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OHSU Drug Effectiveness Review Project Summary Report – Drugs to Treat Overactive Bladder

Date of Review: September 2018

Date of Last Review: May 2015
Literature Search: 03/01/2018

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:
1. How do drugs used to treat overactive bladder (OAB) compare in efficacy and effectiveness?
2. How do drugs used to treat OAB compare in safety and harms?
3. Are there subgroups of patients in whom effectiveness or harms of drugs used to treat OAB differ? Subgroups of interest are demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), and pregnancy.

Conclusions:
- High quality evidence from 4 randomized controlled trials (RCTs) comparing mirabegron to solifenacin found no difference at 12 weeks for reducing incontinence episodes per 24 hours.[1] Moderate quality evidence due to small numbers of events found no difference in adverse event withdrawals.[1] Moderate quality evidence showed urgency episodes were reduced more with mirabegron than solifenacin, but the difference was small (2 RCTs, 0.54 fewer episodes per 24 hours, 95% confidence interval [CI] -0.92 to -0.16).[1]
- Mirabegron was compared to tolterodine extended release (ER) in 5 RCTs which provided moderate to high quality evidence of comparative efficacy.[1] At 8-12 weeks, incontinence episodes were reduced more with mirabegron than tolterodine, but the difference was very small (5 RCTs, 0.15 fewer episodes per 24 hours, 95% CI -0.27 to -0.04).[1] No differences were found in urgency episodes between mirabegron and tolterodine ER. Tolterodine had a higher incidence of dry mouth (8-13% with tolterodine versus 3-4% with mirabegron), but there were no significant differences in adverse event (AE) withdrawals.[1]
- Three small, fair quality RCTs assessed different head to head comparisons for OAB medications. One fair-quality trial (n=119) compared fesoterodine with solifenacin.[2] Significant differences in efficacy were not identified between fesoterodine and solifenacin in this trial. However, significantly more patients receiving fesoterodine withdrew from the study due to AEs compared to solifenacin (10% vs. 0%; p=0.013).[1] Another small, fair-quality trial (n=60) compared darifenacin with trospium over 4 weeks.[3] Measures of urinary frequency, urgency, nocturia, and urge urinary incontinence improved in both groups; however, no statistically significant differences in these outcomes were observed at 2 or 4 week assessments.[1] No serious adverse events (SAEs) or withdrawals due to AEs were noted with darifenacin or trospium ER in this small trial.[1] An additional fair-quality RCT (n=132) comparing solifenacin to oxybutynin immediate release (IR) found fewer patients taking solifenacin withdrew due to adverse events compared to oxybutynin (13% vs. 30%, relative risk [RR] 0.45, 95% CI 0.23 to 0.91).[4] Of the specific adverse events of interest, only the difference in number of participants who experienced dry mouth was significant; solifenacin 5 mg (35.29%) versus oxybutynin IR 15 mg (82.81%) [RR0.43, 95% CI 0.30 to 0.60].[1] The evidence from these 3 trials is insufficient to draw conclusions, primarily due to the small sample size and the lack of corroborating evidence for each head-to-head comparison.[1]

- One good quality retrospective cohort study conducted using the Taiwan National Health Insurance Research Database enrolled patients with diabetes and sought to determine the risk for dementia associated with use of solifenacin, tolterodine, and oxybutynin.[5] The assessment from this study concluded risk for dementia in patients with diabetes was significantly increased with solifenacin, tolterodine and oxybutynin.[5] The adjusted hazard ratios were: solifenacin HR 2.16, 95% CI 1.81 to 2.58; tolterodine HR 2.24, 95% CI 1.85 to 2.73; and oxybutynin HR 2.35, 95% CI 1.96 to 2.81.[1] This study did not control for actual duration of drug exposure and did not formally compare the drugs with each other.[1]

Recommendations:

- There is no significant new comparative evidence from the 2018 Drug Effectiveness Review Project (DERP) report to support differences in efficacy or serious harms between the OAB drugs.
- No further review or research needed at this time. No PDL changes recommended after review of comparative drug costs in the executive session.

Summary of Prior Reviews and Current Policy

Previous Oregon Pharmacy and Therapeutics Committee reviews found no evidence to support differences in efficacy or harms between OAB drugs. The preferred and non-preferred status of the OAB medications on the Preferred Drug List (PDL) are presented in **Appendix 1**. Utilization is guided by PDL status as no PA criteria have been implemented for this class of medications. Preferred OAB medications include fesoterodine and oxybutynin. Almost all of the Oregon Medicaid Fee-For-Service utilization for this class of drugs is for oxybutynin (97%).

Methods:

The June 2018 drug class update on drugs to treat OAB by the Drug Effectiveness Review Project at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:

Eighteen head-to-head trials and 1 observational cohort study are new in this DERP update of the OAB summary review published in 2013. The majority of the RCTs were 8 to 12 weeks in duration, with 1 RCT being 52 weeks.[1] Most of the studies were funded by drug manufacturers. There have not been any new therapeutic agents added to this medication class since 2012. The drugs approved to treat overactive bladder symptoms are outlined in **Table 1.** New comparative evidence was identified for mirabegron, fesoterodine, darifenacin, trospium, tolterodine, oxybutynin, and solifenacin.[1]

Table 1: Drugs Used to Treat Overactive Bladder[1]

Generic Name	Trade Name	Dosage Form/Route	FDA Approval
Mirabegron	Myrbetriq®	Extended-release oral tablet	6/28/2012
Fesoterodine fumarate	Toviaz®	Extended-release oral tablet	10/31/2008
Darifenacin	Enablex®	Extended-release oral tablet	12/22/2004
Solifenacin succinate	Vesicare®	Oral tablet	11/19/2004
Trospium chloride	Generic	Oral tablet Extended-release oral capsule	5/28/2004
Oxybutynin transdermal system	Oxytrol® Gelnique®	Extended-release transdermal film Transdermal gel	2/26/2003 1/27/2009
Tolterodine tartrate	Detrol® Detrol® LA	Oral tablet Extended-release oral capsule	3/25/1998
Oxybutynin chloride	Generic	Oral tablet Extended-release oral tablet	7/16/1975
Flavoxate hydrochloride	Generic	Oral tablet	1/15/1970

The effectiveness outcomes evaluated in the recent randomized controlled trials (RCTs) included the following metrics reported over 24 hours: change in mean number of incontinence episodes; change in mean number of urgency episodes; change in mean number of pads used; and patient symptoms assessments. The harms outcomes included withdrawals due to AEs, SAEs, and specific adverse events associated with anticholinergic medications (constipation, dry mouth, cognitive changes, blurred vision, and cardiac abnormalities).

Head to Head Comparisons

Mirabegron versus Solifenacin

Six RCTs compared mirabegron with solifenacin. Two of these were rated poor quality for multiple reasons, including poor or unclear reporting, imbalance between groups at baseline, and high attrition rates.[1] The remaining 4 studies were of moderate to high quality.[1] The studies were 12 weeks in duration, included 67% to 100% females, and less than 25% of subjects were non-White.[1] Sample sizes ranged from 80 to 1,887 patients and all trials included the most commonly used doses; mirabegron 50 mg per day and solifenacin 5 mg per day.[1] Three RCTs reported the mean change in incontinence episodes per 24 hours.[6-8] For the comparison of mirabegron 50 mg per day versus solifenacin 5 mg per day, there was not a statistically significant difference in incontinence episodes from baseline to 12 weeks (3 RCTs, n=2741, mean difference [MD] -0.061 episodes per 24 hours, 95% CI -0.189 to 0.067).[1] Differences between other doses (mirabegron 25 mg per day, solifenacin 2.5 and 10 mg per day) were also not significant.[1] Confidence in these findings is high; future studies are very unlikely to change them.[1]

Only 2 RCTs measured and reported urgency episodes in a way that could be compared directly between the monotherapy groups.[6,9] Pooling the results of these studies, mirabegron 50 mg per day results in a significantly greater reduction than solifenacin 5 mg per day (mean difference in change from baseline of -0.54 episodes per 24 hours; 95% CI -0.92 to -0.16).[1] Confidence in these findings is moderate due to some inconsistency in the magnitude of the findings; future studies could change the findings.[1] Only 2 trials reported measures of patient assessment of changes in symptoms in a way that could be compared or

combined.[6,9] These 2 RCTs reported changes in the Patient Perception of Bladder Condition scale (6 items, change scores range from -2 to 2 with negative scores indicating improvement), although a clinically meaningful difference between groups has not been established.[1]

Withdrawals due to adverse events were reported in all 4 RCTs, and the pooled DERP assessment shows no difference between groups (5% versus 5%; RR 0.94, 95% CI 0.53 to 1.68).[1] Confidence in these findings is moderate due to small numbers of events.[1] SAEs were reported in 3 RCTs, with less than 2% incidence per group; no differences were observed between mirabegron and solifenacin.[6-8] The pooled DERP relative risk estimate of SAE incidence is 1.15 (95% CI 0.80 to 2.21).[1] Specific adverse events described in the mirabegron versus solifenacin trials included cardiac arrhythmias, falls/syncope, dry mouth and blurred vision. Differences in the frequency of AEs were not apparent, except that a somewhat higher incidence of dry mouth was reported with solifenacin (7.7%) compared to mirabegron (3.8%).[1] Statistical significance was not reported for this outcome.

Mirabegron versus Tolterodine ER

Six comparative RCTs of mirabegron versus tolterodine met inclusion criteria for the DERP update. The percent of female enrollment ranged from 67 to 82% of participants; over 80% of subjects were White in 3 trials, while race was not reported in the other 3 trials.[1] Sample sizes ranged from 749 to 2,444 patients. Five of the RCTs used tolterodine ER 4 mg per day, while one only reported using tolterodine 4 mg once per day without specifying whether the IR or ER formulation was used.[10] Mirabegron dosing ranged from 25 mg to 200 mg per day, with the most common doses being 50 mg and 100 mg per day.[1] Most of the studies were 8 to 12 weeks long, although one study was conducted over 12 months.[1] Pooling data from 5 trials reporting incontinence at 8 to 12 weeks finds that mirabegron 50 mg reduces the number of episodes significantly more than tolterodine ER 4 mg (mean difference in change from baseline -0.15 episodes per 24 hours, 95% CI -0.27 to -0.04).[1] Although this difference is very small, the DERP authors reported high confidence in this finding.[1] Pooling the 4 studies that reported the change in urgency episodes, the difference favors mirabegron but is very small and does not reach statistical significance. (-0.12, 95% CI -0.23 to 0.00; P = 0.052).[1] Confidence in these findings is high; future studies are very unlikely to change them.[1]

Pooling results from 6 RCTs finds no difference between mirabegron 50 mg and tolterodine ER 4 mg daily in the proportions of patients withdrawing due to adverse events (4.7% versus 4.9%, RR 0.97, 95% CI 0.76 to 1.25, I^2 = 0%).[1] Confidence in these findings is moderate, and future studies may alter these results.[1] Rates of serious adverse events were low, with no differences between groups.[1] Across 5 RCTs, the rate of constipation did not differ between mirabegron 50 mg per day and tolterodine ER 4 mg per day at 8 to 12 weeks or at 12 months.[1] Constipation rates were low, around 2%.[1] In 3 short-term trials, spontaneous reporting of dry mouth was more than twice as frequent with tolterodine than with mirabegron (8-13% of patients reporting dry mouth with tolterodine vs. 3-4% with mirabegron).[1]

Fesoterodine versus Solifenacin

One recently published fair-quality trial (n=119) compared fesoterodine with solifenacin.[2] The mean age was 59 years and all participants were female. The primary outcome was change in the 15 point OAB Symptom Scale (OABSS) which sums the score of 4 symptoms (daytime frequency, nighttime frequency, urgency and urgency incontinence).[11] Higher scores on the OABSS scale indicate more severe symptoms. Over 12 weeks, both fesoterodine 4 mg and solifenacin 5 mg significantly reduced OABSS scores (-9.4 vs. -8.2), but the difference between the drugs was not significant.[1] Significantly more patients receiving fesoterodine withdrew from the study due to adverse events compared to solifenacin (10% vs. 0%; p=0.013).[1] More patients receiving fesoterodine compared to solifenacin experienced constipation (5% vs. 2%) and dry mouth (14% vs. 5%); although the differences were not significant (p=0.26 and p=0.19, respectively).[1] This evidence is insufficient to draw conclusions, primarily due to the small sample size and the lack of corroborating evidence.[1]

Trospium versus Darifenacin

One fair-quality trial (n=60) compared darifenacin 7.5 mg with trospium ER 60 mg.[3] The mean age of participants was 64 years, 23% were female, and all subjects were of Asian ethnicity. Over 4 weeks, both groups showed significant improvement in OABSS scores, though the difference between the groups was not significant.[1] Scale scores of urinary frequency, urgency, nocturia, and urge urinary incontinence improved with both darifenacin and trospium, although no significant differences were observed between the groups at 2 and 4 week assessments.[1] There were no serious adverse events or withdrawals due to adverse events, and there was no significant difference in the mean increase in the McMillan & Williams Constipation Assessment Scale (0.93 vs. 0.60; p=0.944).[1] The McMillan and Williams Constipation Assessment Scale is an 8 item, 3-point questionnaire used to assess constipation symptom intensity.[12] Scores may range from 0 (no constipation) to 16 (worst possible constipation).[13]This evidence is insufficient to draw conclusions, primarily due to the small sample size and the lack of corroborating evidence.[1]

Tolterodine versus Oxybutynin

One trial published in 2015 comparing immediate release tolterodine 4 mg with immediate release oxybutynin 5 mg only focused on adverse event outcomes.[14] Based on 8 trials from a 2012 Cochrane systematic review[15] and the additional 2015 trial, tolterodine resulted in fewer withdrawals compared to oxybutynin (pooled RR 0.43, 95% CI 0.27 to 0.59; I^2=33%).[1] Incidence of dry mouth did not differ between groups (2.8% vs. 3.0%; p=0.85), and other specific adverse events of interest were not reported.[1]

Solifenacin versus Oxybutynin

One fair quality RCT (n=132) compared solifenacin 5 mg with oxybutynin IR 15 mg.[4] Mean age was 61 years (43% older than 65; 17% older than 75 years) with 78% women and 90% of subjects were White.[4] Fewer participants treated with solifenacin 5 mg daily withdrew due to adverse events than those given oxybutynin IR 15 mg daily (13% vs. 30%, RR 0.45, 95% CI 0.23 to 0.91).[1] Nine participants who took solifenacin 5 mg reported constipation compared with 4 participants who received oxybutynin IR 15 mg but this difference was not statistically significant (13% vs. 6%, RR 2.12, 95% CI 0.69 to 6.54).[1] Eight participants treated with solifenacin experienced a severe adverse event (12%) versus 18 participants treated with oxybutynin (28%), which was statistically significant (RR 0.42, 95% CI 0.20 to 0.89).[1] Of the specific adverse events of interest, only the difference in number of participants who experienced dry mouth was significant; solifenacin 5 mg (35.29%) versus oxybutynin IR 15 mg (82.81%) RR 0.43, 95% CI 0.30 to 0.60].[1] Confidence in the results of this comparison are low due to having only 1 small study comparing solifenacin to oxybutynin IR.[1]

Other OAB comparisons

No studies were identified for flavoxate, and no comparative evidence was identified for mirabegron compared with fesoterodine, darifenacin, trospium, or oxybutynin; fesoterodine compared with darifenacin, trospium, or oxybutynin; darifenacin compared with tolterodine or oxybutynin; or solifenacin compared with trospium.[1] Additionally, 1 trial which compared solifenacin with darifenacin[16] and 1 trial which compared trospium with oxybutynin and tolterodine[17] were rated poor quality due to unclear allocation concealment, blinding, and attrition and were not discussed in the DERP report.[1]

Evidence in Population Subgroups:

Diabetes

One good quality retrospective cohort study conducted using the Taiwan National Health Insurance Research Database enrolled patients with diabetes and sought to determine the risk for dementia associated with use of solifenacin, tolterodine, and oxybutynin.[5] Patients who were exposed for fewer than 28 days or who received more than 1 OAB drug or drug formulation were excluded; this resulted in 10,279 patients exposed and 592,910 patients not exposed.[1] After age and gender matching, there were 2,540 participants in each group (i.e., solifenacin, tolterodine, oxybutynin, and unexposed control group); participants were

64% male, with a mean age of 62 years.[1] The most frequent cardiovascular morbidity was hypertension (range 40% to 46%).[1] The analysis was adjusted for hypertension, lipid disorders, atrial fibrillation, chronic kidney disease, coronary artery disease, and heart failure.[1] The assessment from this study concluded risk for dementia in patients with diabetes was significantly increased with solifenacin, tolterodine and oxybutynin.[5] The adjusted hazard ratios were: solifenacin HR 2.16, 95% CI 1.81 to 2.58; tolterodine HR 2.24, 95% CI 1.85 to 2.73; and oxybutynin HR 2.35, 95% CI 1.96 to 2.81.[1] This study did not control for actual duration of drug exposure and did not formally compare the drugs with each other.[1]

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Appendix 1: Current Preferred Drug List

Route	Formulation	Brand	Generic	PDL
ORAL	SYRUP	OXYBUTYNIN CHLORIDE	oxybutynin chloride	Y
ORAL	TABLET	OXYBUTYNIN CHLORIDE	oxybutynin chloride	Y
ORAL	TAB ER 24	DITROPAN XL	oxybutynin chloride	Y
ORAL	TAB ER 24	OXYBUTYNIN CHLORIDE ER	oxybutynin chloride	Y
TRANSDERM	PATCH TDSW	OXYTROL	oxybutynin	Y
ORAL	TAB ER 24H	TOVIAZ	fesoterodine fumarate	Y
ORAL	TABLET	FLAVOXATE HCL	flavoxate HCl	N
TRANSDERM	GEL PACKET	GELNIQUE	oxybutynin chloride	N
TRANSDERM	GEL MD PMP	GELNIQUE	oxybutynin chloride	N
ORAL	TABLET	TROSPIUM CHLORIDE	trospium chloride	N
ORAL	CAP ER 24H	TROSPIUM CHLORIDE ER	trospium chloride	N
ORAL	TABLET	DETROL	tolterodine tartrate	N
ORAL	TABLET	TOLTERODINE TARTRATE	tolterodine tartrate	N
ORAL	CAP ER 24H	DETROL LA	tolterodine tartrate	N
ORAL	CAP ER 24H	TOLTERODINE TARTRATE ER	tolterodine tartrate	N
TRANSDERM	PATCH TD 4	OXYTROL FOR WOMEN	oxybutynin	N
ORAL	TABLET	VESICARE	solifenacin succinate	N
ORAL	TAB ER 24H	DARIFENACIN ER	darifenacin	N
ORAL	TAB ER 24H	ENABLEX	darifenacin	N
ORAL	TAB ER 24H	MYRBETRIQ	mirabegron	N