Drug Class Review
on
Overactive Bladder Drugs

Preliminary Scan Report #1

February 2014

Last Summary Review (June 2013)

The Agency for Healthcare Research and Quality has not yet seen or approved this report

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 since the last report. Other important studies could exist.

Date of Report:

A Summary Review of this topic was completed in June 2013, with searches through May 2013.

Date of Previous Update Scans:

This is the first preliminary update scan since the Summary Review.

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 from existing comparative systematic reviews on the efficacy and effectiveness of the overactive bladder drugs in adults?

2. What is the evidence from existing comparative systematic reviews on the harms of overactive bladder drugs in adults?

3. What is the evidence from existing comparative systematic reviews 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

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
- Noncomparative 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

Literature Search
To identify relevant citations, we searched Ovid MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations from May 2013 through February Week 1 2014 using terms for included

drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. To identify recent comparative effectiveness reviews, we searched the websites of the US Agency for Healthcare Research and Quality (www.ahrq.gov), 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). and the Canadian Agency for Drugs and Technologies in Health (www.CADTH.ca). We also searched FDA http://www.fda.gov/Drugs/DevelopmentApproval Process/DrugInnovation/ucm336115 .htm and (http://www.centerwatch.com/drug-information/fda-approvals), as well as, (http://www.fda.gov/medwatch/safety.htm) websites for identification of new drugs, indications, and safety alerts.

Study Selection

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

RESULTS

New Drugs

No new drugs.

New Indications

No new indications.

Boxed Warnings

No new box warnings

Comparative Effectiveness Reviews

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

Randomized Controlled Trials

Medline searches resulted in 36 citations. Of those, 11 were potentially relevant new head-to-head or placebo-controlled trials. An additional 13 trials were previously reported in the Summary Review as published since the search dates of the included systematic reviews for a total of 24 new trials (eight head-to-head studies and 16 placebo-controlled trials). (Table 1). See Appendix A for abstracts of new studies. 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. Potentially relevant overactive bladder trials since summary review

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
Cardozo, 2013	591	Solifenacin 5 mg	Placebo	Patients requesting dose increase were rerandomized at 8 weeks to solfinacin 5 or 10 mg
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 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
Herschorn, 2013	1,305	Mirabegron 25 or 50 mg	Placebo	Phase III trial, patients > 18 years with OAB symptoms
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
Kaplan, 2012	943	Fesoterodine 4 mg	Placebo	Men with persistent storage after receiving alpha blocker, could increase fesoterodine to 8 mg
Kaplan, 2013a	398	Solifenacin plus Tamsulosin	Placebo plus Tamsulosin	Men with residual urgency and frequency
Kaplan, 2013b	222	Solifenacin 6 or 9 mg plus Tamsulosin	Placebo	Men > 45 with lower urinary tract symptoms with bladder outlet obstruction
Konstantinidis, 2013	47	Fesoterodine plus 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
Lee, 2011	176	SR Tolterodine 4 mg plus Doxazosin	Placebo plus Doxazosin	Men aged 50 or older with BPH
Nitti, 2013a	200	Mirabegron 50 or 100 mg	Placebo	All men with lower urinary tract symptoms and bladder outlet obstruction
Niti, 2013b	1,329	Mirabegron 50 or	Placebo	Patients had PAB symptoms

		100 mg		for at least 3 months
Oreskovic, 2012	171	Solifenacin 5 mg	Placebo	Patients had OAB symptoms for at least 6 months
Sand, 2012	704	Oxybutynin topical gel	Placebo	Phase-3 study enrolling all women with urgency-predominant urinary incontinence
Staskin, 2011	883	Fesoterodine 4 mg with optional increase to 8 mg	Placebo	Post-hoc analysis of 2010 study on effect of voluntary dose escalation
Wagg, 2013	794	Fesoterodine 4 mg with optional increase to 8 mg	Placebo	Patients had OAB symptoms for at least 3 months
Weiss, 2013	963	Fesoterodine 4 mg with optional increase to 8 mg	Placebo	Subjects with 2-8 nocturnal urgency episodes per 24 hours
Yamaguchi, 2011	638	Solifenacin 2.5 or 5 mg plus Tamsulosin	Placebo plus Tamsulosin	Men with lower urinary tract symptoms
Yokoyama, 2011	962	Solifenacin 5 or 10 mg	Placebo	Subgroup analysis, Japanese patients, compared changes in nocturia and sleep

SUMMARY

Twenty-four new trials, including eight head-to-head studies, were identified. With the exception of one small trial in women (n=77) which compared darifenacin with solifenacin, the newer OAB drugs were compared with tolterodine, oxybutynin and/or placebo.

Appendix A. Abstracts of potentially relevant new OAB trials (N=24)

Head-to-head trials (N=8)

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 >= 3 months and recorded >= 8 micturitions and >= 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 (<= 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 >=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.

Khullar V. Amarenco G. Angulo JC. Cambronero 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.

Placebo-controlled trials (N=16)

Cardozo L. Amarenco G. Pushkar D. Mikulas J. Drogendijk T. Wright M. Compion G. SUNRISE Study Group. Severity of overactive bladder symptoms and response to dose escalation in a randomized, double-blind trial of solifenacin (SUNRISE). BJU International. 111(5):804-10, 2013 May.

UNLABELLED: WHAT'S KNOWN ON THE SUBJECT? AND WHAT DOES THE STUDY ADD?: Antimuscarinics are effective and well tolerated for treatment of OAB. Studies have found that a flexible dosing strategy can be effective in improving OAB symptoms with minimal impact on tolerability. This study confirms these findings with two doses of solifenacin, and shows that improved outcomes can be achieved by increasing solifenacin dose (from 5 to 10 mg) in patients with more severe symptoms.
OBJECTIVE: To determine the relationship between severity of baseline overactive bladder (OAB) symptoms and requests for solifenacin dose increases, and the efficacy of 5 and 10 mg solifenacin doses in relieving OAB symptoms in patients who requested a dose increase.
PATIENTS AND METHODS: In a 16-week clinical study, patients with OAB were randomized to double-blind treatment with solifenacin or placebo once daily. At week 8, all patients could request a dose increase; these patients entered a second phase of 8 weeks in which those in the solifenacin group were randomized to either 5 or 10 mg doses. The primary efficacy variable was mean change in the number of urgency episodes with or without incontinence per 24 h, measured using the Patient Perception of Intensity of Urgency Scale (PPIUS; grades 3 and 4).
RESULTS: Of 591 patients receiving solifenacin at 8 weeks, 275 (46.5%) requested a dose increase to 10 mg, and were further randomized to receive 10 mg (n = 140) or to remain on 5 mg (n = 135). Patients who requested a dose increase at week 8 generally had more severe OAB symptoms at baseline and a smaller response at week 8 to the initial solifenacin 5 mg dosage than those who did not. Greater reductions in the mean number of severe urgency episodes (PPIUS grades 3 and 4) were observed from week 8 to the end of treatment for patients requesting a dose increase and randomized to 10 mg solifenacin compared with those randomized to remain on 5 mg (mean reductions -0.9 vs -0.4, respectively), although these did not reach statistical significance. Statistically significant reductions were observed in mean total urgency score (TUS; -2.7 vs -0.6; P = 0.010), mean maximum PPIUS urgency rating (-0.3 vs -0.1; P = 0.034) and mean micturition frequency (-0.8 vs -0.1; P = 0.037). For all other OAB variables, greater changes were observed in the solifenacin 10 mg group but these did not reach statistical significance. Of those who requested a dose increase, eight (5.7%) patients randomized to receive 10 mg and one (0.7%) patient randomized to remain on 5 mg reported new or worsening cases of dry mouth.
CONCLUSIONS: Increasing the solifenacin dose to 10 mg further improved OAB symptoms in patients who requested a dose increase after 8 weeks' treatment with 5 mg

solifenacin. The present study supports the view that patients with severe OAB symptoms benefit from a higher antimuscarinic dose.

Herschorn S. Barkin J. Castro-Diaz D. Frankel JM. Espuna-Pons M. Gousse AE. Stolzel M. Martin N. Gunther A. Van Kerrebroeck P. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the beta3 adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder.[Erratum appears in Urology. 2013 Dec;82(6):1457] Urology. 82(2):313-20, 2013 Aug.

OBJECTIVE: To assess the efficacy and tolerability of mirabegron 25 mg and 50 mg once-daily vs placebo in patients with overactive bladder (OAB).

MATERIALS AND METHODS: Patients >18 years with OAB symptoms were recruited to a 2-week, single-blind, placebo run-in. Those with >8 micturitions per 24 hours and >3 urgency episodes were randomized 1:1:1 to once-daily mirabegron 25 mg or 50 mg, or placebo for 12 weeks. Primary endpoints were changes to final visit in mean number of incontinence episodes and micturitions per 24 hours. Key secondary endpoints were changes to final visit in mean volume voided or micturition, change to week 4 in mean number of incontinence episodes and micturitions per 24 hours, changes to final visit in mean level of urgency, number of urgency incontinence episodes, and urgency (grade 3 or 4) episodes per 24 hours. Patient-reported outcomes were assessed using the OAB-questionnaire, Patient Perception of Bladder Condition, and Treatment-Satisfaction-Visual Analog Scale.

RESULTS: Both mirabegron groups demonstrated statistically significant improvements in coprimary endpoints vs placebo. Mirabegron 50 mg demonstrated significantly greater improvements vs placebo in the following: change to final visit in mean volume voided per micturition and change to week 4 in mean number of incontinence episodes per 24 hours. Statistically significant improvements vs placebo were demonstrated by mirabegron 50 mg in all patient-reported outcome scales with no increase in the incidence of treatment-emergent adverse events vs placebo.

CONCLUSION: Mirabegron 25 mg and 50 mg were associated with significant improvements in efficacy measures of incontinence episodes and micturition frequency. Mirabegron was well tolerated vs placebo.

Kaplan, S. A., C. G. Roehrborn, et al. (2012). "Add-on fesoterodine for residual storage symptoms suggestive of overactive bladder in men receiving -blocker treatment for lower urinary tract symptoms." BJU International **109**(12): 1831-1840.

UNLABELLED: Study Type - Therapy (RCT) Level of Evidence 1b What's known on the subject? and What does the study add? Male lower urinary tract symptoms are often attributed to bladder outlet obstruction secondary to benign prostatic hyperplasia and treated with drugs targeting the prostate. However, many men with storage lower urinary tract symptoms may not respond adequately to these agents. Antimuscarinics, with or without an -blocker, may be effective for the treatment of the storage symptoms of overactive bladder in some men. Flexible-dose fesoterodine as an add-on treatment significantly improved urinary frequency and symptom bother, but not urgency episodes (primary endpoint), versus add-on placebo and was well tolerated in men with persistent overactive bladder symptoms despite receiving -blocker.

OBJECTIVE: * To evaluate flexible-dose fesoterodine vs placebo in men with persistent overactive bladder (OAB) symptoms despite receiving -blocker treatment

SUBJECTS AND METHODS: * This was a double-blind, 12-week, flexible-dose trial. * Men with persistent storage symptoms (>= 8 micturitions and >= 3 urgency episodes per 24 h) after receiving an -blocker for >= 6 weeks were randomized to add-on fesoterodine 4 mg or placebo, with optional dose escalation to 8 mg at week 4 and reduction back to 4 mg at week 8 (or matching placebo adjustments). * Subjects completed 3-day diaries, International Prostate Symptom Score (IPSS), Overactive Bladder Questionnaire (OAB-q), Patient Perception of Bladder Condition (PPBC), and Urgency Perception Scale (UPS) at baseline and weeks 4 and 12.
RESULTS: * A total of 943 men were randomized and received at least one dose of study treatment (fesoterodine, n= 471; placebo, n= 472). * Among these, 251 (53%) in the fesoterodine group and 300 (64%) in the placebo group requested dose escalation at week 4 and 35 (7%) and 15 (3%) requested dose reduction at week 8. Changes from baseline to week 12 in urgency episodes (primary endpoint) in the fesoterodine (-3.2) and placebo (-2.9) groups were not significantly different (P= 0.196), but improvements in micturitions (P= 0.009) and OAB-q symptom bother score (P= 0.007) were significantly greater with fesoterodine. * At week 4, significantly greater improvements in micturitions (P= 0.006), severe urgency episodes (P= 0.006), IPSS storage score (P= 0.022), OAB-q symptom bother score (P= 0.004), and OAB-q health-related quality of life (P= 0.041), but not urgency episodes (P= 0.062), were observed with add-on fesoterodine. * Dry mouth (fesoterodine, 21%; placebo, 6%) and constipation (fesoterodine, 6%; placebo, 2%) were the most common adverse events. Dysuria and urinary retention were reported by 3% and 2% of subjects, respectively, in the fesoterodine add-on group vs 1% and <1% of subjects, respectively in the placebo add-on group. One subject in each group had acute urinary retention requiring catheterization.
CONCLUSIONS: * Flexible-dose fesoterodine was well tolerated as an add-on treatment in men with persistent storage symptoms. * Changes in urgency episodes at week 12 (primary endpoint) and many secondary endpoints were not significantly different between fesoterodine and placebo add-on treatment; however, improvements in frequency and symptom bother were significantly greater with fesoterodine. * These data suggest that there remains a limited understanding of the optimal evaluation and treatment of men with LUTS.

Kaplan, S. A., K. McCammon, et al. (2013). "Safety and tolerability of solifenacin add-on therapy to -blocker treated men with residual urgency and frequency." Journal of Urology **189**(1 Suppl): S129-134.

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.

Kaplan SA. He W. Koltun WD. Cummings J. Schneider T. Fakhoury A. Solifenacin plus tamsulosin combination treatment in men with lower urinary tract symptoms and bladder outlet obstruction: a randomized controlled trial. European Urology. 63(1):158-65, 2013 Jan.

BACKGROUND: Alpha blockers are prescribed to manage lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Antimuscarinics are prescribed to treat overactive bladder (OAB).
OBJECTIVE: To investigate the safety of a combination of solifenacin (SOLI) and tamsulosin oral controlled absorption system (TOCAS) in men with LUTS and bladder outlet obstruction (BOO).
DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, parallel-group, placebo-controlled study in men aged >45 yr with LUTS and BOO for >3 mo, total International Prostate Symptom Score (IPSS) >8, BOO index >20, maximum urinary flow rate (Q(max)) <12 ml/s, and voided volume >120 ml.
INTERVENTIONS: Once-daily coadministration of TOCAS 0.4 mg plus SOLI 6 mg, TOCAS 0.4 mg plus SOLI 9 mg, or placebo for 12 wk.
OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Primary (safety) measurements: Q(max) and detrusor pressure at Q(max) (P(det)Q(max)). Other safety assessments included postvoid residual (PVR) volume. Secondary end points included bladder contractile index (BCI) score and percent bladder voiding efficiency (BVE). An analysis of covariance model compared each TOCAS plus SOLI combination with placebo.
RESULTS AND LIMITATIONS: Both active treatment groups were noninferior to placebo at end of treatment (EOT) for P(det)Q(max) and Q(max). Mean change from baseline PVR was significantly higher at all time points for TOCAS 0.4 mg plus SOLI 6 mg, and at weeks 2, 12, and EOT for TOCAS 0.4 mg plus SOLI 9 mg versus placebo. Both treatment groups were similar to placebo for BCI and BVE. Urinary retention was seen in only one patient receiving TOCAS 0.4 mg plus SOLI 6 mg. Limitations of the study were that prostate size and prostate-specific antigen level were not measured.

CONCLUSIONS: TOCAS 0.4 mg plus SOLI 6 mg or 9 mg was noninferior to placebo at EOT for P(det)Q(max) and Q(max) in men with LUTS and BOO, and there was no clinical or statistical evidence of increased risk of urinary retention.

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.

Lee, S. H., B. H. Chung, et al. (2011). "Initial combined treatment with anticholinergics and -blockers for men with lower urinary tract symptoms related to BPH and overactive bladder: a prospective, randomized, multi-center, double-blind, placebo-controlled study." Prostate Cancer & Prostatic Diseases **14**(4): 320-325.

We aimed to evaluate the efficacy and safety of combination treatment using anticholinergics with -blocker for initial treatment of both overactive bladder (OAB) and other lower urinary tract symptoms (LUTS), secondary to BPH. A 12-week, randomized, double-blind, placebo-controlled trial was conducted at four urology clinics in Korea, involving men, aged 50 years or older, with LUTS related to BPH and OAB. A total of 176 patients were randomly assigned to receive doxazosin (4 mg) plus placebo or doxazosin (4 mg) plus tolterodine SR (4 mg), once a day for 12 weeks. Changes from baseline in total International Prostate Symptom Score (IPSS), bladder diary variables, patient perception of bladder condition (PPBC), uroflowmetry, postvoid residual volume and IPSS subscores (voiding and storage) were analyzed. Of the 176 enrolled patients, 91 had doxazosin gastrointestinal therapeutic system (GITS) and placebo, and 85 had combined medication with doxazosin GITS and tolterodine SR. Compared with the doxazosin plus placebo group, the doxazosin plus tolterodine group showed significant reductions in IPSS storage subscore and improvement in the quality of life item, urgency episodes, as well as in micturition frequency at weeks 4 and 12. However, it failed to

improve PPBC at week 4 as well as at week 12. Earlier intervention with anticholinergics plus -blocker was tolerated well, including the questions about urinary retention (n=1) and dry mouth (n=2). Initial combination treatment of anticholinergics plus -blocker showed positive results for men with LUTS related to BPH and OAB symptoms and did not increase the risk of urinary retention.

Nitti VW. Rosenberg S. Mitcheson DH. He W. Fakhoury A. Martin NE. Urodynamics and safety of the beta3-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. Journal of Urology. 190(4):1320-7, 2013 Oct.

PURPOSE: Bladder outlet obstruction often presents as storage and voiding symptoms. We investigated urodynamic parameters in men with lower urinary tract symptoms and bladder outlet obstruction treated with the beta3 agonist mirabegron, a new therapy for overactive bladder symptoms.

MATERIALS AND METHODS: A total of 200 men 45 years old or older with lower urinary tract symptoms and bladder outlet obstruction were randomized to receive once daily mirabegron 50 mg (70) or 100 mg (65), or placebo (65) for 12 weeks. The primary urodynamic parameters assessed were change from baseline to end of treatment in maximum urinary flow and detrusor pressure at maximum urinary flow (noninferiority margins -3 ml per second and 15 cm H2O, respectively). We evaluated adverse events and vital signs.

RESULTS: Treatment with mirabegron 50 and 100 mg was noninferior to placebo based on the lower and upper limits of the 95% CI, respectively, for maximum urinary flow and detrusor pressure at maximum urinary flow. The adjusted mean difference vs placebo was 0.40 (95% CI -0.63, 1.42) and 0.62 ml per second (95% CI -0.43, 1.68) for maximum urinary flow, and -5.94 (95% CI -13.98, 2.09) and -1.39 cm H2O (95% CI -9.73, 6.96), respectively, for detrusor pressure at maximum urinary flow. The incidence of adverse events was similar for mirabegron and placebo.

CONCLUSIONS: Mirabegron did not adversely affect voiding urodynamics (maximum urinary flow and detrusor pressure at maximum urinary flow) compared with placebo after 12 weeks of treatment.

Nitti VW. Auerbach S. Martin N. Calhoun A. Lee M. Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. Journal of Urology. 189(4):1388-95, 2013 Apr.

PURPOSE: Many patients with overactive bladder discontinue pharmacotherapy due to suboptimal efficacy or side effects. Mirabegron, a beta3-adrenoceptor agonist, may offer an effective and well tolerated alternative treatment for overactive bladder.

MATERIALS AND METHODS: A randomized, double-blind, placebo controlled trial was conducted in the United States and Canada. After a 2-week placebo run-in period, adults with overactive bladder symptoms for 3 or more months were randomized 1:1:1 to receive placebo, 50 or 100 mg mirabegron once daily for 12 weeks. Efficacy data were collected via patient completed diaries and quality of life assessments. Co-primary efficacy end points were changes from baseline to final visit in mean number of incontinence episodes per 24 hours and micturitions per 24 hours. Key secondary micturition and incontinence end points were also evaluated. Safety assessments included

treatment emergent adverse events, laboratory assessments, vital signs, electrocardiograms and post-void residual volume.
RESULTS: Compared to placebo, 50 and 100 mg mirabegron groups demonstrated statistically significantly greater mean decreases (95% CI) from baseline for incontinence episodes (-1.13 [-1.35, -0.91], -1.47 [-1.69, -1.25] and -1.63 [-1.86, -1.40]) and micturitions (-1.05 [-1.31, -0.79], -1.66 [-1.92, -1.40] and -1.75 [-2.01, -1.48]) per 24 hours ($p < 0.05$). Significant improvements in all key secondary end points were observed for both mirabegron doses vs placebo. The incidence of frequently reported treatment emergent adverse events (hypertension, urinary tract infection, headache, nasopharyngitis) was similar in the mirabegron and placebo groups. Dry mouth was reported for 1.5%, 0.5% and 2.1% of patients in the placebo, 50 and 100 mg mirabegron groups, respectively.
CONCLUSIONS: Once daily mirabegron in a 50 or 100 mg dose is an effective treatment for overactive bladder symptoms with a low occurrence of side effects.

Oreskovic, S., I. But, et al. (2012). "The efficacy and safety of solifenacin in patients with overactive bladder syndrome." Collegium Antropologicum **36**(1): 243-248.

The aim of the randomised, double blind, placebo controlled study was to evaluate the efficacy, tolerability and safety of solifenacin, a once-daily M3 selective receptor antagonist, in patients with overactive bladder syndrome. Following a single blind 2-week placebo run in period, patients who complained from symptoms of OAB for at least 6 months, were randomized to 4 weeks of solifenacin in 5 mg once daily doses or placebo. 171 patients were enrolled in the study and 157 patients completed the study. Patients with solifenacin had significantly improved micturitions per 24 hours after first week of treatment (1.75 +/- 0.63 vs. 2.64 +/- 0.48, $p < 0.001$), and after four weeks (1.56 +/- 0.58 vs. 2.71 +/- 0.45, $p < 0.001$) compared to placebo group. The mean number of urgency episodes per 24 hours had significantly decreased in patients with solifenacin compared to placebo after first week (5.75 +/- 1.43 vs. 6.65 +/- 0.65, $p < 0.001$), and after four weeks of treatment (5.77 +/- 1.33 vs. 6.54 +/- 0.50, $p < 0.001$). Solifenacin was also significantly more effective than placebo in reducing the mean number of episodes of severe urgency from baseline to end point (5.83 +/- 1.16 vs. 6.48 +/- 0.50, $p < 0.001$). Compared with changes obtained with placebo, episodes of urinary frequency were significanlty reduced after first week (0.3 vs. -0.5, $p < 0.001$) and four weeks check up periods in patients treated with solifenacin (0.19 vs. -0.15, $p < 0.001$). Episodes of nocturia was significantly reduced in patients treated with solifenacin after first week (0.3 vs. -0.5, $p < 0.001$), and after four weeks treatment period (0.45 vs. -0.50, $p < 0.001$). The number of incontinence episodes was also significantly decreased in solifenacin group compared to placebo group after first week (1.06 +/- 0.57 vs. 2.74 +/- 0.47, $p < 0.001$) and four weeks check up (0.96 +/- 0.57 vs. 2.75 +/- 0.43, $p < 0.001$). The most common adverse effects with solifenacin were dry mouth and constipation. Adverse effects were mild or moderate severity. The discontinuation rate owing to adverse effects was 4.5%-6.7% with solifenacin and 3.8%-6.1% with placebo, respectively. According to subjective estimation, significant improvement was achieved in 71 (92.21%) of patients treated with solifenacin and in 68 (85%) patients treated with placebo there was no change in OAB symptoms compared to baseline values. UDI score was significantly improved after solifenacin (22.26 +/- 5.91 vs. 29.61 +/- 8.45, $p < 0.001$) compared to placebo. IIQ score was significantly decreased in patients with solifenacin (36.25 +/- 10.34 vs. 46.86 +/-

6.81, p < 0.001) compared to placebo. In conclusion, solifenacin is a safe and effective treatment alternative for patients with overactive bladder symptoms.

Sand, P. K., G. W. Davila, et al. (2012). "Efficacy and safety of oxybutynin chloride topical gel for women with overactive bladder syndrome." American Journal of Obstetrics & Gynecology **206**(2): 168.e161-166.

OBJECTIVE: This subgroup analysis of a phase-3 study evaluated the efficacy and safety of oxybutynin chloride topical gel (OTG) in women with overactive bladder syndrome (OAB).

STUDY DESIGN: Women (n = 704) with urgency-predominant urinary incontinence received OTG or placebo for 12 weeks. The primary endpoint was change from baseline to last observation in number of daily incontinence episodes. Treatments were compared with the use of analysis of covariance.

RESULTS: OTG significantly reduced the number (mean +/- standard deviation) of daily incontinence episodes (OTG, -3.0 +/- 2.8 episodes; placebo, -2.5 +/- 3.0 episodes; P < .0001), reduced urinary frequency (P = .0013), increased voided volume (P = .0006), and improved select health-related quality-of-life domains (P <= .0161) vs placebo. Dry mouth was the only drug-related adverse event significantly more common with OTG (7.4%) than with placebo (2.8%; P = .0062).

CONCLUSION: OTG was well tolerated and provided significant improvement in urinary symptoms and health-related quality of life in women with OAB.

Staskin, D., V. Khullar, et al. (2011). "Effects of voluntary dose escalation in a placebo-controlled, flexible-dose trial of fesoterodine in subjects with overactive bladder." Neurourology & Urodynamics **30**(8): 1480-1485.

AIMS: To characterize the response to fesoterodine treatment for overactive bladder (OAB) in subjects who did or did not choose to dose escalate in a flexible-dose study.

METHODS: Subjects were randomized to fesoterodine 4 mg or placebo. At week 2, subjects could remain on 4 mg (non-escalators) or choose to increase to 8 mg (escalators) for the remaining 10 weeks (sham escalation for placebo). Subjects completed 3-day bladder diaries at baseline, week 2 and week 12 noting micturitions, urgency episodes, and urgency urinary incontinence (UUI) episodes.

RESULTS: Sixty-three per cent of 438 subjects randomized to fesoterodine and 73% of 445 randomized to placebo dose escalated. At baseline, fesoterodine escalators had significantly more micturitions and urgency episodes than fesoterodine non-escalators (P<0.001); at week 2, before dose escalation, diary-dry rate and improvement in micturitions and urgency episodes were significantly greater among fesoterodine non-escalators versus escalators (P<0.001); and by week 12, after dose escalation, diary-dry rate and improvements in micturitions and UUI episodes were similar between fesoterodine non-escalators and escalators (P>0.05). The placebo escalator group did not demonstrate a similar response over placebo non-escalators following the dose escalation decision point.

CONCLUSION: A rapid and robust response to fesoterodine 4 mg was demonstrated in non-escalators. Subjects who chose to dose escalate to fesoterodine 8 mg at week 2 showed significant improvement by week 12 versus baseline and week 2 (prior to escalation), as well as versus placebo. Dose escalation to 8 mg fesoterodine provided

subjects with efficacy and tolerability similar to those who were satisfied with the 4-mg dose.

Wagg A. Khullar V. Marschall-Kehrel D. Michel MC. Oelke M. Darekar A. Bitoun CE. Weinstein D. Osterloh I. Flexible-dose fesoterodine in elderly adults with overactive bladder: results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population trial. Journal of the American Geriatrics Society. 61(2):185-93, 2013 Feb.

OBJECTIVES: To assess the efficacy and safety of flexible-dose fesoterodine in elderly adults with overactive bladder (OAB).
DESIGN: Twelve-week, randomized, double-blind, placebo-controlled trial.
SETTING: Sixty-one outpatient clinics in Europe, Israel, and Turkey.
PARTICIPANTS: Seven hundred ninety-four individuals aged 65 and older (47% male) with OAB symptoms for 3 months or longer, mean of eight or more micturitions and three or more urgency episodes per 24 hours, at least some moderate problems on Patient Perception of Bladder Condition (PPBC), and Mini-Mental State Examination (MMSE) score of 20 or greater.
INTERVENTIONS: Participants were randomized to fesoterodine or placebo for 12 weeks, with stratification according to age (>75 vs < 75) and dosing time (morning vs evening). Participants receiving fesoterodine started on 4 mg and could increase to 8 mg at week 4 or 8 and de-escalate to 4 mg at week 8 (sham escalation for placebo).
MEASUREMENTS: Changes from baseline in bladder-diary variables (primary endpoint, urgency episodes) and patient-reported outcomes including OAB Questionnaire, Treatment Benefit Scale (TBS), PPBC, Urgency Perception Scale (UPS), and OAB Satisfaction Questionnaire (OAB-S); all observed or reported adverse events.
RESULTS: By week 8, 64% of fesoterodine-treated and 71% of placebo-treated participants opted for dose escalation. At week 12, the fesoterodine group had statistically significantly greater improvement than the placebo group in urgency episodes, micturitions, nocturnal micturitions, incontinence pad use, and OAB Questionnaire scores but not urgency urinary incontinence episodes. Responder rates on TBS, PPBC, UPS, and OAB-S were statistically significantly higher with fesoterodine. Improvements in most diary variables and participant-reported outcomes were greater with fesoterodine than placebo in participants in both age groups and when administered in the morning and evening. Rates of dry mouth and constipation were 34% and 9% with fesoterodine and 5% and 3% with placebo, respectively. Rates of adverse events and discontinuations were generally similar in participants in both age groups. There was no change in MMSE score.
CONCLUSION: Fesoterodine was associated with significantly greater improvements in most diary variables and participant-reported outcomes than placebo and was generally well tolerated in older people.

Weiss JP. Jumadilova Z. Johnson TM 2nd. Fitzgerald MP. Carlsson M. Martire DL. Malhotra A. Journal of Urology. 189(4):1396-401, 2013 Apr. Efficacy and safety of flexible dose fesoterodine in men and women with overactive bladder symptoms including nocturnal urinary urgency.[Erratum appears in J Urol. 2013 Aug;190(2):816]

PURPOSE: Awakening from sleep to urinate is the hallmark of nocturia, a condition that impacts several facets of health related quality of life and for which current therapy is suboptimal. Given the paucity of prospective data on antimuscarinics for the management

of nocturia, we investigated the efficacy and safety of flexible dose fesoterodine for the treatment of nocturnal urgency in subjects with nocturia and overactive bladder.
MATERIALS AND METHODS: Subjects with 2 to 8 nocturnal urgency episodes per 24 hours began a 2-week, single-blind, placebo run-in followed by 1:1 randomization to 12 weeks of double-blind treatment with fesoterodine (4 mg daily for 4 weeks with an optional increase to 8 mg) or placebo using predefined criteria for nocturnal urgency episodes, nocturnal urine volume voided and total 24-hour urine volume voided. The primary end point was change from baseline to week 12 in the mean number of micturition related nocturnal urgency episodes per 24 hours.
RESULTS: Overall 963 subjects were randomized from 2,990 screened, and 82% of subjects treated with fesoterodine and 84% of those treated with placebo completed the study. Significant improvements in the primary end point (-1.28 vs -1.07), in nocturnal micturitions per 24 hours (-1.02 vs -0.85) and in nocturnal frequency urgency sum (-4.01 vs -3.42) were observed with fesoterodine vs placebo (all p <0.01). Health related quality of life measures (overactive bladder questionnaire Symptom Bother -20.1 vs -16.5, sleep 22.3 vs 19.9 and other domains; all p <0.05) were improved with fesoterodine.
CONCLUSIONS: To our knowledge this is the first prospective study to assess antimuscarinic efficacy for reducing nocturnal urgency. Flexible dose fesoterodine significantly reduced nocturnal urgency episodes vs placebo in subjects with overactive bladder.

Yamaguchi, O., H. Kakizaki, et al. (2011). "Solifenacin as add-on therapy for overactive bladder symptoms in men treated for lower urinary tract symptoms--ASSIST, randomized controlled study." Urology **78**(1): 126-133.

OBJECTIVES: To assess the efficacy and safety of solifenacin add-on therapy to tamsulosin in lower urinary tract symptoms (LUTS) men with residual overactive bladder (OAB) symptoms despite tamsulosin monotherapy.
METHODS: In this randomized, multicenter, double-blind study, male LUTS patients aged>=50 years with urgency episodes/24 hours>=2 and micturitions/24 hours>=8 were randomized to 3 groups: 12-weeks tamsulosin plus placebo (TAM+PBO), tamsulosin plus solifenacin 2.5 mg (TAM+SOL), and tamsulosin plus solifenacin 5 mg (TAM+SOL). Changes from baseline to end of treatment in the number of urgency episodes/24 hours (primary endpoint), micturitions, nocturia, urgency incontinence episodes, International Prostate Symptom Scores (IPSS), and Overactive Bladder Symptom Score (OABSS) were compared between the TAM+SOL groups and TAM+PBO. Safety was assessed on adverse events, postvoid residual volume, and maximal urinary flow rate (Qmax.).
RESULTS: Six-hundred thirty-eight men were randomized. Urgency was reduced by 2.2 and 2.4 episodes in the TAM+SOL 2.5 and 5 mg groups, respectively. The TAM+SOL 5 mg group showed significant improvement compared with TAM+PBO (-2.4 vs -1.9, P=.049). The number of micturitions in both TAM+SOL groups were significantly reduced compared with TAM+PBO (both P<.001). IPSS storage symptom score and OABSS significantly improved in both TAM+SOL groups compared with TAM+PBO. Changes in IPSS voiding symptom score and Qmax. were similar in all groups. Four patients (1.9%) in the TAM+SOL 5 mg group had urinary retention, but all recovered after catheterization.

CONCLUSIONS: In male LUTS patients with residual OAB symptoms despite tamsulosin monotherapy, TAM+SOL showed efficacy on urgency, which represents OAB symptoms and was well tolerated.

Yokoyama, O., O. Yamaguchi, et al. (2011). "Efficacy of solifenacin on nocturia in Japanese patients with overactive bladder: impact on sleep evaluated by bladder diary." Journal of Urology **186**(1): 170-174.

PURPOSE: We compared changes in nocturia and sleep related parameters between the anticholinergic solifenacin and placebo in patients with overactive bladder associated with nocturia.
MATERIALS AND METHODS: We performed subgroup analysis of data from a randomized, controlled trial of solifenacin (5 or 10 mg) in Japan. Men and women 20 years old or older with overactive bladder were eligible for study participation. Patients who voided at least once during the night at baseline and who completed efficacy and quality of life assessment at baseline and 12 weeks (treatment end) were included in analysis. We compared placebo with the posttreatment change in nocturia and daytime frequency, volume voided per micturition, sleeping time, hours of undisturbed sleep and sleep related quality of life.
RESULTS: Subgroup analysis included 962 patients. Solifenacin 10 mg significantly decreased nocturia episodes by 0.46 episodes ($p = 0.0449$). Solifenacin 5 and 10 mg significantly increased nighttime volume voided per micturition by 30 and 41 ml ($p = 0.0033$ and <0.0001, respectively). Compared with placebo (33 minutes) the hours of undisturbed sleep significantly increased by 59 and 60 minutes ($p = 0.0196$ and 0.0195) in patients with solifenacin 5 and 10 mg, respectively. Significant improvement was observed in sleep related quality of life for solifenacin 5 and 10 mg (each $p <0.001$). Results must be interpreted with caution due to the exploratory nature of this analysis.
CONCLUSIONS: Solifenacin 10 mg decreases nocturia episodes. Solifenacin 5 and 10 mg increases nighttime volume voided per micturition and may improve quality of sleep and sleep related quality of life in patients with overactive bladder.