Medication Management of Urinary Incontinence

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Objectives

- Describe when medications are used for urinary incontinence (UI)
- Review medications used in UI including mechanism of action, key side effects, route of administration, dosing, and cost
- Discuss medications on the horizon for UI

Types of Incontinence

- Urinary Incontinence
  - Involuntary loss of urine that is objectively demonstrable
  - Medical, financial, social, hygenic concern
- Stress Incontinence
- Urge Incontinence
- Mixed Incontinence
- Overflow Incontinence
- Functional Incontinence
- Total Incontinence

Urinary Incontinence (UI)

- Epidemiology
  - Affects 25 to 45 % of women
    - Female nursing home patients (60 to 78%)
  - In women 19 to 64 years,
    - Stress incontinence is most common followed by mixed and urge incontinence
  - In women 65 to 80 years,
    - Mixed incontinence is most common followed by stress and urge incontinence

Overactive Bladder (OAB) Management

- First-line
  - Behavioral therapies
    - Bladder training
    - Bladder control strategies
    - Pelvic floor muscle training
    - Fluid management
    - *Grade B Evidence*
    - *Add oral anti-muscarinics (Grade C Evidence)*

American Urological Association (AUA). Diagnosis and Treatment of Overactive Bladder (Non-neurogenic) in Adults: AUA/SUFU Guideline. 2012 May

OAB Management

- Second-line
  - Oral anti-muscarinics *(Grade B)*
  - Extended-release versus immediate-release formulations *(Grade B)*
  - Transdermal oxybutynin *(Grade C)*

American Urological Association (AUA). Diagnosis and Treatment of Overactive Bladder (Non-neurogenic) in Adults: AUA/SUFU Guideline. 2012 May

OAB Management

- Clinical principles
  - Dose/agent modification
  - Concurrent conditions
    - Narrow angle glaucoma
    - Impaired gastric emptying
    - History of urinary retention
  - Side effects: constipation and dry mouth
  - Additive effects
    - Other anti-muscarinics

American Urological Association (AUA). Diagnosis and Treatment of Overactive Bladder (Non-neurogenic) in Adults: AUA/SUFU Guideline. 2012 May

OAB Medications and FDA Approval Dates

- Darifenacin (Enablex®)
  - 2004 (2012)
- Fesoterodine (Toviaz®)
  - 2008
- Oxybutynin (Ditropan®, Ditropan® XL; Oxytrol®; Gelnique®)
  - IR 1975 and XL 1998 (2006); Patch 2003; Gel 2011
- Solifenacin (VESIcare®)
  - 2004 (2011)
- Tolterodine (Detrol®, Detrol® LA)
  - IR 1998 (2005) and LA 2000 (2012)
- Trospium (Sanctura®, Sanctura® XR)
  - IR 2004 (2011) and XR 2007 (2012)

American Urological Association (AUA). Diagnosis and Treatment of Overactive Bladder (Non-neurogenic) in Adults: AUA/SUFU Guideline. 2012 May
Drugs@FDA.gov (Accessed April 5, 2013)

Review of OAB Medications

- FDA-approved indications
- Mechanism of action (MOA)
- Pharmacokinetics (PK)
- Key side effects
- Key drug interactions
- Contraindications/Warnings and Precautions
- Pregnancy-risk category
- Dose and route of administration
- Cost

FDA-Approved Indications

	DARI	FESO	OXYB	SOLI	TOLT	TROS
OAB with symptoms of urinary frequency, urge, or UI	X	X		X	X	X
Antispasmodic for neurogenic bladder			X			
Treatment of symptoms associated with detrusor over-activity due to a neurological condition			X			

DARI=darifenacin; FESO=fesoterodine; OXYB=oxybutynin; SOLI=solifenacin; TOLT=tolterodine; TROS=trospium; OAB=Overactive bladder

Mechanism of Action (MOA)

	DARI	FESO	OXYB	SOLI	TOLT	TROS
Antagonizes effects of acetylcholine on muscarinic receptor			X	X		X
Competitive antagonist of muscarinic receptors		X			X	
Selective antagonist of M3 muscarinic receptor subtype	X (highly)					
Direct antispasmodic effect on smooth muscle			X			

DARI=darifenacin; FESO=fesoterodine; OXYB=oxybutynin; SOLI=solifenacin; TOLT=tolterodine; TROS=trospium

Pharmacokinetics (PK)

	DARI	FESO	OXYB	SOLI	TOLT	TROS
Absorption (oral)	15–19%	52%	6% Patch (high)	90%	77%	4–16%
Distribution	163L	169L	193L	600L	113L	600L
Protein Binding	~98%	~50%	>99%	~98%	>96%	48–85%

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Pharmacokinetics (PK)

	DARI	FESO	OXYB	SOLI	TOLT	TROS
Half-life (hrs)	13–19	~7	IR: 2–3 XL:13 Patch: 30–64	45–68	IR: 2 LA: 7	IR: 20 XR:36
Metabolism	CYP3A4 and 2D6	Pro-drug→ 5-HMT (active) CYP3A4 and 2D6	CYP3A4	Extensive; active metabolite; CYP3A4	Active metabolite; CYP2D6 and 3A4	Esterase hydrolysis and conjugation
Excretion	Urine (60%); feces (40%)	Urine (70%); feces (7%)	Urine	Urine (69%); feces (23%)	Urine (77%); feces (17%)	Urine (6%); feces (85%)

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5-HMT= 5-hydroxymethyl tolterodine

Key Side Effects

	DARI	FESO	OXYB	SOLI	TOLT	TROS
Xerostomia (dry mouth)	19–35%	19–35%	Oral: 29–71% Patch: 4–10%	11–28%	IR: 35% ER: 23%	IR:9–22% XR: 10.7%
Constipation	15–21%	4–6%	Oral: 7–15% Patch: 3%	5–13%	IR: 7% ER: 6%	IR:9–10% XR: 8.5%
Headache	>1%	<1%	Oral: 6–10%	3–6%	IR: 7% ER: 6%	IR:4–7%
Dizziness	<2%	<1%	Oral: 4–17%	N/A	IR: 5% ER: 2%	<1%
Somnolence	N/A	<1%	Oral: 2–14%	<1%	Both: 3%	<1%
Dry eyes	2%	1–4%	Oral: 3–6%	<2%	Both: 3%	1–2%
Vision changes	N/A	N/A	Patch: 3%	4–5%	IR: 2% ER: 1%	1%
ALT increase	N/A	1%	N/A	N/A	N/A	N/A
Local site reaction	N/A	N/A	Patch: 17%	N/A	N/A	N/A

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Key Drug Interactions

	DARI	FESO	OXYB	SOLI	TOLT	TROS
Anti-cholinergics	X	X	X	X	X	X
Strong 3A4 inhibitors (ketoconazole, itraconazole, clarithro-mycin)	Use with caution; Do not use >7.5 mg/day	Use with caution; Do not use doses of >4 mg/day	N/A	Use with caution; Do not exceed 5 mg/day	Use with caution; Do not exceed 1 mg BID (IR) and 2 mg/day (ER)	N/A
3A4 inducers	X	X	X	X	X	N/A
2D6 inhibitors	X	X	N/A	N/A	X	N/A
Meds eliminated by ATS (vancomyin, morphine, metformin)	N/A	N/A	N/A	N/A	N/A	↓ Use with caution

Key Contraindications

	DARI	FESO	OXYB	SOLI	TOLT	TROS
Uncontrolled narrow angle glaucoma	X	X	X	X	X	X
Urinary retention	X	X	X	X	X	X
Paralytic ileus	X	–	–	–	–	–
Gastric retention	–	X	X	X	X	X
GI or GU obstruction	X	–	–	–	–	–
Severely ↓ GI motility	–	–	X	–	–	–

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Key Warnings and Precautions

	DARI	FESO	OXYB	SOLI	TOLT	TROS
Angioedema	X	X	X	X	X	X
CNS effects	X (Somnolence)	X (Somnolence)	X (Somnol)	X (Somnolence)	X (Somnolence)	X (Somnolence)
Heat prostation	X	X	X	X	–	–
Myasthenia gravis	X	X	X	–	X	X
QT prolongation	–	–	–	X	X	–

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Pregnancy–Risk Category

	DARI	FESO	OXYB	SOLI	TOLT	TROS
Risk B			X			
Risk C	X	X		X	X	X

Risk B: Defined as either animal reproduction studies have not demonstrated fetal risk, but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in the 1st trimester and there is no evidence of risk in later trimesters.

Risk C: Defined as either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Special Populations

	RENAL IMPAIRMENT
DARI	No adjustment required
FESO	Use with caution Dose adjust in patients with CrCl <30 ml/min Maximum dose: 4 mg once daily
OXYB	Use with caution
SOLI	Use with caution Dose adjust in patients with CrCl <30 ml/min Maximum dose: 5 mg once daily
TOLT	Use with caution Dose adjust in patients with CrCl 10-30 ml/min IR: 1 mg BID LA: 2 mg once daily CrCl < 10ml/min- Use is not recommended
TROS	Use with caution Dose adjust in patient with CrCl <30 ml/min IR: 20 mg daily at bedtime XR: Use is not recommended

Special Populations

	HEPATIC IMPAIRMENT (CHILD-PUGH)
DARI	Class B: Do not exceed 7.5 mg once daily Class C: Use is not recommended
FESO	N/A
OXYB	Use with caution
SOLI	Class B: Do not exceed 5 mg once daily Class C: Use is not recommended
TOLT	Use with caution IR: 1 mg BID Class A or B LA: 2 mg once daily Class C: LA: Use is not recommended
TROS	N/A

Dose and Route of Administration

	Immediate-Release	Extended-Release	Patch	Gel
DARI	N/A	7.5 once daily Max: 15 mg once daily	N/A	N/A
FESO	N/A	4 mg once daily Max: 8 mg once daily	N/A	N/A
OXYB	5 mg BID-TID Max: 5 mg (4xday)	XL: 5-10 mg once daily; if needed ↑ 5 mg/week; Max: 30 mg once daily	3.9 mg/day twice weekly	3%: 3 pumps (84 mg) once daily 10%: 1 sachet (100 mg) once daily
SOLI	N/A	5 mg once daily Max: 10 mg once daily	N/A	N/A
TOLT	2 mg BID	LA: 4 mg once daily	N/A	N/A
TROS	20 mg BID	XR: 60 mg once daily	N/A	N/A

Effects of Food

	DARI	FESO	OXYB	SOLI	TOLT	TROS
Take with food	N/A	N/A	N/A	N/A	N/A	-
Take on empty stomach	N/A	N/A	N/A	N/A	N/A	Should be administered at least 1 hour before a meal; Fatty meal reduces absorption and bioavailability
Alcohol	N/A	Avoid	N/A	N/A	N/A	Should not be consumed within 2 hrs

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Cost Comparison (30-day supply)

	DARI	FESO	OXYB	SOLI	TOLT	TROS
Immediate-release	N/A	N/A	N/A	N/A	2mg (BID): $270	20 mg (BID) $250
Generic	N/A	N/A	5 mg (BID): $33	N/A	$200	$170
Extended-release	7.5- and 15- mg: $200	4- and 8-mg: $190	5-, 10-, and 15-mg: $165	5- and 10-mg: $230	2- and 4-mg: $220	60 mg: $225
Generic	N/A	?	$96	?	?	$200
Patch	N/A	N/A	$320	N/A	N/A	N/A
Gel	N/A	N/A	3%: $211 10%:$244	N/A	N/A	N/A

Suggested Wholesale Price (SWP):
www.amerisourcebergen.com
[Accessed April 10, 2013]

Oxybutynin Transdermal Patch

- Oxytrol® for Women
- FDA-approved January 25, 2013
- Prescription to over-the-counter (OTC) for women only
  - Partial switch
  - Prescription status for treatment of OAB in men
- Patient autonomy
- 3.9 mg/24-hour
- Available Fall 2013 per Merck press release
- Cost?

OnabotulinumtoxinA (Botox®)

- Intradetrusor onabotulinumtoxinA *(Grade C)*
  - Inhibits acetylcholine and ATP release at the parasympathetic nerve terminal (flaccid muscle paralysis)
  - Third-line and carefully selected patients
  - FDA-approved in adults who have an inadequate response to or are intolerant of anti-muscarinic medication
    - Overactive bladder (100 units as 0.5 ml in 20 sites)
    - Detrusor overactivity associated with a neurologic condition (spinal cord injury, multiple sclerosis) (200 units as 1 ml in 30 sites)

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On the Horizon

- β-3-adreno-renoreceptor agonists
  - Detrusor relaxation
  - Storage phase of micturition, not voiding phase
  - Increases bladder capacity but does not adversely affect the voiding bladder contraction
    - Mirabegron (approved in Japan; Phase III trials US)
    - Adverse drug effects >3%: hypertension, urinary tract infection, headache, and nasopharyngitis
  - Solabegron (Phase II trials)

Summary

- Behavioral therapy
- Medication
  - Similar mechanism of action
  - Selectivity of muscarinic receptor
- Key differences
  - Side effects, drug interactions, dosing, and route of administration
- Generic availability (cost)
- Over-the-counter (OTC) option
- New class of medication