Urinary Incontinence, Benign Prostatic Hyperplasia & Irritable Bowel

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Outline & Objectives

See auxiliary handout
Urinary Incontinence
Urinary Incontinence

• Involuntary loss of urine causing a social or hygienic problem
• Very common & underreported
• Poorer quality of life
• Depression, loss of self-control, loss independence.
• Curtail activities for fear of an accident

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Urinary Incontinence

- Incidence in non-institutionalized female patients over 60 years old: 38% (by MESA)
  - 1/3 surveyed had urine loss once weekly
  - 16% noted UI daily
- 1/2 as common in men (estimated 9%) and correlates with age

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Anatomy (from Rudy, T. lecture notes 1995 Pharmacology)

Anatomy of urinary tract system

Detrusor muscle (cholinergic)
Internal sphincter (alpha)
External sphincter
Anatomy of Urinary Tract System
How the bladder works

Thompson, JF Geriatric Urological Disorders in Koda Kimble, MA et al Applied Therapeutics: the Clinical Use of Drugs

• Central Nervous System input
  – Brain stem micturation center under inhibitory control
    • Bladder relaxation and filling
    • Sphincter closure

• Increase in bladder volume
  • Stimulates receptors in bladder wall
  • Impulses are transmitted to sacral nerves to spinal cord

• When patient needs to urinate, brain stem micturation center
  • Impulse to spinal cord to detrusor muscle via cholinergic stimulation
  • Detrusor Muscle contraction
How the bladder works

Thompson, JF Geriatric Urological Disorders in Koda Kimble, MA et al Applied Therapeutics: the Clinical Use of Drugs

- **Internal sphincter:** Involuntary
  - Alpha
    - Alpha agonist activity causes muscle contraction keeping urine contained
    - Alpha antagonism relaxes the muscle allowing urine to flow

- **External sphincter:** Voluntary
  - Striated muscle
  - Contraction prevents flow of urine
Medications which affect Lower Urinary Tract Function

- Diuretics
- Alpha receptor antagonists / agonists
- Calcium channel blockers
- Narcotic analgesics
- Sedative hypnotics
- Antipsychotics
- Anticholinergics/ Antidepressants, tricyclic
- Alcohol/ caffeine

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Mechanisms of Urinary Incontinence

- Abnormalities of urethra
- Abnormalities of the bladder
- Both

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Urge Urinary Incontinence

Detrusor Overactivity
Urge Urinary Incontinence
(from Rudy, T. lecture notes 1995 Pharmacology)

Urge Urinary Incontinence = overactive detrusor muscle (increased cholinergic impulse causing increased contractility of bladder muscle)

involuntary contraction of detrusor muscle

Detrusor muscle (cholinergic)
Internal sphincter (alpha)
External sphincter
# Symptoms of Urge UI

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Bladder Overactivity (urge UI)</th>
</tr>
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<tbody>
<tr>
<td>Urgency</td>
<td>Yes</td>
</tr>
<tr>
<td>Frequency W/Urgency</td>
<td>Yes</td>
</tr>
<tr>
<td>Leaking during activity</td>
<td>No</td>
</tr>
<tr>
<td>Amount per episode</td>
<td>Large</td>
</tr>
<tr>
<td>Ability to reach toilet</td>
<td>No or just barely</td>
</tr>
<tr>
<td>Nocturnal incontinence</td>
<td>Yes</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Usually</td>
</tr>
</tbody>
</table>
Pharmacology for Urge UI (UUI)

- **Anticholinergic / Antispasmodics**
  - muscarinic type cholinergic receptors
  - efferent parasympathetic nerve cause detrusor contraction
    - Oxybutynin (Ditropan®) (and XL product)
    - Tolterodine (Detrol®) (and XL product)
    - Solifenacin (Vesicare®)
    - Darifenacin (Enablex®) (extended release product)
    - Trospium (Sanctura®)
Oxybutynin XL for Urge UI
Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002

XL vs. placebo have statistically significant

- less incidences of UI
- better continence
- decreased number of micturitions /day
- increased volume voided / micturition

– IR vs. XL:
- no statistically sign differences in same parameters.

– Discontinuance rate for
- XL 7%
- IR 27%
Oxybutynin Immediate Release for Urge UI (UUI)

- First choice and gold standard
- 25% pts discontinue due to side effects
  - hypotension (α blockade)
  - sedation (histamine - 1 blockade)
  - anticholinergic Side Effects
- Start low dose and titrate monthly to max
- CI: glaucoma, GI obstruction, ileus, megacolon, ulcerative colitis, myasthenia gravis
  - (CI=contraindicated)
### Main markers comparing agents
(from package inserts using highest dose)

<table>
<thead>
<tr>
<th></th>
<th>Incontinence episode/ week</th>
<th>Micturitions/ day</th>
<th>Volume /void</th>
<th>DC Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>15.9</td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Oxybutinin XL</td>
<td>-15.8</td>
<td></td>
<td></td>
<td>7%</td>
</tr>
<tr>
<td>Baseline</td>
<td>22.1</td>
<td>10.9</td>
<td>141</td>
<td>2.4%</td>
</tr>
<tr>
<td>Tolterodine LA</td>
<td>22.1</td>
<td>10.9</td>
<td>141</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>-11.8 (CI crosses 0)</td>
<td>10.9</td>
<td>141</td>
<td>2.4%</td>
</tr>
<tr>
<td>Baseline</td>
<td>18.2</td>
<td>12.1</td>
<td>145.9</td>
<td>1.5%</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>-10.5</td>
<td>12.1</td>
<td>145.9</td>
<td>1.5%</td>
</tr>
<tr>
<td>Baseline</td>
<td>No data</td>
<td>10.1</td>
<td>173.7</td>
<td>3.3%</td>
</tr>
<tr>
<td>Darfenacin</td>
<td>No data</td>
<td>10.1</td>
<td>173.7</td>
<td>3.3%</td>
</tr>
<tr>
<td>Baseline</td>
<td>13.49</td>
<td>12.94</td>
<td>154.80</td>
<td>7.3%</td>
</tr>
<tr>
<td>Trospium</td>
<td>-17.34</td>
<td>12.94</td>
<td>154.80</td>
<td>7.3%</td>
</tr>
</tbody>
</table>
Oxybutynin XR vs. Tolterodine XR


• OPERA:
  – 12 week DB, active control study 10 mg oxybutynin vs. 4 mg tolterodine to women with 21-60 UUI episodes/week.

• Weekly UUI episodes similar between meds

• Oxybutynin more effective reduce micturition frequency
  – 23% women oxybutynin zero episodes compared with 16.8% in the tolterodine group
Solfenacin (Vesicare®)

- New agent with possible higher affinity for muscarinic subtype 3
- Maybe less side effects
Darifenacin (Enablex®)
Kay AG, Wesnes KA BJU International 96: 1055-1062; 2005

• Healthy volunteer data show that darifenacin did not affect cognitive, cardiac or visual function versus dicyclomine (known anti-cholinergic)
• Both agents decreased salivary flow.
Trospium (Sanctura®)
Rudy, D Cline K et al Urology 67: 275-280; 2006

- Anticholinergic mainly in peripheral non-selective muscarinic activity
- 12 week 658 patient study parallel, double blind
- Decreased # of daily toilet voids at week 1, 4 and 12
- At 12 weeks placebo -1.76 versus trospium -2.67
Other (less effective, no safer or not studied) agents:

- **Tricyclic Antidepressants**
  - possibly mixed UI
    - decrease bladder contractility & output resistance
  - possibly nocturnal
  - children’s drug of choice

- **Propantheline**: modestly effective for UUI
  - 15 mg tid, 60 mg at bedtime
  - high side effect profile, modest effectiveness

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Urge Urinary Incontinence

• Belladonna and opium suppositories
  – Used mostly after surgery for spasm
  – Belladonna = anticholinergic medication
Duloxetine versus placebo overactive bladder


- 306 patients randomized to 12 week placebo controlled, double blind trial.
- Voiding episodes/24 hours reduced -1.81 versus -0.62 for placebo. (p < 0.001)
- Voiding intervals reduced 29.46 minutes versus 6.51 placebo p < 0.001
- 78% placebo versus 59% of duloxetine finished study.
Surgery for Urge Urinary Incontinence (UUI)

- UUI - non-surgical
- maybe: innervation or implantation of sacral nerve stimulator or cystoplasty (enlargement)
- One small study (n=26) botulinum toxin in detrusor muscle had preliminary success

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Stress Urinary Incontinence

Urethral Underactivity
Stress Urinary Incontinence

Urethra innervation/ internal sphincter weak causes leakage when pressure in bladder increases (due to exercise/coughing, etc). Weak alpha activity of internal sphincter.
## Symptoms of Stress UI

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Urethral Under-activity (stress UI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Frequency With Urgency</td>
<td>Rarely</td>
</tr>
<tr>
<td>Leaking during activity</td>
<td>Yes</td>
</tr>
<tr>
<td>Amount per episode</td>
<td>Usually small</td>
</tr>
<tr>
<td>Ability to reach toilet</td>
<td>Yes</td>
</tr>
<tr>
<td>Nocturnal incontinence</td>
<td>Rare</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Seldom</td>
</tr>
</tbody>
</table>
Urethral Underactivity/ Stress UI

• Female: childbirth, pregnancy, age, menopause, cognitive impairment, obesity
• Male risk factor: surgery or injury
• Goals of therapy
  – Stimulating alpha adrenergic receptors in the smooth muscle of bladder neck
    • Alpha blockade exacerbates this problem
  – Enhance supportive structures in the urethral epithelium

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Estrogens for Stress UI

• Local / systemic estrogens one of the mainstays of therapy since the 1940s

• Proposed mechanisms:
  – enhance proliferation urethral epithelium
  – local circulation
  – number/ sensitivity of alpha adrenergic receptors

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Estrogens for stress UI

• Women’s Health Initiative Data actually show that estrogen +/- progestrone increased the incidence of urinary incontinence (all types).
• Highest risk with Stress UI

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Estrogens for stress UI

- Topical estrogen?
- Topical estrogen products almost 100% absorbed.
- Data?

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Alpha Adrenergic Agonists: for Stress UI

- Open trials:
  - ephedrine, norfenefrine, PPA, midodrine.

- Placebo controlled trials in mild/mod stress
  - PPA, norfenefrine and norephedrine support modest efficacy of these agents
  - Adverse effects: hypertension, HA, dry mouth, nausea, insomnia, restlessness.

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Alpha adrenergic Agonists for Stress UI

• PPA (phenylpropanolamine): withdrawn from market due to increased risk of stroke in women.

• Contraindicated:
  – Hypertension
  – Headache
  – Dry Mouth
  – Tachyarrhythmias
  – Myocardial infarction
  – Cor pulmonale
  – Renal failure
  – Narrow angle glaucoma
5HT/NE & Stress UI
duloxetine (Cyambalta)

• Inhibition of pre-synaptic neuron re-uptake of serotonin and noradrenaline in sacral spinal cord, believed to increase urethral sphincter contractions.
• 3 published trials - mild to moderate severity reduced # episodes vs. placebo
• Not FDA Approved for Stress UI/approvable in 2003
• Adverse events mild-to moderate
• Nausea

Zinner NR Expert opinion on Investigational Drugs. 2003; 12: 1559-1566
Duloxetine & Stress UI

• 494 patients in Europe and Canada stress UI
• Incontinence episode frequency (IEF) reduced significantly with duloxetine (50% versus 29% placebo.)
• Nausea most frequent adverse effect and common reason for discontinuance.
Duloxetine for Stress UI
(Millard, RJ, Moore, K et al duloxetine vs. Placebo BJU International 93:311-318)

• 458 women in double blind placebo controlled trial 12 weeks
• Baseline incontinence episode frequency (IEF) 18.4 week.
• Patients in duloxetine group 59.5% had a 50-100 % reduction in IEF compared with 43% of placebo treated patients.
• Interval between voiding increased significantly (20.4 versus 8.5 minutes)
SSRI addendum

• "families and caregivers of patients being treated with antidepressants for major depressive disorders or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and other symptoms, as well as the emergence of suicidality."
Surgery for Stress UI

• Not first line:
• SUI surgery females:
  – reposition urethra/ support
  – urethral resistance augmentation (sling)
• SUI surgery males:
  – collagen
  – artificial urethral sphincter (gold standard)

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
## Symptoms with Urinary Incontinence based on type

**Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002**

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<td>Leaking during activity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Amount per episode</td>
<td>Large</td>
<td>Usually small</td>
</tr>
<tr>
<td>Ability to reach toilet</td>
<td>No or just barely</td>
<td>Yes</td>
</tr>
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<td>Nocturnal incontinence</td>
<td>Yes</td>
<td>Rare</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Usually</td>
<td>Seldom</td>
</tr>
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Overflow Urinary Incontinence

Either Urethral Overactivity
or
Bladder Underactivity
Overflow UI

Urethral Overactivity – blockage of sphincter by enlarged prostate (M) or cystocele or surgical overcorrection (F).
Bladder Underactivity- weakening of detrusor muscle
Both mechanisms cause incomplete voiding! Urine remains in bladder.

Detrusor (cholinergic)
Internal sphincter (alpha)
External sphincter
## Symptoms of Overflow UI

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002

<table>
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<th>Symptoms</th>
<th>Urethral Overactivity</th>
<th>Bladder Underactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Frequency w/ Urgency</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Amount of urine per episode</td>
<td>Incomplete void</td>
<td>Incomplete void</td>
</tr>
<tr>
<td>Ability to reach toilet</td>
<td>Probably no</td>
<td>Probably no</td>
</tr>
<tr>
<td>Nocturnal incontinence</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Urinary retention/ Pain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Medications for patients with Overflow UI

• Urethral Overactivity
  – need something to relax urethra
    • alpha blockade (both males and females)
    • dihydrotestosterone reduction in males (BPH)
    • Whole next part of the lecture devoted to this

• Bladder Underactivity
  – need something to stimulate the bladder
    • Cholinergics
    • Catheterization
Overflow UI: caused by Bladder Underactivity

- Bethanachol, a cholinergic agonist that stimulates bladder contraction
- Bad SE: muscle/ abdominal cramps & diarrhea, CI in patients with asthma, heart disease

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
If all else fails…
Catheterization

• Self Catheterization
  – Post void residual (PVR) is measured by a bladder scanner.
  – Self cath is necessary for PVR > 400 mL

• Suprapubic Catheter is surgical implanted
RISKS: UTI/ nephrolithiasis

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Intermittent Catheters

From Southwest Medical Online (southwestmedical.com)
Medications may help with cath

- Symptom relief from tolterodine or oxybutynin in patients who self-cath
  - enhance storage in bladder and relax detrusor

- Alpha 1 receptor antagonists may help to relax internal bladder sphincter in patients who have UUI and retention of the internal bladder sphincter.

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Surgeries for Overflow UI

- Urethral overactivity: anatomical obstruction (TURP - males: see next section)
- Females: cystocele correction
Mechanisms of UI: Mixed UI/Others

• May have mixed picture
  – bladder overactivity + urethral underactivity
  – bladder overactivity + impaired contractility of bladder especially common in elderly ===
    detrusor hyperactivity w/impaired contractility

• Functional Incontinence: dementia, immobile

Rovner, Wyman, Lackner, Guay Urinary Incontinence Pharmacotherapy 2002
Functional Incontinence

• Gill, et al in Arch Intern Med 2005:
  cholinesterase inhibitors used for Alzheimers increase the likelihood that a patient will be prescribed an anticholinergic for urinary incontinence. 4.5% versus 3.1% placebo.
  Thought that with alzheimers, the patient will have functional incontinence anyhow.
  May be a side effect of Cholinesterase inhibitors (exelon, aricept, reminyl)
  Role for pharmacists.
Drug Therapy of Persistent Urinary Incontinence

Thompson, JF Geriatric Urological Disorders in Koda Kimble, MA et al Applied Therapeutics: the Clinical Use of Drugs

<table>
<thead>
<tr>
<th>Urge</th>
<th>Stress</th>
<th>Overflow</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic</td>
<td>Weak</td>
<td>a) Block of urethra</td>
<td>Unable Unwilling</td>
</tr>
<tr>
<td>increase –</td>
<td>urethra –</td>
<td>b) Weak detrusor</td>
<td></td>
</tr>
<tr>
<td>Spasm of</td>
<td>innervated by alpha</td>
<td></td>
<td></td>
</tr>
<tr>
<td>detrusor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Anti-cholinergics:**
  - Oxybutinin
  - Tolteridone
  - Flavoxate
  - Imipramine
  - Propantheline
  - Dicyclomine

- **Alpha agonists:**
  - Pseudoephedrine

- **Alpha antagonists:**
  - Prazosin

- Cholinergic agonist:
  - bethanachol

- catherization

- None
Benign Prostatic Hyperplasia (BPH)
Benign Prostatic Hyperplasia

- 80% elderly men develop pathologic changes associated with BPH (autopsy)
- Between 63 to 65 years old peak incidence

Lee, M. Benign Prostatic Hyperplasia. Pharmacotherapy 2002
Normal Prostate Physiology

• Prostate small heart-shaped gland located below the urinary bladder
  – Normal 4- 20 gram
  – With BPH, largest 50-80 gram

• Functions:
  – Secrete fluids of ejaculation
  – Provide secretions with antibacterial effect high concentration of zinc.

Lee, M Benign Prostatic Hyperplasia Pharmacotherapy 2002
Prostates

- 3 types tissue
  - epithelial
  - stromal
  - capsule

In normal prostate epith:stromal tissue is 1:2, with BPH
epith:stromal is 1:5

- Stromal tissue (Smooth muscle tissue) is embedded w/ alpha 1 receptors
  - stimulation causes smooth muscle contraction - compresses urethra

- Capsule - (outer shell) connective and smooth muscle. Also has alpha 1
Testosterone and Prostates

**Testosterone**
(testicular androgen)

**Androstenedione**
(adrenal androgen)

**Dihydrotestosterone (DHT)**
(active metabolite)

**Estrogen**
Responsible in periphery to enhance stromal tissue

**5 α reductase**

**Location**
- **Type 1**
  - Hair
  - Skin
  - Liver
- **Type 2**
  - Prostate

**Action**
- **Type 1**
  - Acne
  - Body & facial hair
- **Type 2**
  - Prostate growth
Medications to Avoid in BPH

- AVOID Testosterone replacement
- AVOID $\alpha$ – agonists = decongestants
- AVOID anticholinergics & meds like them
  - antihistamines, phenothiazines, tricyclic antidepressants
  - antispasmodics, Parkinsons medications
- AVOID diuretics

Lee, M Benign Prostatic Hyperplasia Pharmacotherapy 2002
Evaluation

• Rule out prostate or bladder cancer
• Rule out neurogenic bladder
• Rule out Urinary Tract Infection (UTI)
• Rule out medications
• Physical Exam- digital exam
• Perception guides therapeutic plan
• American Urology Association (AUA) symptom Index/ Bordasky Index

Lee, M Benign Prostatic Hyperplasia Pharmacotherapy 2002
Evaluation

• Uroflometer:
  – Peak & average urinary flow rate (normal = 10-15 mL/second)

• Post void residual (normal is 0 mL).
  – After patient empties bladder, straight cath inserted to drain any urine in bladder.
  – PVR > 30 mL implies failure of bladder emptying/ predispose to UTI

• Labwork:
  – SCr/ BUN renal failure outlet obstructive
  – PSA = prostate specific antigen
  – Urinalysis - hematuria / Urinary tract infection

Lee, M Benign Prostatic Hyperplasia Pharmacotherapy 2002
AUA (American Urological Society)  
Urinary Symptom index

- Sensation of not voiding
- Urinate again < 2 hours after previous void
- Stopped and started again during urination
- Weak urinary stream
- How often push or strain to start urinating
- How many times have you gotten up during night?

- Thompson, JF Geriatric Urological Disorders in Koda Kimble, MA et al  
  Applied Therapeutics: the Clinical Use of Drugs
International prostate symptom score (IPSS)

• 0 Not at all  1 Less than 1 time in 5  2 Less than half the time  3 About half the time
  4 More than half the time  5 Almost always

• Incomplete emptying
  – Over the past month, how often have you had a sensation of not emptying your
    bladder completely after you finish urinating?  0 1 2 3 4 5

• Frequency
  – Over the past month, how often have you had to urinate again less than two hours
    after you finished urinating?  0 1 2 3 4 5

• Intermittency
  – Over the past month, how often have you found you stopped and started again several
    times when you urinated?  0 1 2 3 4 5

• Urgency
  – Over the last month, how difficult have you found it to postpone urination?  0 1 2 3 4 5

• Weak stream
  – Over the past month, how often have you had a weak urinary stream?  0 1 2 3 4 5

• Straining
  – Over the past month, how often have you had to push or strain to begin urination?  0 1
    2 3 4 5
IPSS (International prostate symptom score)

- **Nocturia**
  
  None  
  1 time 2 times 3 times 4 times 5 times or more

  Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning? 0 1 2 3 4 5

- **Quality of life due to urinary symptoms**
  
  0 Delighted 1 Pleased 2 mostly satisfied 3 Mixed – about equally satisfied and dissatisfied 4 Mostly dissatisfied 5 Unhappy 6 Terrible

  If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that? 0 1 2 3 4 5 6

- **Total score:** 0-7 Mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic.
Benign Prostatic Hyperplasia
(Non pharmacologic treatment)

• Minor BPH - watchful wait
  – Behavior
    • fluid restriction prior to bedtime
    • frequent voiding

• Moderate disease
  – treatment to avoid complications:
    • intractable urinary retention,
    • voiding symptoms
    • increased post void residual

• Moderate/ Severe: surgery (TURP)
Case

• What kind of symptoms does our patient have?
• What kind of work-up does he/she need?
• What are the results from the work-up?
Pharmacologic Therapy for BPH: Agents that reduce prostate size

- Finasteride - competively inhibits type II 5α-reductase
  - decreases DHT levels by 70%
  - indicated moderate to severe disease especially large prostates (50-60 gram)
  - Severe = urethral cath, slow onset 6 mo!
  - Also useful in patients who will not tolerate effects of α- blockade due to CV disease

Lee, M Benign Prostatic Hyperplasia Pharmacotherapy 2002
Finasteride (Proscar)

- Reduces prostate size by 25%
- Increases peak urinary flow rate 1.6-2 ml/sec
- Improves voiding symptoms 30% of pts
- Disadvantages:
  - takes 6 to 12 months to work
  - objective improvement rates relatively low
  - expense

Lee, M Benign Prostatic Hyperplasia Pharmacotherapy 2002
Finasteride

- High protein bound
- Liver metabolized - no drug interactions
- Biologic half life longer than actual: effects last 2 weeks (decrease serum DHT levels)
- Treat for at least 6 - 12 months
- Take as long as responds, results not maintained once off drug

Lee, M. Benign Prostatic Hyperplasia Pharmacotherapy 2002
Finasteride

- Ejaculation disorders/ Erectile dysfunction
- Nausea/abdominal pain, rash, gynecomastia
- Pregnancy Category X:
  - contraindicated with pregnant females -
    - should not handle
    - have contact with semen from person taking

Lee, M Benign Prostatic Hyperplasia Pharmacotherapy 2002
Evaluating Finasteride Therapy

• Normal doses reduce PSA levels by 50%
• If after 6 mos, patient adhere to therapy and PSA not reduced by 50%, evaluate for prostate cancer
• If increase PSA evaluate prostate cancer

Lee, M Benign Prostatic Hyperplasia Pharmacotherapy 2002
Dutasteride (Avodart)

Andriole GL, Kirby REuropean Urology 2003; 44: 82-88

• Dual 5α- reductase inhibitor in clinical trials for hair loss and BPH
  – 4 clinical trials (n=5655) vs placebo
    • reduced PSA by 50% vs. placebo
    • side effects impotence, decreased libido, ejaculation, and gynecomastia
    • no effect on bone metabolism, bone density, or lipid.
  – 1 trial added tamsulosin to therapy (n=327) showed similar safety profile
  – Avoid handling medication if pregnant
α-adrenergic antagonists

• Three generations:
  – 1st- never used: poor side effect profile
  – 2nd generation: 2-4 week onset
    • prazosin (Minipress®)
    • terazosin (Hytrin®)
    • doxazosin (Cardura®)
  – 3rd generation $\alpha_{1A}$ specific - 1 day onset
    • tamsulosin (Flomax®)
    • alfuzosin (Uroxatral®)
Second & Third Generation α antagonists

• Efficacy: 2nd and 3rd generation same efficacy
  – increase urinary flow rate 2-3 mL/sec 60-70% of patients
  – reduce post-void residual
• Will work for 2-3 years
• Do not alter PSA levels

Lee, M Benign Prostatic Hyperplasia Pharmacotherapy 2002
Second generation $\alpha$ blockers

- Start low, go slow
- Hypotension / Syncope
  - especially first dose
  - peripheral alpha receptors also blocked
  - take right as go to bed - then patient IN bed when hypotensive.
- Orthostatic Hypotension, Dizziness
Tamsulosin (Flomax®)  
3rd Generation $\alpha$ blocker

- Selective for $\alpha_{1A}$ receptors  
  - 70% receptors in prostate
- Low affinity for $\alpha_{1B}$ receptors  
  - so no hypotension, HR changes
- No dose titration necessary
- Addition to patient low blood pressure or adequately controlled on other medications possible
- Floppy Iris Syndrome – Side effect
Alfuzosin (Uroxatrol®)
3rd Generation blocker

• Pooled analysis 3 parallel randomized, Double Blind, Placebo controlled 3 month studies with Lower Urinary Tract Symptom
  – Alfuzosin improved IPSS by -6 vs -4.2 plac.
  – Alfuzosin improved peak urinary flow rate by 2.3 vs. 1.1 with placebo
  – Adverse effects dizziness 6.1 vs 2.9 placebo
  – No significant changes in blood pressure
Silodosin

• alpha 1 A adrenoceptor selective antagonist
• Available in Japan as Urief
• Submitting NDA to FDA currently
• Phase 3 multicenter study compared silodosin to tamsulosin (half approved US dose) and placebo. Change in IPSS -8.3 silodosin, -6.8 tamsulosin, -5.3 placebo
• Better than placebo, not inferior to tamsulosin
Apoptosis?

• Doxasozin & terazosin shown to also induce apoptosis of prostate smooth muscle cells
• Tamsulosin does not have this effect
• Postulated that the quinazoline nucleus
• Prevention/treatment prostate cancer
Saw Palmetto & BPH
Dvorkin L, Song KY The Annals of Pharmacotherapy 36:1443-1452

• Popular herb treatment in US of BPH
• Many names most common are:
  – Serona repens = s. repens
  – sabal (fructus)
• No standardized dosage forms
  – berries
  – teas
  – serona extracts
Saw Palmetto and BPH

Dvorkin L, Song KY The Annals of Pharmacotherapy 36:1443-1452

• Mechanism of Action - unknown
  – dihydrotestosterone - may involve $5^{\alpha}$ reductase
  – Antiestrogen may be competitive block of the translocation of estrogen receptors to nucleus
  – decreased sex hormone binding globulin
  – stimulation apoptosis
Saw palmetto
Dvorkin L, Song KY The Annals of Pharmacotherapy 36:1443-1452

• Many studies show efficacy
  – 2 studies & 1 meta-analysis
    • improved IPSS (score) outcomes (urgency, hesitancy, frequency) and QOL measures
    • size of prostate or volume of prostate not affected
  – S repens vs. finasteride
    • similar improvement IPSS (score), QOL
    • S repens showed no change in peak flow, PSA, FSH, LH or testosterone level
    • Prostate size S repens 6% reduction vs. finasteride 18%
Saw palmetto

Dvorkin L, Song KY The Annals of Pharmacotherapy 36:1443-1452

• Saw palmetto vs alfuzosin  n=63
  – peak flow 48% improve vs alfuzosin 72%

• 3 mo trial  saw palmetto vs prazosin
  – similar for irritable symptoms

• Both trials improved symptoms, decreased urinary frequency and increased flow rate

• $\alpha_1$ antagonists greater efficacy, few statistically significant differences.

• Treatment 1-2 mos before response
Surgery

- Gold standard for treatment with moderate to severe BPH prostatectomy (either transurethrally (TURP) or suprapubically).
- Highest rate of symptom improvement & highest rate of complications
- TURP - scope trough urethra open bladder neck (small prostates) 1 hour surgery
- Open Prostatectomy- larger prostates – hospitalization, recoup.
Irritable Bowel Syndrome
Irritable Bowel (IBS) Incidence/Prevalence

- Some estimates of 5-20% population
- 67% of cases are women
- 3 subtypes are equally common and sometimes overlap
Pathophysiology Theory

Wall, GC Lower Gastrointestinal Disorders in Young, Koda-Kimble Applied Therapeutics: the Clinical Use of Drugs 2005

• Pain
  – silent gut nociceptors - due to ischemia or infection
  – increase excitability of neurons of dorsal horn lead to gut hyperalgesia

• Serotonin
  • 95% 5HT receptors located in GI tract
    – (enterochrofin cells, neurons, smooth muscle)
  • GI smooth muscle contraction & relaxation
  • GI sensory function
  • Upregulation/Downregulation = fluctuation
Pathophysiology Theory

Wall, GC Lower Gastrointestinal Disorders in Young, Koda-Kimble Applied Therapeutics: the Clinical Use of Drugs 2005

- Altered colonic motility
  - Diarrhea predominant
    - exaggerated response to cholecystokinin after eating - increased propulsions - diarrhea
  - Constipation predominant
    - fewer colonic propulsions post-prandial
  - Bloating
    - poor fermentation of carbohydrates
Rome II Criteria

• Required Diagnostic Criteria
  – At least 12 weeks (not consecutive) in 12 months of abdominal pain or discomfort that has at least 2 of 3 features
    • relieved by defecation
    • onset associated with change in frequency of stool
    • onset associated with a change in stool form

Kitt D, Butler K. “What is the evidence for the pharmacotherapy of Irritable Bowel Syndrome?”
PMG Department of Pharmacy Rx Question of the Month October 2003
Rome II Criteria
Supporting Diagnostic Criteria

– general
  • abdominal fullness, bloating, swelling
  • Mucus passage during BM
  • feeling incomplete voiding

– IBS with constipation
  • < 3 BM each week
  • lumpy, hard stools
  • straining during BM

– IBS with diarrhea
  • > 3 BM per day
  • loose, watery stools
  • urgency
    – having to rush to have a BM

• Kitt D, Butler K. “What is the evidence for the pharmacotherapy of Irritable Bowel Syndrome?” PMG Department of Pharmacy Rx Question of the Month October 2003

• BM=bowel movement
• IBS=irritable bowel syndrome
Psychological Component

• Overlaps functional abdominal disorders
  – fibromyalgia
  – functional dyspepsia
  – chronic fatigue syndrome

• 40 to 60% patients with IBS have psychological manifestations

From Spruill & Wade: Irritable Bowel Disease Pharmacotherapy 2002
American Gastroenterology Association

• GI symptoms are exacerbated by stress

• Psychological disturbances affect IBS & behavior of patients with this disorder

• IBS can lead to a reduced health related Quality of Life (QOL)
  » From Spruill & Wade: Irritable Bowel Disease
  » Pharmacotherapy 2002
Algorithm for the diagnosis and management of IBS

Wall, GC Lower Gastrointestinal Disorders in Koda-Kimble Applied Therapeutics: the Clinical Use of Drugs 2005

- ROME II Criteria
- Screening of Organic Disease
Work-up

• Rule Out Dietary Causes
  – Celiac sprue- allergy to wheat gluten
  – Lactose Intolerance - dairy
  – Sorbitol, diet gum/ candy, fructose, complex carbohydrates
  – Caffeine, artificial sweeteners
  – Shelf life of food patient is eating
  – Food elimination based on IGG testing?

• Rule Out medications (herbals too)

From Lecture Notes 3-16-1998 Mark Reichelderfer MD
Work up 2005

• If patient is > 50 years old, needs work up.
• If patient is < 50 years old and has any of these Alarm Symptoms require work-up:
  – Weight loss
  – Gastrointestinal bleeding
  – Anemia
  – Fever
  – Frequent nocturnal symptoms
• History and Rome II Criteria (or Manning)
Algorithm for the diagnosis and management of IBS

Wall, GC. Lower Gastrointestinal Disorders in Young, Koda-Kimble. Applied Therapeutics: the Clinical Use of Drugs 2005

- ROME II Criteria
- Screening of Organic Disease
  - Positive IBS Diagnosis
  - Symptom Assessment
    - Constipation
    - Diarrhea
    - Pain/Bloating
Constipation Predominant
Irritable Bowel Syndrome
Algorithm for the diagnosis and management of IBS

Wall, GC Lower Gastrointestinal Disorders in Young, Koda-Kimble Applied Therapeutics: the Clinical Use of Drugs

1: dietary fiber
2: osmotic laxative
3: tegaserod (female)
Constipation Predominant IBS Treatment

• Fiber (bulk laxative - not absorbed from GI tract, dissolve swell in water)
• Use fiber like a drug (start specific dose, titrate to toxicity)
  – Bran
  – Psyllium - Metamucil
  – Methylcellulose – Citrucel
  – Polycarbophil- Fibercon

From Lecture Notes 3-16-1998 Mark Reichelderfer MD
High fiber diets

• Conflicting data on high fiber diets.
• Baseline diet = 13 gram fiber/day
• Group one = 10 gram fiber/day
• Group two=30 gram fiber/day
• Both groups showed a benefit in pain/symptom scores from therapy
Products

• Fiber products

From www.metamucil.com & www.citruce.com
Laxatives for Constipation Pre-dominant IBS

Kitt D, Butler K. “What is the evidence for the pharmacotherapy of Irritable Bowel Syndrome?” PMG Department of Pharmacy Rx Question of the Month October 2003

- Commonly used, although no studies
- Osmotic
  - sorbitol
  - lactulose
  - polyethylene glycol
- Stimulant laxatives (senna, bisacodyl) should be reserved as rescue agents
  - risk laxative dependence
  - potential structural damage
Constipation Predominant IBS
Tegaserod (Zelnorm®)

• Approved July 2002 for FDA approved for short-term (less than 12 weeks) symptomatic treatment of females with constipation predominant IBS.

• Approved in 2004 chronic constipation for males and females under age 65.

• Voluntary suspension of marketing 2006

• Now available via a treatment IND restricted access program

Lovell S. Haxby D, Ketchum K Zelnorm: what’s evidence for IBS? OSHP Interactions vol26:no5
Constipation Predominant IBS
Tegaserod (Zelnorm®) cont.

- 5HT₄ partial agonist

Three, 12-week prospective, DB randomized trials.

- Results complicated by:
  - changing of study endpoints during trial
  - high placebo rate
  - pts w/ severe constipation allowed rescue laxative & pts w/ severe diarrhea allowed loperamide rescue

Lovell S, Haxby D, Ketchum K Zelnorm: what’s evidence for IBS? OSHP Interactions vol26:no5
Constipation Predominant IBS
Tegaserod (Zelnorm®) cont.

relief score showed no difference between placebo.

• altered score relief criteria, showed 2 mg bid and 6 mg bid significantly were better than placebo, with NNT 11.6 and 12.2.

• used altered score relief criteria showed no difference in treatment group.

  • Lovell S. Haxby D, Ketchum K Zelnorm:what’s evidence for IBS? OSHP Interactions vol26:no5
Constipation Predominant IBS
Tegaserod (Zelnorm®)

• No treatment effect in male patients.
  • Only 224 men in trials, results not reported

• Limited effect in female patients
  • 12 need to be treated to have one success
  • Are results clinically impressive?
  • < 50% patients are “responders”

• What do we do after 12 weeks?
  • One open-label study of 12 months safe and well tolerated.
  • Still not FDA approved for indication
Tegaserod (Zelnorm®) continued

• Withdrawal from market: new analysis of 29 short –term studies including 11600 patients versus 7000 patient placebo

• Risk of severe cardiovascular adverse events (angina, heart attacks, & strokes) higher in patients treated with tegaserod
Inclusion Criteria Tegaserod treatment IND
http://www.zelnorm.com/index.jsp

• Women under the age of 55 years
• Currently suffering with IBS-C or Chronic Idiopathic Constipation
• No satisfactory response to other available treatments and/or patients who had satisfactory improvement of their symptoms with prior Tegaserod treatment
Exclusion criteria – Zelnorm new treatment IND

- History or current diagnosis of cardiovascular ischemic disease
- Symptoms suggestive of cardiovascular ischemic disease
- Presence of any cardiovascular risk factors according to NIH guidelines
- Uncompensated depression or anxiety or suicidal ideation or behavior
- Physician and patient full disclosure of risk
- Informed consent.
Diarrhea Predominant Irritable Bowel Syndrome
Algorithm for the diagnosis and management of IBS

Wall, GC Lower Gastrointestinal Disorders in Young, Koda-Kimble Applied Therapeutics: the Clinical Use of Drugs

ROME II Criteria

Screening of Organic Disease

Symptom Assessment

Positive IBS Diagnosis

Constipation

Diarrhea

Pain/Bloating

1. loperamide
2. diphenoxylate/atropine
3. cholestyramine
Anti-diarrheals for Diarrhea
Predominant IBS

- slows GI propulsions increasing time in colon
- Enhances water/electrolyte reabsorption
- Enhances sphincter tone
- Diphenoxylate (Lomotil)
- Loperamide (Immodium)
- Both dosed regularly for prevention

From Spruill & Wade: Irritable Bowel Disease Pharmacotherapy 2002
Cholestyramine

• Bile Acid Sequestrant
  – Used for cholesterol management
  – Used for diarrhea associated pseudomembranous colitis
  – Idiopathic bile acid malabsorption following cholecystectomy
    • Gall bladder stores bile acids and concentrates them
    • Releases bile acid when fatty meal eaten
    • In patients without gall bladder, bile acids go directly to GI tract, sometimes causing diarrhea
    • Diarrhea predominant Irritable Bowel

• Watch for drug interactions
Alosetron (Lotrenex®)  Kitt D, Butler K. “What is the evidence for the pharmacotherapy of Irritable Bowel Syndrome?” PMG Department of Pharmacy Rx Question of the Month October 2003

• Indications
  – Use only females with severe diarrhea IBS
    • abdominal pain or discomfort severe & frequent
    • frequent BM urgency or fecal incontinence
    • disability or limited daily activities
  – Symptoms for > 6 months
  – Second line agent for patients who failed alternatives
Alosetron (Lotrenex®)  Kitt D, Butler K. “What is the evidence for the pharmacotherapy of Irritable Bowel Syndrome?” PMG Department of Pharmacy Rx Question of the Month October 2003

- 6 trials
  - Large 370-801 patients / trial diagnosed Rome II
  - Showed improvement stool frequency & consistency
- 3 /6 trials
  - Showed benefit pain/urgency
- 2/6 trials
  - Showed improvement in urgency/ overall response
Alosetron (Lotrenex®)  Kitt D, Butler K. “What is the evidence for the pharmacotherapy of Irritable Bowel Syndrome?” PMG Department of Pharmacy Rx Question of the Month October 2003

- Selective 5HT₃ receptor antagonist
- Activation 5HT₃ regulate visceral pain, colonic transit, & GI secretions
- Lack of evidence in men for IBS
- Side effects
  - GI discomfort/pain
  - Nausea
  - Constipation
  - Ischemic colitis caused withdrawal in 2002
Alosetron Prescribing Requirements

• Physician: enrolled GSK Prescribing program
  www.lotronex.com/physicianinfo.htm,

• Patients must be counselled about risks/benefits

• Lotronex medication guide
  www.lotronex.com/download/medication_guide

• Patient must sign patient - physician agreement

• Must affix prescribing sticker to every written prescription (fax or phone invalid)

• Patient receives a medication guide & follow-up survey enrollment form with every prescription.
Alosetron (Lotrenex®) for Diarrhea Predominant IBS

• Selective 5HT₃ receptor antagonist
• Activation 5HT₃ regulate visceral pain, colonic transit, & GI secretions
• Withdrawn and reintroduced late 2002 with prescribing restrictions
• Serious GI events:
  – ischemic colitis
  – serious complications of constipation

Lotrenox prescribing information www.lotronex.com
Alosetron (Lotrenex®) for Diarrhea Predominant IBS

• New labeling - lower dose than when approved previously
• If ineffective in 4 weeks: increase dose
• If ineffective after 4 more weeks, discontinue drug
• Monitor constipation and ischemic colitis
  – constipation lasting 4 days - discontinue/hold
  – constipation lasting 8 consecutive days - discontinue

Lotrenox prescribing information www.lotronex.com
Cilansetron (Calmactin)

Chey WD, Cash BD Expert Opinion on Investigational drugs. 14(2): 185-93; 2005

• 5 HT 3 receptor antagonist
• In trials now to decrease GI motility
• In 2 large randomized Double blind studies by abstract only: cilansetron more effective than placebo at improving overall abdominal pain and diarrhea.
• SE- ischemic colitis 3.77/ 1000 person years (similar to alosetron)
• Risk management plan and post-market surveillance will be similar to Lotronex.
• As of 2005, not approvable in US.
Pain and Bloating Type of Irritable Bowel Syndrome
**Algorithm for the diagnosis and management of IBS**

Wall, GC Lower Gastrointestinal Disorders in Young, Koda-Kimble Applied Therapeutics: the Clinical Use of Drugs

- **ROME II Criteria**
- **Screening of Organic Disease**
  - **Positive**
    - IBS Diagnosis
- **Symptom Assessment**
  - **Constipation**
  - **Diarrhea**
  - **Pain/Bloating**
    - 1. hyoscamine
    - 2. dicyclomine
    - 3. amitriptyline or nortriptyline others
Anticholinergics/Antispasmodics for IBS

- Propantheline (ProBanthine®)
- Hyoscamine (Levsin®) sublingual
- Dicyclomine (generic)
- Librax® - clindium / chlordiazepoxide
- Donnatol® - atropine, scopolamine, and hyoscyamine with phenobarbital

1) From Lecture Notes 3-16-1998
Mark Reichelderfer MD
Anticholinergic Side Effects

- Blurred vision: Can’t see
- Dry mouth: Can’t spit
- Urinary Retention: Can’t pee
- Constipation: Can’t -----
- Decreased Sweating: - heat stroke risk
- Forgetfulness
- Sedation
- Depression/ Anxiety
Antidepressants for IBS

• Anti-depressants -
  – Additional effect of GI motility & visceral responses.
  – Antidepressants will exert benefits for IBS prior to mood effects.
Tricyclic Antidepressants

Kitt D, Butler K. “What is the evidence for the pharmacotherapy of Irritable Bowel Syndrome?” PMG Department of Pharmacy Rx

Question of the Month October 2003

• 7 studies
  – 5 are randomized & controlled
  – limited by small size, duration, inconsistent use meds, dated definitions IBS & ?

Methodology
  • amitriptyline (2 studies, n = 14-22)
  • desipramine (2 studies, n=28-31)
  • trimipramine (3 studies, n= 50-428)

– Outcomes: abdominal pain, frequency BM, overall response to treatment/global improvement
Tricyclic Antidepressants

Kitt D, Butler K. “What is the evidence for the pharmacotherapy of Irritable Bowel Syndrome?” PMG Department of Pharmacy Rx Question of the Month October 2003

• May decrease small intestinal transit time.
• Diarrhea predominant patients benefit from side effect.
• 5/6 trials show statistically significant global improvement compared to placebo
• Moderate pain at baseline, some response
• Low to moderate dose… not dose related
IBS: SSRIs
Kitt D, Butler K. “What is the evidence for the pharmacotherapy of Irritable Bowel Syndrome?” PMG Department of Pharmacy Rx Question of the Month October 2003

• Paroxetine used in 2 trials of non-depressed patients with IBS (n=20-257).
• Limitation - high dropout rate, high rate of anxiety disorders (concomitantly), and lack of published statistics.
• Improvement in pain.
• In smaller trial, stool frequency improved independent of whether diarrhea or constipation predominant.
Algorithm for the diagnosis and management of IBS

Kitt D, Butler K. “What is the evidence for the pharmacotherapy of Irritable Bowel Syndrome?” PMG Department of Pharmacy Rx Question of the Month October 2003

ROME II Criteria

Screening of Organic Disease

Positive IBS Diagnosis

Symptom Assessment

Constipation
1. dietary fiber
2. osmotic laxative
3. tegaserod (female)

Diarrhea
1. loperamide
2. diphenoxylate/atropine
3. cholestyramine
4. alosetron - GI MD

Pain/Bloating
1. hyoscine
2. dicyclomine
3. amitriptyline or nortriptyline others

Symptom Assessment

Positive IBS Diagnosis

Screening of Organic Disease

ROME II Criteria