER 4 mg, or placebo. \* Subjects completed 3-day bladder diaries, the Patient Perception of Bladder Condition (PPBC) and the Urgency Perception Scale (UPS) at baseline and weeks 1, 4 and 12 and the OAB Questionnaire at baseline and week 12.

RESULTS: \* A total of 2417 subjects were randomized. At week 12, fesoterodine 8 mg showed superiority over tolterodine ER 4 mg and placebo on UUI episodes (primary endpoint), micturitions, urgency and most other diary endpoints, and on the PPBC, UPS and all OAB Questionnaire scales and domains (all P  $< 0.05$ ). \* Superiority of

fesoterodine 8 mg over tolterodine ER 4 mg was seen as early as week 4 (3 weeks after escalation to fesoterodine 8 mg). At week 1, fesoterodine 4 mg was superior to placebo on most diary variables, the PPBC and the UPS (all  $P < 0.05$ ). Dry mouth and constipation rates were 28% and 4% with fesoterodine, 13% and 3% with tolterodine ER, and 5% and 2% with placebo. \* Discontinuation rates as a result of adverse events were 5%, 3% and 2% for fesoterodine, tolterodine ER and placebo, respectively.

**CONCLUSIONS:** \* In this randomized study, which is the largest to compare antimuscarinic efficacy performed to date, fesoterodine 8 mg was superior to tolterodine ER 4 mg for UUI episodes, micturitions and urgency episodes, as well as for self-reported patient assessments of bladder-related problems, urgency, symptom bother and health-related quality of life. \*The superiority of fesoterodine 8 mg over tolterodine ER 4 mg was observed as early as 3 weeks after escalation from fesoterodine 4 mg for most outcomes.

Konstantinidis C. Samarinas M. Andreadakis S. Xanthis S. Skriapas K. "Lower urinary tract symptoms associated with benign prostatic hyperplasia: combined treatment with fesoterodine fumarate extended-release and tamsulosin-a prospective study." *Urologia Internationalis*. 90(2):156-60, 2013.

**OBJECTIVE:** To evaluate the efficacy and safety of fesoterodine extended-release (ER) plus tamsulosin in men with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

**PATIENTS AND METHODS:** Men aged >50 years, with LUTS, prostate volume <60 ml and International Prostate Symptom Score (IPSS) >13 were enrolled in this study. 173 consecutive patients were treated initially with tamsulosin (0.4 mg) for 1 week. At the second visit, 47 patients out of the sample of 173 who were still experiencing inconvenient LUTS were randomized into two groups. The first group received a therapy with tamsulosin and fesoterodine combination (group 1,  $n = 24$ ) while the second continued the therapy with the single administration of tamsulosin (group 2,  $n = 23$ ) for an additional 4-week period.

**RESULTS:** There was no statistically significant difference in age, prostate volume, Q, and postvoid residual urine between the two groups. A statistical significance appeared in the combination group regarding the storage and the total IPSS values among the second and third visits ( $10.5 + 1.4$  to  $8.5 + 1.3$  and  $16.1 + 1.8$  to  $13.7 + 1.5$  respectively).

**CONCLUSION:** Regarding bothersome LUTS and storage symptoms, fesoterodine ER and tamsulosin combination was significantly more effective than the single administration of tamsulosin.

Khullar V. Amarenco G. Angulo JC. Cambroner J. Hoye K. Milsom I. Radziszewski P. Rechberger T. Boerrigter P. Drogendijk T. Wooning M. Chapple C. Efficacy and tolerability of mirabegron, a beta(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. *European Urology*. 63(2):283-95, 2013 Feb.

**BACKGROUND:** Mirabegron, a beta(3)-adrenoceptor agonist, has been developed for the treatment of overactive bladder (OAB).

**OBJECTIVE:** To assess the efficacy and tolerability of mirabegron versus placebo.

**DESIGN, SETTING, AND PARTICIPANTS:** Multicenter randomised double-blind, parallel-group placebo- and tolterodine-controlled phase 3 trial conducted in 27 countries in Europe and Australia in patients > 18 yr of age with symptoms of OAB for > 3 mo.

**INTERVENTION:** After a 2-wk single-blind placebo run-in period, patients were randomised to receive placebo, mirabegron 50mg, mirabegron 100mg, or tolterodine extended release 4 mg orally once daily for 12 wk.

**OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS:** Patients completed a micturition diary and quality-of-life (QoL) assessments. Co-primary efficacy end points were change from baseline to final visit in the mean number of incontinence episodes and micturitions per 24h. The primary comparison was between mirabegron and placebo with a secondary comparison between tolterodine and placebo. Safety parameters included adverse events (AEs), laboratory assessments, vital signs, electrocardiograms, and postvoid residual volume.

**RESULTS AND LIMITATIONS:** A total of 1978 patients were randomised and received the study drug. Mirabegron 50-mg and 100-mg groups demonstrated statistically significant improvements (adjusted mean change from baseline [95% confidence intervals]) at the final visit in the number of incontinence episodes per 24h (-1.57 [-1.79 to -1.35] and -1.46 [-1.68 to -1.23], respectively, vs placebo -1.17 [-1.39 to -0.95]) and number of micturitions per 24h (-1.93 [-2.15 to -1.72] and -1.77 [-1.99 to -1.56], respectively, vs placebo -1.34 [-1.55 to -1.12];  $p < 0.05$  for all comparisons). Statistically significant improvements were also observed in other key efficacy end points and QoL outcomes. The incidence of treatment-emergent AEs was similar across treatment groups. The main limitation of this study was the short (12-wk) duration of treatment.

**CONCLUSIONS:** Mirabegron represents a new class of treatment for OAB with proven efficacy and good tolerability.