

Overactive Bladder Syndrome: Recognizing Symptoms and Recommending Treatment

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Objectives

1. Recognize and describe signs and symptoms that characterize OAB.
2. Compare and contrast therapy for OAB with respect to efficacy, safety and cost.
3. Describe contraindications and common adverse effects of OAB therapies.
4. Given a patient case, recommend appropriate treatment options.

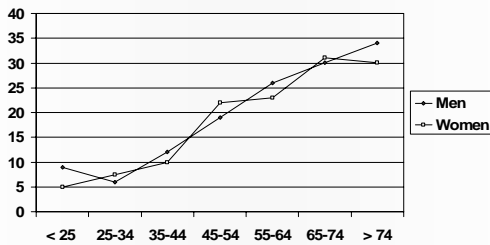
Overactive Bladder Syndrome

- Overactive Bladder (OAB) Syndrome
Defined in 2001:
 - Urinary urgency with or without incontinence, frequency and nocturia
 - Not associated with infection or other pathology
- Significant consequences
- Urinary incontinence accounts for \$26 B in annual cost

Urge vs. Stress Incontinence

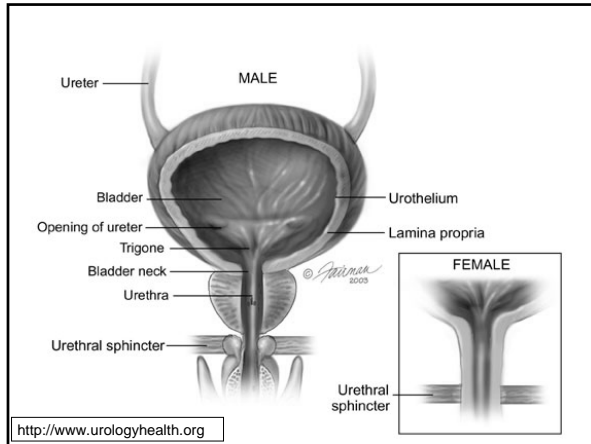
- Urge Urinary Incontinence
 - Feeling of urgency or need to void with loss of urine
 - May or may not have any "warning time"
- Stress Urinary Incontinence
 - Loss of urine with physical activity, typically sneezing or coughing
- Mixed Incontinence
- Overflow Incontinence

Prevalence of OAB



Urinary Tract Physiology

- Urine contained within the bladder by pressure from the urethral sphincter
- During voiding:
 - Urinary sphincter relaxes
 - Detrusor muscle contracts
 - Urine is forced from the bladder through the urethra
- Regulated by the parasympathetic nervous system via muscarinic cholinergic receptors



Drug Receptors in OAB

- Anti-OAB agents target muscarinic-type cholinergic receptors.
- 5 receptor subtypes identified ($M_1 - M_5$)
 - Tissues contain a blend of receptors
 - M_2 found in: detrusor, heart
 - M_3 found in: detrusor, smooth muscle, brain, eyes
- Still learning the importance of drug selectivity ratios

Pathophysiology of OAB

- Many factors / neurotransmitters are involved.
- Main problem is detrusor overactivity
 - Involuntary contractions
 - Weak or impaired contractions
 - Incomplete emptying reduces functional bladder capacity
- Urethral sphincter weakness is main cause of SUI

Causes and Contributors

- Mobility Impairment
- Urinary Tract Dysfunction
- Diminished Cognitive Status
- Neurologic Damage
- Systemic Disease
 - DM, CHF
- Prostatic Enlargement
- Estrogen Deficiency
- Drug Adverse Effects
 - Caffeine
 - Diuretics
 - Alpha-1 adrenergic antagonists
 - Agents that may decrease bladder contractility

Diagnosis of OAB

- Only 15% of patients with OAB will seek treatment
- Based on thorough history
 - Screening questions at annual physical
 - Past GU disorders
 - Screen for contributing conditions
 - Voiding diary
 - Establish frequency, volume, patterns
 - PE
 - Urinalysis

Nonpharmacologic Therapy

- Treat underlying causes
- Consider strategies to manage remaining symptoms:
 - Behavioral interventions / education
 - Muscle training
 - Incontinence products
 - Electrical stimulation
 - Surgical intervention

Behavioral Therapy

- First-line therapy
- Can be more effective than medications
- Education about:
 - Bladder function, proper intake of fluids and caffeine
 - Effects of medications
- “Bladder training”
 - Scheduled voiding
 - Urge suppression techniques
 - Pelvic muscle exercises

Incontinence Products

- Many products available:
 - Panty Liners
 - Pads
 - Briefs
 - Undergarments
 - Underwear
 - Bed / Chair pads
- Help patients maintain “social continence” and maintain perineal hygiene

Incontinence Products

- Incontinence pads vs. sanitary pads
- Products generally targeted to:
 - Type/ severity of incontinence
 - Sex
 - Functional status
 - Convenience / preference
- Online questionnaires available to help patients select products

Incontinence Products

- Possible Complications
 - Skin irritation
 - Check every 2 hours
 - Change every 2-4 hours with continual loss
 - Use barrier creams/ ointments as per infants
 - Urine odor
 - Products containing chlorophyll decrease odor
 - Delayed skin healing
 - Report any skin breakdown to HCP

Drug Therapy Options for Incontinence

- Anticholinergic Agents
 - Oxybutynin
 - Tolterodine
 - Trospium
 - Darifenacin
 - Solifenacin
- Estrogen / HRT: no longer recommended
- Alpha-adrenergic antagonists
- Imipramine
- Desmopressin
- Duloxetine

Anticholinergic Agents

Consider:

- Efficacy
- Safety (especially CNS)
- Drug Interactions
 - Potential to interact with CYP450
- Convenience of administration
- Cost

Anticholinergic Agents

Generally:

- Agents similarly effective
 - Patients more likely to report improvement in symptoms (60%) than those taking placebo (45%)
 - RR 1.41 (95% CI 1.29-1.54)
 - Reduces leakage episodes by 1 per 48 hours
- All agents associated with ADRs:
 - No difference by group in withdrawal due to ADRs
 - 2 -3 times higher risk of dry mouth

Oxybutynin (Ditropan[®], generic)

- Antimuscarinic and antispasmodic properties
 - Also reported to have anesthetic properties
- Efficacy:
 - Reduces incontinence episodes by more than 50% in ~70% of patients
 - Reduction in # of episodes by ~ 80%
- Metabolized via CYP3A4
 - Active metabolite desethyl-oxybutynin
 - Inhibitors may increase levels by up to 100%
- Large dose range (5-20mg per day)
- Dosed up to TID

Oxybutynin Extended Release (Ditropan XL[®])

- 24 hr controlled release (OROS system)
- Similar efficacy to IR oxybutynin
- Less dry mouth, but dose related
- Metabolized via CYP3A4
 - Inhibitors may increase levels by up to 100%
- Dosing and administration:
 - Range 5 - 20mg QD
 - Increase weekly PRN
 - XL doses equivalent to IR doses
 - XL tablets should not be crushed or chewed

Transdermal Oxybutynin (Oxytrol®)

- Matrix patch releases 3.9 mg oxybutynin per day through skin
- Similar efficacy to IR oxybutynin
- Much lower levels of both parent drug and active metabolite:
 - Less dry mouth (94% vs 38%, $p < .001$)
 - Less constipation (50% vs 21% with patch)
 - May cause skin irritation
- No drug interaction studies have been done
- Dosed Q 3-4 days, limited dosing flexibility

Tolterodine (Detrol®)

- Similarly effective to IR oxybutynin
- May be *slightly* better tolerated than IR oxybutynin
 - Dry mouth still occurs in up to 35%
- Drug Interactions:
 - Metabolized via CYP2D6 to active metabolite
 - Variable response, some people naturally fast or slow metabolizers
- Recommended max dose 1 mg BID if used with -azole antifungals, cyclosporine, or reduced hepatic or renal function

Tolterodine (Detrol LA®)

- Extended release capsule
- Possible improved efficacy compared to short acting formulation
 - 70% reduction in episodes, compared to 60% for IR formulation, $p < .05$
- Fewer patients report dry mouth
 - 23% vs 30%, $p < .02$
- Dosing: 4 mg QD
 - Reduce to 2 mg daily in patients with hepatic or renal dysfunction or CYP enzyme inhibitors

Trospium Chloride (Sanctura®)

- Quaternary ammonium anticholinergic and antispasmodic agent
 - Will not cross BBB, theoretically less cognitive adverse effects
- Similar efficacy to IR Oxybutynin
- Less dry mouth than oxybutynin, similar other ADRs
- No CYP actions
- Usual dose 20mg PO BID (without food)
 - Reduce to 20 mg QD in elderly or those with renal dysfunction

Solifenacin (Vesicare®)

- M₃ selective antagonist
 - M₂/M₃ selectivity may result in fewer ADRs
- Similar efficacy to tolterodine BID
- Up to 20 % of patients report dry mouth
 - Dose dependent
 - Possibly higher rates of constipation and blurred vision
- Metabolized by CYP 3A4
- Once daily dosing (5 -10 mg QD)
 - Reduce dose to 5mg QD in liver and renal disease or in patients taking CYP3A4 inhibitors

Darifenacin (Enablex®)

- M₃ selective antagonist
- Similar efficacy to other agents
 - Lengthens “warning time”
- Dry mouth reported in 20-35% of patients
- Metabolized by CYP450 3A4 and 2D6
- No effect on cognitive tasks in elderly patients
- Dosed 7.5 – 15 mg QD
 - Limit to 7.5 mg in liver disease or patients on CYP inhibitors

Warnings and ADRs

- All anticholinergics are contraindicated:
 - Urinary Retention
 - Gastric Retention
 - Uncontrolled Narrow Angle Glaucoma
- Use caution:
 - Controlled Narrow Angle Glaucoma
 - Bladder or GI outlet Obstruction
 - Decreased GI motility
 - Drug Interactions
 - **Elderly Patients**

Counseling Points

- Response is variable
- Expect anticholinergic ADRs
 - May have blurred vision, use caution
 - May decrease heat tolerance and ability to sweat
 - Decrease dose or switch agents if ADRs are intolerable
- Contact health care provider if:
 - Severe abdominal pain
 - Constipation for 3+ days

Relative monthly AWP

- Oxybutynin (generic): \$30
- Ditropan: \$94
- Ditropan XL: \$95
- Oxytrol Patch: \$86
- Detrol: \$110
- Detrol LA: \$96
- Sanctura: \$90
- Enablex: \$99
- Vesicare: \$105
- Incontinence Pads: ~ \$30

Summary

- OAB affects about one out of every 6 adults in the US.
- Behavioral therapies are effective.
- Anticholinergic therapy most commonly used.
- Newer agents are better tolerated than oxybutynin and tolterodine.
- Not all patients will become continent, but may still result in improvement in symptoms.

Patient Case 1

Consider an 82 year old female patient:

- Resident of a nursing home
- Frequent complaints of urinary urgency, with episodes of incontinence daily and nightly
- No AD, U/A and blood chemistry WNL

Which of these options could be recommended as initial drug therapy?

- Trospium 20 mg QD
- Oxybutynin 2.5mg QD
- Tolterodine LA 4 mg QD
- Oxybutynin Patch BIW
- Solifenacin 5 mg QD

Patient Case 2

Consider a 55 year old post-menopausal woman:

- Frequent complaints of urinary urgency, with episodes of incontinence daily and nightly
- Ambulatory, no mobility limits
- No AD, U/A and blood chemistry WNL

Which of these options would you recommended as initial drug therapy?

- Trospium 20 mg QD
- Oxybutynin 5mg BID
- Tolterodine LA 4 mg QD
- Oxybutynin Patch BIW
- Solifenacin 5 mg QD

Thank you
