Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Drugs for BPH

Date of Review: July 2016

Date of Last Review: May 2014
Literature Search: May 2016

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

Conclusions:

- One new guideline, 3 systematic reviews and one Food and Drug Administration (FDA) safety alert have been published for benign prostatic hypertrophy (BPH) therapies since the last review.[1-5]
- There is evidence that therapies for BPH all significantly improve the International Prostate Symptom Score (IPSS) compared to placebo by -3.69 to -7.06 points. Doxazocin and terazosin were associated with the most improved IPSS scores of -7.06 and -6.76, respectively.[1] The IPSS is a validated tool comprised of up to 35 points based on 8 questions. A minimally important difference is a decrease of 3 or more points; a moderate improvement is a decrease of 5 or more points; and marked improvement in symptoms is a decrease of 8 or more points.[2]
- Evidence from the Agency for Healthcare Research and Quality (AHRQ) found alpha-1 blockers to have similar or superior outcomes to newer therapies, or combination of therapies, for BPH. Alpha-1 blockers silodosin and tamsulosin changed IPSS scores by -7.8 and -7.2, respectively (weighted mean difference [WMD] -0.63; 95% CI, -1.62 to 0.36).[3] Other evidence showed tadalafil and tamsulosin resulted in -5.6 and -5.9 IPSS point reduction, respectively (WMD 0.07; 95% CI, -2.12 to 2.23). The addition of an alpha-1 blocker (tamsulosin or alfuzosin) to tadalafil provided an additional 1.6 point IPSS decrease over alpha-1 blocker monotherapy (-10.4 vs. -8.6; WMD -2.01; 95% CI, -4.03 to -0.00). Similar differences were seen with the combination of tadalafil and finasteride compared to finasteride alone (-5.5 vs. -4.5 points (CI not provided).
- Adverse events were more common with silodosin compared to placebo and tamsulosin. Tadalafil was associated with higher risk of adverse events compared to tamsulosin.[3]
- Guideline recommendations from the National Institute for Health and Care Excellence (NICE) support current preferred drug list (PDL) placement for drugs used in the treatment of BPH.[4]

Recommendations:

- No changes are recommended to the PDL or prior authorization criteria for BPH treatments.
- Consider costs in executive session.

Previous Conclusions/Conclusions:

- There is no new evidence for comparative effectiveness or harms outcomes between drugs used for BPH. No further review or research needed at this time.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
A systematic review evaluated the comparative effectiveness of monotherapies for the treatment of BPH. Drugs included in the review were the following: terazosin, doxazosin, tamsulosin, alfuzosin, silodosin, naftopidil, finasteride, dustasteride, tolterodine, fesoterodine, and solifenacin.[1] The primary outcome was change in IPSS. One hundred twenty-four trials were included with two-thirds having a treatment duration longer than one year. The median age of patients was 65 years with a median baseline IPSS score of 17.85 with moderate to severe symptoms.[1] The evidence was rated as moderate in quality. In placebo comparisons, a network meta-analysis found BPH therapies to decrease IPSS scores by -3.69 to -7.06 points. The largest decreases were found with doxazosin (absolute effect [AE] -7.06; 95% CI, -10.41 to -3.71) and terazosin (AE -6.76; 95% CI, -10.16 to -3.35). Significant IPSS changes were seen for all treatments except tolterodine and solifenacin. Most changes in IPSS were comparable to each other except for doxazocin and terazosin which were found to be significantly more effective than tamsulosin, alfuzosin, tadalafil, naftopidil, dutasteride, finasteride, tolterodine and solifenacin.[1] A significantly higher incidence of adverse effects (RR 1.33 to 2.10) was found with doxazosin, terazosin, silodosin, fesoterodine and tadalafil. Therapies that were associated with the highest incidence of withdrawals due to adverse events were: alfuzosin, terazosin, dutasteride, tolterodine, tadalafil, sildenafil and vardenafil.[1]

A systematic review by AHRQ evaluated medications for symptom management associated with BPH.[3] Evidence was analyzed from 57 RCTs and 5 observational studies which included the following medications: silodosin, tolterodine, solifenacin, festoterodine, mirabegron, tadalafil and sildenafil.[3] In a review of alpha-1 blockers, 4 12-week trials found silodosin to be more effective than placebo in improving lower urinary tract symptoms (LUTS) caused by BPH with a weighted mean difference (WMD) in IPSS score of -2.7.[3] Silodosin was compared to tamsulosin in trials lasting 4 to 12 weeks and was found to reduce IPSS scores similar to tamsulosin (-7.8 vs. -7.2) but with a degree of heterogeneity (I^2 = 76%). More adverse events were associated with silodosin compared to tamsulosin, however, withdrawal rates were similar.[3] For anticholinergics, combination therapy of tolterodine, solifenacin and fesoterodine combined with alpha-1 blockers were similar in efficacy to alpha-1 blocker monotherapy. There was insufficient evidence to compare the adverse events of combination versus monotherapy.[3] For phosphodiesterase-5 (PDE-5) inhibitors, tadalafil improved IPSS scores more than placebo in a pooled analysis of 10 12-week trials (n=3516) of mostly white participants (-5.5 vs. -3.4, respectively). Four small trials found tadalafil combined with an alpha-1 blocker to be more effective in symptom improvement than alpha-1 blocker monotherapy (-10.4 and -8.6) respectively.[3] A one-point improvement in IPSS scores was found with tadalafil/finasteride combination over finasteride monotherapy. Tadalafil was similar to tamsulosin in improving IPSS scores, -5.6 vs. -5.9, in men studied for 3 months. Evidence for sildenafil comparisons were deemed insufficient. Adverse events with tadalafil are similar to alpha-1 blockers but withdrawals related to adverse events are higher.[3] For

beta-3 adrenergic agonist, there was insufficient evidence on mirabegron to draw efficacy conclusions.[3] Limitations to the evidence were risk of performance and detection bias, limited applicability to patients over 70 years of age and high percentage of patients in PDE-5 inhibitor trials having erectile dysfunction. Long term effects on blood pressure, drug interactions and maintenance of symptom improvement has not been studied.

A systematic review and meta-analysis analyzed the efficacy and safety of dutasteride compared to placebo in men with symptomatic BPH.[5] Seven RCTs, 2 open-label extension trials and 2 finasteride comparison trials were included (n=12,129). The primary outcome was the change in urinary symptoms assessed by changes in IPSS. Dutasteride was more effective in decreasing IPSS compared to placebo (weighted mean difference [WMD] -1.78, 95% CI, -3.01 to -0.55) but with significant heterogeneity (I^2 = 69%).[3] Symptom improvement was similar in dutasteride and finasteride comparisons. Dustasteride was associated with adverse events more commonly than placebo (RR 1.04; 95% CI, 1.00 to 1.07). Withdrawal rates were similar between groups.[5]

New Guidelines:

National Institute for Health and Care Excellence (NICE)

In 2015 a guideline on the assessment and management of the lower urinary tract in men was released.[4] Recommendations as they pertain to drug treatment are: men with symptomatic lower urinary tract symptoms (LUTS) unresponsive to conservative management should be offered drug therapy with an alpha-1 blocker; men with enlarged prostates (estimated at ≥30 gms or PSA >1.4 ng/ml) and at risk of progression should be offered an 5-alpha reductase inhibitor; and combination therapy with an 5-alpha reductase inhibitor and an alpha-1 blocker should be offered to men with moderate to severe LUTS and enlarged prostate. Men with LUTS should not be offered a PDE-5 inhibitor for the sole treatment of LUTS.[4]

New FDA Drug Approvals:

None identified.

New Formulations/Indications:

None identified.

New FDA Safety Alerts:

In July of 2014 the FDA warned of the possibility of intraoperative floppy iris syndrome (IFIS) during cataract and glaucoma surgery in some patients on or previously treated with alpha-1 blockers, including tamsulosin.[6]

References:

1. Yuan JQ, Mao C, Wong S, et al. Comparative effectiveness and safety of monodrug therapies for lower urinary tract symptoms associated with benign prostatic hyperplasia. *Medicine*; 94:e974. Doi: 10.1097/MD0000000000000974.
2. Barry MJ, Williford WO, Chang Y et al. Benign prostatic hyperplasia specific health 30 status measures in clinical research: how much change in the American Urological 31 Association symptom index and the benign prostatic hyperplasia impact index is 32 perceptible to patients? J Urol 1995; 154: 1770–4 3.
3. Brasure M, MacDonald R, Dahm P, et al. Newer medications for lower urinary tract symptoms attributed to benign prostatic hyperplasia: a review. Comparative Effectiveness Review No. 178. AHRQ Publication No. 16-EHC024-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed June 2, 2016.
4. National Clinical Guideline Centre for Acute and Chronic Conditions. Lower urinary tract symptoms in men: assessment and management. London (UK): *National Institute for Health and Care Excellence (NICE)*, 2015. June: no: 97.
5. Park T, Choi JY. Efficacy and safety of dutasteride for the treatment of symptomatic benign prostatic hyperplasia (BPH): a systematic review and meta-analysis. *World J Urol* 2014: 32:1093-1105. DOI: 10.1007/s00345-014-1258-9.
6. Food and Drug Administration. Flomax (tamsulosin) hydrochloride capsules safety warning. July 2014 Drug Safety Labeling Changes. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm197087.htm. Accessed April 30, 2016.
7. Roehrborn C, Perez I, Roos E, et al. Efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin treatment (Duodart®) compared with watchful waiting with initiation of tamsulosin therapy if symptoms do not improve, both provided with lifestyle advice, in the management of treatment-naïve men with moderately symptomatic benign prostatic hyperplasia: 2-year CONDUCT study results. *BJU Int* 2015;116:450-459.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAP ER 24H	FLOMAX	TAMSULOSIN HCL	Y
ORAL	CAP ER 24H	TAMSULOSIN HCL	TAMSULOSIN HCL	Y
ORAL	CAPSULE	TERAZOSIN HCL	TERAZOSIN HCL	Y
ORAL	TABLET	CARDURA	DOXAZOSIN MESYLATE	Y
ORAL	TABLET	DOXAZOSIN MESYLATE	DOXAZOSIN MESYLATE	Y
ORAL	TABLET	FINASTERIDE	FINASTERIDE	Y
ORAL	TABLET	PROSCAR	FINASTERIDE	Y
ORAL	CAPSULE	AVODART	DUTASTERIDE	N
ORAL	CAPSULE	DUTASTERIDE	DUTASTERIDE	N
ORAL	CAPSULE	RAPAFLO	SILODOSIN	N
ORAL	TAB ER 24	CARDURA XL	DOXAZOSIN MESYLATE	N
ORAL	TAB ER 24H	ALFUZOSIN HCL ER	ALFUZOSIN HCL	N
ORAL	TAB ER 24H	UROXATRAL	ALFUZOSIN HCL	N
ORAL	CAPSULE	JALYN	DUTASTERIDE/TAMSULOSIN	N

Appendix 2: New Clinical Trials

A total of 347 citations were manually reviewed from the literature search. After further review, 346 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining trial is briefly described in the table below. The full abstract is included in Appendix 3.

Table 1: Description of Clinical Trial

Study	Comparison	Population	Primary Outcome	Results
Roehrborn, et al[7] OL, PG, RCT	Dutasteride 0.5 mg and tamsulosin 0.4 mg vs. (D/T) Watchful waiting ± tamsulosin if no symptom improvement (WW)	Treatment naïve men with moderately symptomatic BPH (IPSS score of 8-19) at risk of progression n = 742	Symptomatic improvement from baseline to 24 months, measured by IPSS	D/T: -5.4 points WW: -3.6 points (ETD 1.8; 95 % CI -2.5 to -1.2; P < 0.001)
Abbreviations: IPSS = International Prostate Symptom Score (IPSS); OL = open label; PG = parallel group; RCT = randomized controlled trial				

Appendix 3: Abstracts of Clinical Trials

Roehrborn C, Perez I, Roos E, et al. Efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin treatment (Duodart®) compared with watchful waiting with initiation of tamsulosin therapy if symptoms do not improve, both provided with lifestyle advice, in the management of treatment-naïve men with moderately symptomatic benign prostatic hyperplasia: 2-year CONDUCT study results. *BJU Int* 2015;116:450-459.

Objective: To investigate whether a fixed-dose combination (FDC) of 0.5 mg dutasteride and 0.4 mg tamsulosin is more effective than watchful waiting with protocol-defined initiation of tamsulosin therapy if symptoms did not improve (WW-All) in treatment-naïve men with moderately symptomatic benign prostatic hyperplasia (BPH) at risk of progression. **Methods**: This was a multicentre, randomised, open-label, parallel-group study (NCT01294592) in 742 men with an International Prostate Symptom Score (IPSS) of 8–19, prostate volume ≥30 mL and total serum PSA level of ≥1.5 ng/mL. Patients were randomised to FDC (369 patients) or WW-All (373) and followed for 24 months. All patients were given lifestyle advice. The primary endpoint was symptomatic improvement from baseline to 24 months, measured by the IPSS. Secondary outcomes included BPH clinical progression, impact on quality of life (QoL), and safety. **Results**: The change in IPSS at 24 months was significantly greater for FDC than WW-All (–5.4 vs −3.6 points, $P < 0.001$). With FDC, the risk of BPH progression was reduced by 43.1% ($P < 0.001$); 29% and 18% of men in the WW-All and FDC groups had clinical progression, respectively, comprising symptomatic progression in most patients. Improvements in QoL (BPH Impact Index and question 8 of the IPSS) were seen in both groups but were significantly greater with FDC ($P < 0.001$). The safety profile of FDC was consistent with established profiles of dutasteride and tamsulosin. **Conclusion**: FDC therapy with dutasteride and tamsulosin, plus lifestyle advice, resulted in rapid and sustained improvements in men with moderate BPH symptoms at risk of progression with significantly greater symptom and QoL improvements and a significantly reduced risk of BPH progression compared with WW plus initiation of tamsulosin as per protocol.

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to April Week 3 2016

Search Strategy:

#	Searches	Results	Annotations
1	Doxazosin/	841	
2	Finasteride/	1646	
3	Dutasteride/	442	
4	silodosin.mp.	214	
5	alfuzosin.mp.	401	
6	tamsulosin.mp.	1256	
7	1 or 2 or 3 or 4 or 5 or 6	4129	
8	limit 7 to (english language and humans and yr="2014 -Current")	301	
9	limit 8 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or randomized controlled trial or systematic reviews)	143	

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to April Week 3 2016

Search Strategy:

#	Searches	Results	Annotations
1	benign prostatic hypertrophy.mp. or Prostatic Hyperplasia/	11249	
2	limit 1 to (english language and humans)	8840	
3	limit 2 to yr="2014 -Current"	879	
4	limit 3 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial or controlled clinical trial or meta-analysis or practice guideline or randomized controlled trial or systematic reviews)	204	

Benign Prostatic Hypertrophy (BPH) Medications

Goal(s):

- BPH with urinary obstruction is an OHP-funded treatment only when post-void residuals are 150 mL or more.
- Restrict use for male pattern baldness and erectile dysfunction, which are not OHP-funded conditions.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Will the prescriber consider switching to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4

Approval Criteria		
4. Is the request for an alpha-1 blocker, and does the patient have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction?	**Yes:** Go to #5	**No:** Go to #6
5. Has the patient tried and failed a 2-month trial of a preferred alpha-1 blocker?	**Yes:** Approve an alpha-1 blocker for up to 12 months	**No:** Pass to RPh. Deny until patient has tried and failed a covered alternative
6. Does the patient have a diagnosis of benign prostatic hypertrophy (BPH) or enlarged prostate with obstruction?	**Yes:** Approve for up to 12 months	**No:** Go to #7
7. Does the patient have a diagnosis of unspecified urinary obstruction or BPH without obstruction?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #8
8. RPh Only: All other conditions need to be evaluated to see if diagnosis is funded: **Funded:** covered diagnoses related to prostate may be approved for 1 year. **Not Funded:** unfunded diagnoses (e.g., hair growth, erectile dysfunction) should be denied (not funded by the OHP). • Alpha-1 blockers and 5-alpha reductase inhibitors may be used concurrently for BPH up to 1 year. Alpha-1 blockers may be discontinued once prostate is reduced to normal size. • If urine retention (obstructive), ask for more specific diagnosis.		

Renewal Criteria		
1. Is the request for an alpha-1 blocker and does the patient have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction?	**Yes:** Go to #2	**No:** Go to #3
2. Has the patient also been taking a 5-alpha reductase inhibitor for the last year?	**Yes:** Recommend against combination therapy exceeding 1 year.	**No:** Approve for the shorter of 12 months or length of the prescription

3. Does the patient have a diagnosis of BPH or enlarged prostate with obstruction?	**Yes:** Approve for up to 12 months	**No:** Go to #4
4. Does the patient have a diagnosis of unspecified urinary obstruction or benign prostatic hyperplasia without obstruction?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #5
5. RPh only: All other indications need to be evaluated as to whether they are a funded condition: • Alpha Blockers and 5-alpha reductase inhibitors may be used concurrently for BPH up to 1 year. Alpha-blockers may be discontinued once prostate is reduced to normal size. • If urine retention, obstructive, ask for more specific diagnosis.	If funded and clinic provides supporting literature, approve for up to 12 months.	If non-funded, deny (not funded by the OHP).

P&T Review: *7/16 (KS); 11/12; 9/10; 3/10; 5/08; 2/06*
Implementation: *2/21/13; 1/1/11; 4/20/10; 5/22/08; 7/1/06; 9/30/05*