Drug Class Review

Overactive Bladder Drugs

Preliminary Scan Report #4

September 2017

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 on new randomized controlled trials and comparative effectiveness reviews as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Dates of Previous Reports

Summary Review: June 2013 (searches through May 2013)
Update #4, March 2009 (searches through December 2008)
Update #3, December 2005 (searches through July Week 3 2005)
Update #2, May 2005 (searches through 2004)
Update #1, January 2004 (searches through 2002)
Original Report, February 2003 (searches through 2002)

Dates of Previous Scans

Expanded Scan: January 2016
Scan #2: March 2015
Scan #1: February 2014

Scope and Key Questions

The Pacific Northwest 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

Table 1. Included interventions

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Dosage Form/Route</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>Enablex®</td>
<td>Extended-release oral tablet</td>
<td>12/22/2004</td>
</tr>
<tr>
<td>Fesoterodine fumarate</td>
<td>Toviaz®</td>
<td>Extended-release oral tablet</td>
<td>10/31/2008</td>
</tr>
<tr>
<td>Flavoxate hydrochloride</td>
<td>generic</td>
<td>Oral tablet</td>
<td>12/16/2004</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>Myrbetriq®</td>
<td>Extended-release oral tablet</td>
<td>6/28/2012</td>
</tr>
<tr>
<td>Oxybutynin chloride</td>
<td>Ditropan XL®</td>
<td>Extended-release oral tablet</td>
<td>12/16/1998</td>
</tr>
<tr>
<td></td>
<td>Gelnique</td>
<td>Transdermal gel</td>
<td>1/27/2009</td>
</tr>
<tr>
<td>Oxybutynin transdermal system</td>
<td>Oxytrol®</td>
<td>Extended-release transdermal film</td>
<td>2/26/2003</td>
</tr>
<tr>
<td>Solifenacin succinate</td>
<td>Vesicare®</td>
<td>Oral tablet</td>
<td>11/19/2004</td>
</tr>
<tr>
<td></td>
<td>Detrol® LA</td>
<td>Extended-release oral capsule</td>
<td>12/22/2000</td>
</tr>
<tr>
<td>Trospium chloride</td>
<td>generic</td>
<td>Oral tablet, extended-release oral capsule</td>
<td>8/13/2010</td>
</tr>
</tbody>
</table>

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

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from January 2016 through August 2017 using terms for included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan (shaded in Table 1). We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, new populations, and new serious harms (e.g., boxed warnings). 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.hsrdr.ehsresearch.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 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
No newly approved drugs were identified.
One new drug, propiverine hydrochloride (Mictoryl) has been approved in Canada (January 2017) and the manufacturer will seek FDA approval and marketing in the United States. We identified 1 head-to-head trial comparing this drug to tolterodine ER.

**Identified in previous Preliminary Update Scan**
None.

**New Serious Harms (Boxed Warnings)**

**Identified in this Preliminary Update Scan**
None identified.

**Identified in previous Preliminary Update Scan**
None.

**New Comparative Effectiveness Reviews**

**Identified in this Preliminary Update Scan**
We identified 3 potentially relevant comparative effectiveness reviews. One is an update to a 2012 review by the Agency for Healthcare Research and Quality, which is currently ongoing. The other 2 reviews were published in 2016: 1 by the Agency for Healthcare Research and Quality and 1 by the Ontario Drug Policy Research Network. Abstracts for the published reviews are available in Appendix A.


[www.effectivehealthcare.ahrq.gov/reports/final.cfm](www.effectivehealthcare.ahrq.gov/reports/final.cfm)


**Identified in previous Preliminary Update Scan**
None.

**Randomized Controlled Trials**
**Identified since the Summary Review**

Medline searches for this scan yielded 66 citations, of which 6 head-to-head trials and 4 placebo-controlled trials were determined to be eligible for a report update. Cumulatively, since the last report, we have identified 14 potentially relevant head-to-head trials and 32 potentially relevant placebo-controlled trials that would be eligible for a report update.

The majority of newly identified head-to-head evidence compares newer overactive bladder drugs with older drugs. Of the 14 new head-to-head trials, 8 trials compare newer drugs (2 fesoterodine, 5 mirabegron, 1 solifenacin + mirabegron) with older drugs. Characteristics of head-to-head trials are listed in Table 1, below, and abstracts of these studies are available upon request. Twenty-eight percent of placebo-controlled trial evidence was of mirabegron. Placebo-controlled trials are listed in Table 2, below, and abstracts are also available upon request.

**Table 2. New head-to-head trials of overactive bladder drugs (N=14)**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Population Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaplan, 2010</td>
<td>2,417</td>
<td>Fesoterodine 8 mg</td>
<td>ER Tolterodine 4 mg</td>
<td>Subjects with &gt;1 urgency incontinence episode and ≥ 8 micturitions per 24 hours</td>
</tr>
<tr>
<td>Chapple, 2013</td>
<td>2,444</td>
<td>Mirabegron 50 or 100 mg</td>
<td>ER Tolterodine 4 mg</td>
<td>Patients with OAB symptoms for at least 3 months</td>
</tr>
<tr>
<td>Khullar, 2013</td>
<td>1,978</td>
<td>Mirabegron 50 or 100 mg</td>
<td>ER Tolterodine 4 mg</td>
<td>Patients with OAB symptoms for at least 3 months</td>
</tr>
<tr>
<td>Kuo, 2015</td>
<td>1,126</td>
<td>Mirabegron 50 mg</td>
<td>ER Tolterodine 4 mg</td>
<td>Patients with symptoms of overactive bladder in Taiwan, Korea, China, and India</td>
</tr>
<tr>
<td>But, 2012 SOLIDAR</td>
<td>77</td>
<td>Solifenacin 5 mg</td>
<td>Darifenacin 7.5 mg</td>
<td>Open label, all women, Slovenian patients</td>
</tr>
<tr>
<td>Ercan, 2015</td>
<td>119</td>
<td>Solifenacin 5 mg</td>
<td>Fesoterodine 4 mg</td>
<td>Turkish patients</td>
</tr>
<tr>
<td>Vecchioli ScaldaZZa, 2016</td>
<td>80</td>
<td>Solifenacin 5 mg</td>
<td>Mirabegron 50 mg</td>
<td>Women with overactive bladder</td>
</tr>
<tr>
<td>Kosilov, 2015</td>
<td>239</td>
<td>Solifenacin 10 mg</td>
<td>Mirabegron 50 mg or Solifenacin 10 mg/Mirabegron 50 mg</td>
<td>Elderly men and women with initial frequency of incontinence episodes ≥3/day</td>
</tr>
<tr>
<td>Hsiao, 2011</td>
<td>48</td>
<td>Solifenacin 5 mg</td>
<td>ER Tolterodine 4 mg</td>
<td>Women, post-marketing study</td>
</tr>
<tr>
<td>Kosilov, 2016</td>
<td>338</td>
<td>Solifenacin</td>
<td>Trospium</td>
<td>Men &gt;50 years old with benign prostatic hyperplasia</td>
</tr>
<tr>
<td>Abrams, 2015 SYMPHONY</td>
<td>1,306</td>
<td>Solifenacin/Mirabegron</td>
<td>Solifenacin 5 mg</td>
<td>Male and female patients aged &gt;18 years with OAB for &gt;3 months</td>
</tr>
<tr>
<td>Jafarabadi, 2015a</td>
<td>94</td>
<td>Tolterodine 2 mg BID</td>
<td>Oxybutynin 5mg TDS</td>
<td>Iranian women, 45 years and older</td>
</tr>
<tr>
<td>Jafarabadi, 2015b</td>
<td>301</td>
<td>Tolterodine</td>
<td>Oxybutynin</td>
<td>Iranian women, 45 years and older, overactive bladder and detrusor overactivity</td>
</tr>
<tr>
<td>Dede, 2013</td>
<td>90</td>
<td>Tolterodine Trospium</td>
<td>Oxybutynin</td>
<td>Women with urge urinary incontinence</td>
</tr>
</tbody>
</table>

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

**Secondary Publications**

Since the last report, there are a total of 19 secondary publications related to studies already included in the full report identified in prior scans. None of these are related to the head-to-head trials described above and none were identified in the present scan.

**Placebo-Controlled Trials**
Since the last report, there have been 32 new placebo-controlled trials identified (4 new this scan), with 9 of mirabegron and 7 of fesoterodine.

Table 2. New placebo-controlled trials (N=32)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of trials</th>
<th>New this scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fesoterodine</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Solifenacin + Tamsulosin</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Tamsulosin + Fesoterodine</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tolterodine ER</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tolterodine SR + Doxazosin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>

**SUMMARY**

Cumulatively, we have identified no new FDA-approved drugs or new serious harms (boxed warnings) since the Summary Review. We identified 2 published reviews and 1 ongoing review that are potentially relevant to this topic. We have identified a total of 14 new head-to-head trials, including 8 trials of newer drugs (2 fesoterodine, 5 mirabegron, 1 solifenacin + mirabegron) compared with older drugs. Additionally, there are 32 new placebo-controlled trials.
APPENDIX A. COMPARATIVE EFFECTIVENESS REVIEWS


Newer Medications for Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: A Review

Structured Abstract

Objective. To assess the efficacy, comparative effectiveness, and adverse effects of newer drugs to treat lower urinary tract symptoms (LUTS) attributed to benign prostatic hyperplasia (BPH).

Data sources. Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials, and Ovid Embase® bibliographic databases; hand searches of references of relevant studies.

Review methods. We searched bibliographic databases through July 2015. Two investigators screened titles and abstracts of search results and full text of relevant references for eligibility. Eligible studies evaluated efficacy and/or harms of one alpha blocker (AB) (silodosin), several antimuscarinics (tolterodine, solifenacin, fesoterodine), one beta-3 adrenoceptor agonist (mirabegron), and several phosphodiesterase type 5 (PDE-5) inhibitors (tadalafil, sildenafil) or combination therapy with one of these medications. They included randomized controlled trials (RCTs) with duration of at least 1 month and observational studies for long-term (>1 year) adverse events. We assessed risk of bias for RCTs, extracted data, pooled data for analysis when appropriate and feasible, and evaluated strength of evidence for comparisons on an outcome specific basis.

Results. We synthesized evidence from 57 unique RCTs and 5 observational studies. Trials were generally short term (e.g., 12 weeks). Silodosin was more effective than placebo in improving LUTS but was similar to tamsulosin and had more adverse effects, including abnormal ejaculation. Solifenacin/AB combination therapy was better than placebo, but tolterodine/AB, solifenacin/AB, and fesoterodine/AB combination therapy were similar to AB monotherapy, and combination therapy often had more adverse effects. Tadalafil improved LUTS more than placebo but had more adverse effects. Tadalafil and tamsulosin were similar in improving LUTS. We identified trials testing other drugs (mirabegron, oxybutynin, darifenacin, sildenafil, and vardenafil) but found the evidence insufficient to draw conclusions about efficacy, comparative effectiveness, or adverse effects. Evidence was insufficient to assess long-term efficacy, prevention of symptom progression (e.g., acute urinary retention or need for surgical intervention), or adverse effects.

Conclusions. Several drugs newly used for LUTS attributed to BPH, alone or in combination with older AB, showed evidence of efficacy in short-term studies; however, comparative effectiveness for silodosin, fesoterodine/AB combination, and tadalafil showed that outcomes
were similar to older AB monotherapy and adverse effects were often higher with the newly used drugs or combination therapies. Evidence on long-term efficacy and adverse effects was insufficient.


Executive Briefing

- This report assessed the current evidence regarding the comparative efficacy and safety of pharmacotherapies in the treatment of overactive bladder (OAB) syndrome through a systematic review and Bayesian network meta-analysis.
- Previously published evidence syntheses are limited in scope, outcomes or statistical comparisons. Most focus on the anticholinergic agents compared to placebo or each other, and more recent reviews including newer pharmacotherapies such as mirabegron report a limited number of outcomes. The availability of comprehensive, high-quality comparative evidence on all approved pharmacologic treatments available in Canada is lacking; as such, previously published evidence syntheses were updated and expanded to form the evidence base for a comprehensive review of efficacy and safety outcomes reported in randomized controlled trials.
- Outcomes assessed for efficacy were frequency of micturitions, nocturia, urgency and incontinence episodes over a 24 hour period, and patient quality of life.
- Outcomes assessed for safety were dry mouth, constipation, arrhythmia, withdrawals (all-cause, due to adverse events, or due to a lack of clinical response).
- The pharmacotherapies reviewed were compared with each other or no therapy (placebo). Dual therapy with anticholinergic and β3- adrenoceptor agonists was also considered, as were comparisons to onabotulinumtoxin A (Botox). Outcomes were assessed at 12 weeks (frequency of micturitions and incontinence episodes over a 24 hour period) and end of study (all other outcomes).
- The systematic review located a total of 101 unique randomized controlled trials (RCTs) reported in 168 publications. A total of 79 unique RCTs reported outcomes of interest