Drugs to Treat Overactive Bladder

Washington Drug Archive Report

Washington P&T Committee

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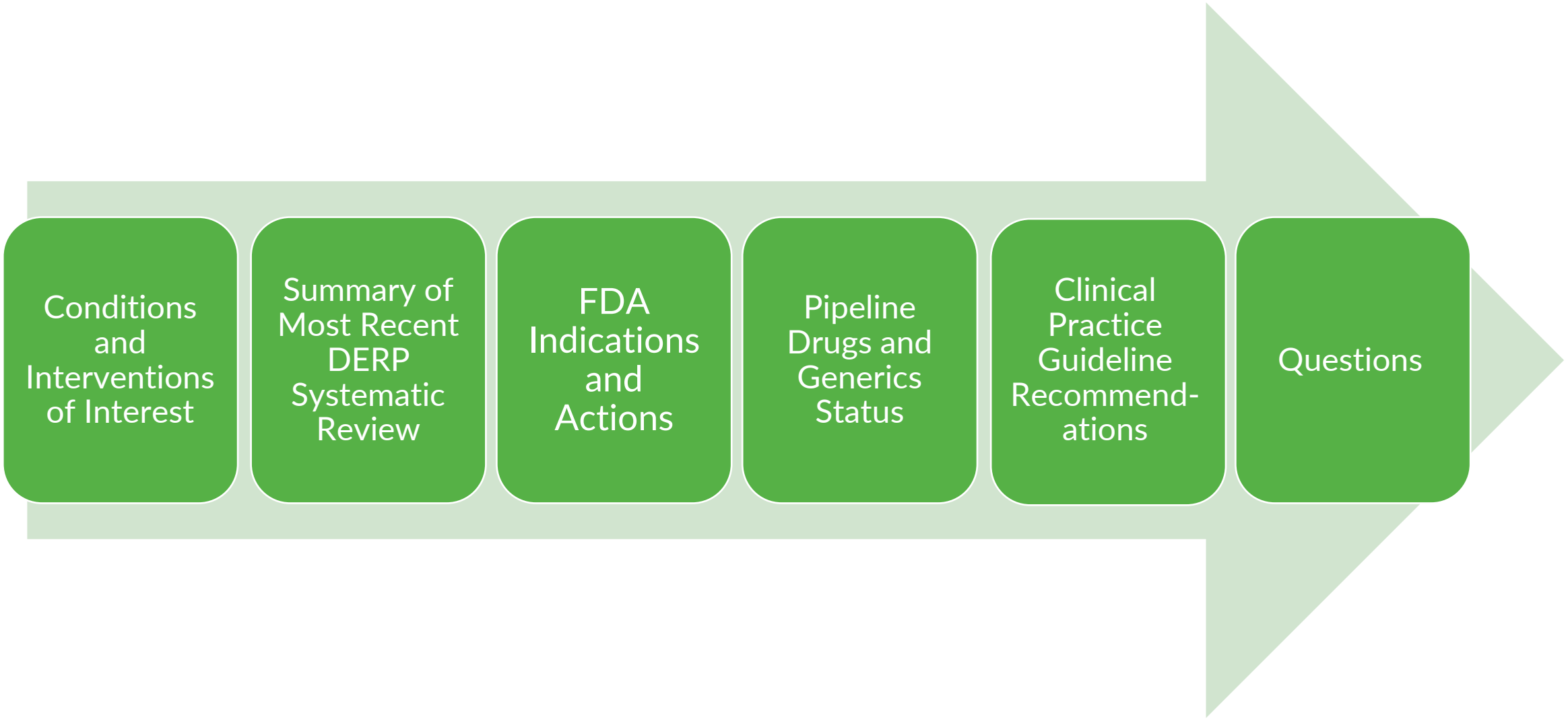
OHSU

Aim of Project

- The Drug Effectiveness Review Project (DERP) aims to present information to the Washington State Pharmacy and Therapeutics (P&T) Committee with topic reports on 9 drug classes that are candidates to be archived from active review by the Committee
- The 9 drug classes identified by the Washington Health Care Authority (HCA) as archive candidates are:
  - Anticoagulants
  - Antiemetics
  - Antiplatelets
  - Asthma controllers
  - Asthma quick relief drugs
  - Long-acting opioids
  - **Overactive bladder drugs**
  - PCSK9 inhibitors
  - Statins

*Drug class in **green** is presented in this report*

Overview


Conditions and Interventions of Interest
Summary of Most Recent DERP Systematic Review
FDA Indications and Actions
Pipeline Drugs and Generics Status
Clinical Practice Guideline Recommend-ations
Questions

Overactive Bladder: Definition

- Overactive bladder (OAB)
  - A syndrome of urinary urgency often with urinary frequency and nocturia, in absence of pathological factors
    - Some patients with OAB also have symptoms of urge or stress urinary incontinence (UI)
  - In males, it is common to associate the more nonspecific condition of lower urinary tract symptoms, or LUTS, which include symptoms primarily associated with OAB (urine storage issues)
    - Common urine storage issues in males are often secondary to bladder outlet obstruction (BOO) due to benign prostatic hyperplasia (BPH)

Overactive Bladder: Epidemiology

- OAB syndrome is common and increases with age
  - Prevalent in 15% to 23% of US adults
  - Some studies report prevalence is similar in females and males, others report prevalence is higher in females
    - Proportion with ***urge UI*** reported as more frequent in females
- Risk factors for OAB include smoking, obesity, arthritis, depression, heart disease, and irritable bowel syndrome
  - Specific to males: prostate disease
  - Specific to females: neurological conditions, diabetes, pregnancy, urinary tract infection, uterine prolapse, hysterectomy, menopause
- A study in 2012 demonstrated prevalence was highest in African American individuals, and lowest in White males

Treatments for Overactive Bladder

- First-line treatments include behavior modifications
  - Pelvic floor muscle exercises and bladder training
  - Fluid management, achieve healthy weight with diet and exercise
- Pharmaceutical agents are second-line treatments
  - For males, important to consider if OAB is caused by BPH (if yes, medications to minimize blockage are next-line treatments)
  - Antimuscarinic agents
    - Reduce bladder contractions
  - β3-adrenergic agonists
    - Promote bladder relaxation during the filling stage
- Third-line treatments
  - Peripheral tibial nerve stimulation, sacral neuromodulation, and botulinum toxin injections

Summary of Most Recent DERP Products

Last Report	2018
Date Presented	June 2018
Report Title	*Drugs to Treat Overactive Bladder*
Search Dates	From inception (most databases) through February 2018
Authors	Pacific Northwest Evidence-based Practice Center researchers
Surveillance Since Most Recent Report	
• No surveillance reports since most recent report (last scan in 2017)	

PICOS of Most Recent DERP Report

- *Population*
  - Adults with UI or OAB (urgency, frequency, leakage, and dysuria)
- *Comparators*
  - Another listed intervention (head-to-head)
- *Outcomes*
  - Incontinence and urgency episodes, number of pads used
  - Patient symptom assessments
  - Adverse events (AEs; serious AEs, specific AEs, withdrawals due to AEs)
- *Study Designs*
  - Comparative randomized controlled trials, systematic reviews (good quality and published 2013 or later), comparative cohort or case-control studies (for harms only)

PICOS of Most Recent DERP Report

- *Interventions*

Name	Brand Name	FDA Approval Date	Formulation	Mechanism
Darifenacin	Enablex	December 22, 2004	ER oral tablet	Muscarinic antagonist
Fesoterodine fumarate	Toviaz	October 31, 2008	ER oral tablet	Muscarinic antagonist
Flavoxate HCl	*Generic* only	January 15, 1970	Oral tablet	Muscarinic antagonist
Mirabegron	Myrbetriq	June 28, 2012	ER oral tablet	β3 adrenergic agonist
Oxybutynin chloride	Generic	July 16, 1975	Oral tablet, ER tablet	Muscarinic antagonist
	Gelnique	January 27, 2009	Transdermal gel	
Oxybutynin	Oxytrol	February 26, 2003	ER transdermal film	Muscarinic antagonist
Solifenacin succinate	Vesicare	November 19, 2004	Oral tablet	Muscarinic antagonist
Trospium chloride	*Generic* only	May 28, 2004	Oral tablet, ER capsule	Muscarinic antagonist
Tolterodine tartrate	Detrol	March 25, 1998	Oral tablet, ER tablet	Muscarinic antagonist

Abbreviations. ER: extended release; FDA: US Food and Drug Administration; HCl: hydrochloride.

Key Questions in Most Recent DERP Report

1. How do drugs used to treat overactive bladder compare in effectiveness and harms?
2. Are there subgroups of patients in whom effectiveness or harms of drugs used to treat overactive bladder differ?
    a. Subgroups include populations with different demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), and pregnancy

Summary of Findings in Most Recent DERP Report (slide 1 of 2)

- 2018 report
  - Included 42 head-to-head RCTs, 1 (*or more*) systematic reviews, and 1 cohort, cumulative since original report
- Summary of key findings
  - 6 for mirabegron versus solifenacin
  - 6 for mirabegron versus tolterodine extended release (ER)
  - 1 for fesoterodine versus solifenacin
  - 3 for fesoterodine versus tolterodine immediate release (IR)/ER
  - 1 for darifenacin versus solifenacin
  - 1 for darifenacin versus trospium ER
  - 6 for solifenacin versus tolterodine IR/ER
  - 1 for solifenacin versus oxybutynin IR
  - 1 for trospium ER versus tolterodine
  - 1 for trospium ER versus oxybutynin
  - 15 for tolterodine IR/ER versus oxybutynin IR/ER

Summary of Findings in Most Recent DERP Report (slide 2 of 2)

- Summary of key findings (cont.)
  - Although mirabegron was found statistically more effective than solifenacin and tolterodine in a few outcomes, the differences were small and likely not clinically meaningful
  - Solifenacin and fesoterodine were more effective than tolterodine, but the differences were small and likely not clinically meaningful
  - Although there were differences in specific AEs between mirabegron and the other drugs (particularly dry mouth [higher with tolterodine]), these did not lead to differences in AE withdrawals or serious AEs
  - Solifenacin and tolterodine resulted in fewer AE withdrawals than oxybutynin
  - No differences in effectiveness of oxybutynin compared with tolterodine, and oxybutynin compared with solifenacin; however higher rates of AE withdrawals with oxybutynin

New FDA Drugs and Indications Since Most Recent DERP Report

- **New drugs**
  - Vibegron (brand name, Gemtesa)
    - β3 adrenergic agonist approved December 20, 2020
    - Oral tablet 75 mg, once daily
- **New indications**
  - Fesoterodine fumarate (Toviaz)
    - Expanded for neurogenic detrusor overactivity (NDO) in pediatric patients ≥ 6 years and ≥ 25 kg (June 2021)
  - Mirabegron (Myrbetriq)
    - Expanded to allow for use in combination with solifenacin succinate (a muscarinic antagonist) for overactive bladder (April 2018)
    - Expanded for neurogenic detrusor overactivity (NDO) in pediatric patients ≥ 3 years and ≥ 35 kg (March 2021)

FDA-Approved Indications

- Indications as of January 23, 2024

Generic Name (Brand Name)	Overactive Bladder with Symptoms of Urge Urinary Incontinence, Urgency, and Frequency	NDO in Pediatric Patients
Darifenacin (Enablex)[a]	√	
Fesoterodine fumarate (Toviaz)	√	√ (≥ 6 years and ≥ 25 kg)
Flavoxate HCl (generic only)	√	
Mirabegron (Myrbetriq)	√	√ (≥ 3 years and ≥ 35 kg)
Oxybutynin chloride (generic tablet, Gelnique[a])	√	√ (ER tablet only; ≥ 6 years)
Oxybutynin (Oxytrol)[b]	√	
Solifenacin succinate (Vesicare)	√	
Trospium chloride (generic only)	√	
Tolterodine tartrate (Detrol)	√	
Vibegron (Gemtesa)[c]	√	

Notes. [a] Brand discontinued since last report; [b] Two products with 1 for men only and 1 for women only; [c] Newly approved since last report.
Abbreviations: ER: extended release; HCl: hydrochloride; NDO: neurogenic detrusor overactivity.

New FDA Warnings, Pipeline Drugs Since Most Recent DERP Report

- **New boxed warnings**
  - No new boxed warnings or general warnings for all included drugs since last report
- **Pipeline therapies**
  - 1 new pipeline drug in phase 3 trials for the indication of stress urinary incontinence
    - Iltamiocel (AMDC-USR)
      - Autologous muscle-derived cells for urinary sphincter repair (stem cell therapy)
      - Injectable delivery

Generic Drug Status & Brand Discontinuations

Name	Generic Availability	Status
Darifenacin	Yes	Already available as generic with last report • *Enablex brand discontinued*
Fesoterodine fumarate	Yes	***Newly available as generic since last report***
Flavoxate HCl	Yes	Already available as generic with last report
Mirabegron	No	Estimated loss of exclusivity September 26, 2024; multiple applications for generic manufacturing have been submitted
Oxybutynin chloride	Yes	Tablet was available as generic with last report Transdermal gel, generic status unclear (appears to be in litigation) • *Gelnique brand discontinued*
Solifenacin succinate	Yes	***Likely newly available as generic since last report***
Trospium chloride	Yes	Already available as generic with last report
Tolterodine tartrate	Yes	Already available as generic with last report
Vibegron	No	Estimated loss of exclusivity December 23, 2034; no applications for generic manufacturing have been submitted at this time

Abbreviations. HCl: hydrochloride.

Clinical Practice Guidelines (slide 1 of 3)

- Treatment of OAB/UI in females
  - First-line treatments are nonpharmacologic
    - Education on pelvic floor muscle exercises, bladder training
    - Lifestyle behaviors (achieving healthy weight, healthy diet and exercise, fluid control)
  - Treat for vaginal atrophy with topical estrogen if needed
  - Medications if initial treatments do not provide adequate relief
    - Recommendations to continue nonpharmacologic approaches in combination with medications
    - Extended release formulations are preferred if available (according to American Urological Association)
    - Continue medications as long as improvements continue and without bothersome side effects

Note. Primary source UpToDate; recommendations cross-referenced and verified against key clinical practice guidelines (slide 19).

Clinical Practice Guidelines (slide 2 of 3)

- Treatment of OAB/UI in females
  - Pharmacologic agents
    - β3 adrenergic agonists recommended first because of increased risk for adverse events (including dementia) with antimuscarinic agents
      - Recommendation despite recognition of higher costs with newer agents
    - For those who are prescribed antimuscarinic agents, trospium and darifenacin are preferred; more (but limited) evidence for poor central nervous system penetration by these drugs, compared with similar agents
      - Start with lowest dose and reassess in 2 to 6 weeks; titrate as needed per patient response and side effects
  - If OAB/UI symptoms continue with medications, refer to specialist (third-line therapies include tibial nerve stimulation, botulinum toxin, sacral neuromodulation, laser therapy)

Note. Primary source UpToDate; recommendations cross-referenced and verified against key clinical practice guidelines (slide 19).

Clinical Practice Guidelines (slide 3 of 3)

- Treatment of OAB/UI in males
  - Often referred to as nonspecific condition of lower urinary tract symptoms, or LUTS, in males
  - Evaluate whether symptoms are due to BPH (with BOO, which is most common) or OAB
  - First line treatments are nonpharmacologic
    - Education on pelvic floor exercises, bladder training
    - Lifestyle behaviors (achieving healthy weight, healthy diet and exercise, fluid control)
  - Medications if initial treatments do not provide adequate relief
    - Initial trial of medication for BPH (alpha-adrenergic receptor blockers, phosphodiesterase-5 inhibitors)
    - If with isolated OAB, β3 adrenergic agonists recommended first over antimuscarinic agents
    - Mixed OAB with BOO is most common; treat BPH/BOO first

Note. Primary source UpToDate; recommendations cross-referenced and verified against key clinical practice guidelines (slide 19).

Key Clinical Practice Guidelines

Focus	Date	Title of Guideline
American College of Obstetricians and Gynecologists (ACOG)		
Clinical update and prevention	2020	Overactive Bladder
American College of Physicians		
Nonsurgical management	2014	Nonsurgical Management of Urinary Incontinence in Women
American Urological Association (AUA)		
Overactive bladder in adults	2019	Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults
European Association of Urology		
Nonsurgical management	2018	Assessment and Nonsurgical Management of Urinary Incontinence

Questions?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