Pharmacology: Genitourinary

Lecturer: JACOBS
Pharmacology: Genitourinary

Conditions Covered In This Lecture:

- Benign prostatic hyperplasia (BPH)
- Erectile dysfunction
- Urinary Incontinence
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Benign Prostatic Hyperplasia

Prostate

• Fibrous, muscular, and glandular (secretory) organ
• Acts as a conduit for urine and semen
• **Contracts** during ejaculation to prevent “retrograde” movement of semen into the bladder
• Secretes **Prostatic fluid** (20-30% of semen):
  • Alkaline, milky white, rich in zinc
  • Helps to neutralize acidity of vaginal fluids (along with seminal vesicle fluid) to promote sperm survival
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Related Anatomy

bladder
ureters
seminal vesicle
vas (ductus) deferens
ejaculatory ducts
Cowper’s gland
bladder neck
urethra

Transition Zone
Anterior Fibromuscular Stroma
Prostatic urethra
Peripheral Zone
Central Zone
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Benign Prostatic Hyperplasia

**BPH** = Benign Prostatic Hyperplasia

**Hypertrophy**: abnormal and excessive cell growth (enlargement)

**Hyperplasia**: abnormal and excessive cell division

What stimulates prostatic hyperplasia?
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transition zone section

circulating testosterone (T)

5α-reductase

dihydrotestosterone (DHT)

stromal cells

glandular cells

ducts
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Stimulation of cell division by DHT causes glandular hyperplasia and organ enlargement.

corpora amylacea (calcifications)

DHT → Androgen Receptor (AR) → AR-Dependent Gene Expression → Growth Factors (e.g. IGF-1) Biomarkers (e.g. PSA)
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Common Features

• Benign (non-metastatic; adenomatous) growth of prostate
• Commonly affects transition zone, promoted by DHT
• Advanced cases can become highly nodular
  (multiple fibrous adenomas)
  Increased risk of prostate cancer? (see slide 24)
• Age-related progression
  • 50% of 50 year-olds
  • 75% of 80 year-olds
• About 50% of cases produce ‘problematic’ symptoms
• Affects 14 million men in US
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Complications of BPH:
- Restriction of urethral diameter
- Bladder compression
- Bladder neck obstruction
  - possible occlusion by 3rd prostate lobe – like a ball valve

Possible Symptoms:
- Reduced bladder capacity
- Reduced urine flow
- Urinary pain
- Hematuria (blood in urine)
- Difficulty initiating urination
- Incomplete voiding
- UTI, cystitis
- May lead to elevated PSA (from prostatic irritation, infection)
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Therapeutic Approaches:

**Catheterization** ("Foley" catheter)
- Risk of infection with long-term use

**Surgical, examples:**
- Prostatic Stent
- Transurethral Resection of the Prostate (TURP)

Images: Mayo Clinic
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Therapeutic Approaches: Pharmacological

**Alpha-1 blockers**

**GOAL:** Decrease contractility (of the trigone muscle, internal urethral sphincter muscle, and prostate gland)

**5α-reductase inhibitors**

**GOAL:** Inhibit androgen (DHT) production
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Therapeutic Approaches:

**Alpha-1 blockers**

**Selective $\alpha_1$ adrenergic antagonists:**

- **Alfuzosin** (Uroxatral®)
- * **Doxazosin** (Cardura®)
- * **Prazosin** (Minipress®)
- **Silodosin** (Rapaflo®)
- **Tamsulosin** (Flomax®)
- * **Terazosin** (Hytrin®)

* **Doxazosin, Terazosin:**
  
  FDA: approved for BPH *and hypertension*

**Prazosin:**

FDA: approved for hypertension (BPH is off-label)
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**STORAGE REFLEX**

- **RED = sympathetic (NE)**
- RED = afferent stretch receptors (storage reflex active)

- **RELAX DETRUSOR**
  - \( \beta_2 \)

- **CONTRACT TRIGONE + IN. SPHIN.**
  - \( \alpha_1 \) innervation of TRIGONE and INTERNAL URETHRAL SPHINCTER

- So, \( \alpha_1 \) blockers \( \downarrow \) tone of bladder neck and outlet

**VOIDING REFLEX**

- **GREEN = parasympathetic (ACh)**
- GREEN = afferent stretch receptors (storage reflex silenced)

- **BLUE = spinobulbal reflex pathways** (INHIBITS SYMPATHETIC TONE)

---

**Sympathetic \( \alpha_1 \) innervation of TRIGONE and INTERNAL URETHRAL SPHINCTER**

So, \( \alpha_1 \) blockers \( \downarrow \) tone of bladder neck and outlet

**IMAGES:** Nature Reviews Neuroscience
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Where are $\alpha_1$ receptors located? (actions)

Three subtypes: $\alpha_{1A}$, $\alpha_{1B}$, $\alpha_{1D}$

Vasoconstriction $\alpha_{1B}$ (+ $\alpha_{1D}$ *)
Decreases perfusion of skin; GI tract; kidney; brain
also: erectile tissue,

* role of D is somewhat elusive

Contraction $\alpha_{1A}$
Contracts sphincters $\alpha_1$

Increased force (positive inotropy)
$\alpha_{1A}$, $\alpha_{1B}$

Mydriasis: $\alpha_{1A}$ (radial muscle)

Piloerection $\alpha_1$
(arreector pili)
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Relative selectivity for receptor subtypes

- **Prazosin**: \(\alpha_{1A} = \alpha_{1D} = \alpha_{1B}\)
- **Terazosin**: \(\alpha_{1A} = \alpha_{1D} = \alpha_{1B}\)
- **Doxazosin**: \(\alpha_{1A} = \alpha_{1D} = \alpha_{1B}\)
- **Alfuzosin**: \(\alpha_{1A} = \alpha_{1D} = \alpha_{1B}\)

\[\begin{align*}
\text{Piperazinyl quinazolines} \\
\text{Benzenesulfonamide} \\
\text{Indole}
\end{align*}\]

- **Tamsulosin**: \(\alpha_{1A} = \alpha_{1D} > \alpha_{1B}\)
- **Silodosin**: \(\alpha_{1A} > \alpha_{1D} > \alpha_{1B}\)

Administration: all **ORAL**
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PK Properties: *CLASS: Piperazinyl quinazolines*

**Prazosin**
- Bioavailability: 40-80% *(VARIABLE)*
- HALF-LIFE: 3 hr *(SHORT)*
- Duration: 7-10 hr
  *(Thus, BID Dosing)*

**Terazosin**
- Bioavailability: 90%
- HALF-LIFE: 12 hr
- Duration: 18-24 hr

**Doxazosin**
- Bioavailability: 65%
- HALF-LIFE: 22 hr
- Duration: >24 hr*
  *(BOTH normal and ER tab have similar duration)*

**Alfuzosin**
- Bioavailability: 50% *(WITH FOOD, only 25% if fasting!)*
- HALF-LIFE: 10 hr
- Duration of action: >24 hr*
  *(extended release tab ONLY)*
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**PK Properties:** *CLASS: Benzenesulfonamides*

**Tamsulosin**
- Bioavailability: >90% (*FASTING*)
  (reduced to 60% by food)
- Absorption: **SLOW**
- HALF-LIFE: 5 hr
- APPARENT half-life (absorption included): 14 hr
- Duration of action: ~ 24 hr

**PK Properties:** *CLASS: Indoles*

**Silodosin**
- Bioavailability: 32% (*low*)
- HALF-LIFE: 5-20 hr (*variable*)
- Duration of action: ~ 24 hr
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Metabolism / Excretion

All drugs are major CYP3A4 substrates

For the following, AVOID STRONG CYP3A4 inhibitors:

• Alfuzosin
• Silodosin
• Tamsulosin

Terazosin is the LEAST metabolized
30% excreted as parent drug (both urine, feces)

Silodosin is metabolized partly by GLUCURONIDATION;
AVOID UDP-glucuronyltraferase inhibitors:

• Probenecid
• Valproic acid
• Fluconazole
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Adverse Effects

First-dose effect: orthostatic hypotension
  • syncope
  • reflex tachycardia
Effect minimized by dosing at bedtime
Also by minimizing first dose

More $\alpha_{1A}$-selective drugs: Tamsulosin, Silodosin are **LESS likely** to cause hypotension
(but also lack the BP benefits of the
  *Piperazinyl quinazolines*)

**Sulfa Allergy:** Use caution with Tamsulosin
  • rash, hives, or worse conditions
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Adverse Effects

Reduced/retrograde ejaculation:
• Caused by relaxation of bladder neck
• Ejaculate follows ‘path of least resistance’
• Enters bladder, flushed out with urine
• Affects 15-30% of patients
• Dose-related effect

VERY RARE: priapism
• long-lasting and ‘inappropriate’ erection

enough already!
Affects only about 1:50,000 patients
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**Benign Prostatic Hyperplasia**

Other receptors and their responses in the prostate

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$-Adrenoceptors</td>
<td>contraction</td>
</tr>
<tr>
<td>$\beta$-Adrenoceptors (subtypes)</td>
<td>relaxation</td>
</tr>
<tr>
<td>5-HT$_2$A/5-HT$_2$c receptors</td>
<td>contraction</td>
</tr>
<tr>
<td>Endothelins (ET$_A$ and ET$_B$)</td>
<td>contraction</td>
</tr>
<tr>
<td>Tachykinin Nk$_2$ receptors</td>
<td>contraction</td>
</tr>
<tr>
<td>Androgen receptors</td>
<td>modulate growth of prostate</td>
</tr>
</tbody>
</table>

Future drugs may exploit the presence of other receptors present in prostate
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Therapeutic Approaches:

5α-reductase Inhibitors
- Finasteride (Proscar®)
- Dutasteride (Avodart®)

Combinations
- Tamsulosin/Dutasteride (Jalyn®)

Gene Expression

```
T       DHT
5α-reductase
```

```
AR
AR
Gene Expression
```

"Androgen Response Element"
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Type I 5α-reductase

Type II 5α-reductase

Skin, Liver

Testicles

Prostate

Hair follicles

Finasteride

Dutasteride

1/3 of DHT

2/3 of DHT

T

T

13
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Prostate Cancer Prevention Trial (PCPT)
- National Cancer Institute (NCI)
- South West Oncology Group (SWOG)

18,882 men, 55 years or older
Recruited: 1994-97
5 mg/day finasteride or placebo
Duration: 7 years
Conclusion: 25% reduction in CaP
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**BOTH** Finasteride and Dutasteride are approved for *treating* BPH and *preventing* CaP

**NEITHER** is approved for *treating* CaP
(CaP is treated with: LHRH agonists/antagonists + AR antagonists)

**Common adverse effects:**
- Breast enlargement (gynecomastia), tenderness
- Decreased libido
- Impotence
- Ejaculatory disorder
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Precaution:

- **Finasteride**: possibility of birth defect (*hypospadias*) in fetus. Pregnant women should not handle *crushed* tablets.
- There is *some* concern about finasteride in *semen*, BUT:


Effects of Finasteride, a Type 2 5-Alpha Reductase Inhibitor, on Fetal Development in the Rhesus Monkey (*Macaca mulatta*)


1Department of Safety Assessment, Merck Research Laboratory, West Point, Pennsylvania 19486
2Department of Enzymology, Merck Research Laboratory, Rahway, New Jersey 07065
3Developmental Laboratories, Merck Research Laboratory, Hoddesdon, Hertfordshire EN10 0UB, England
4California Regional Primate Research Centre, University of California, Davis, California 95616
5Department of Pediatrics, University of California, Davis, California 95616
6Department of Radiology, University of California, Davis, California 95616

Pregnant female monkeys were administered, throughout pregnancy, **daily doses of finasteride**, within and above the range of semen levels of the drug, and effects on the offspring were assessed. No abnormalities were observed in the offspring, even at doses 60–750 times levels found in the semen of men treated with recommended doses of finasteride, suggesting a **large safety margin** for potential human exposures (from semen).
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**PK properties** (main differences in color)

<table>
<thead>
<tr>
<th>Finasteride</th>
<th>Dutasteride</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Admin: ORAL</td>
<td>• Admin: ORAL</td>
</tr>
<tr>
<td>• Bioavail: 60%</td>
<td>• Bioavail: 60%</td>
</tr>
<tr>
<td>• $V_d$: 76 L</td>
<td>• $V_d$: 300-500 L</td>
</tr>
<tr>
<td>• log P: 3.03 (LESS hydrophobic)</td>
<td>• log P: 5.09 (MORE hydrophobic)</td>
</tr>
<tr>
<td>• Metabolism: CYP3A4</td>
<td>• Metabolism: CYP3A4</td>
</tr>
<tr>
<td>Metabolites:</td>
<td>Active metabolite:</td>
</tr>
<tr>
<td>Not very active</td>
<td>6-hydroxydutasteride</td>
</tr>
<tr>
<td>• Half-life: 6 h</td>
<td>• Half-life: 5 wk</td>
</tr>
<tr>
<td>• Excretion: feces, urine</td>
<td>• Excretion: feces, urine</td>
</tr>
</tbody>
</table>
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Erectile Dysfunction

Etiology of ED (not always mutually exclusive)

(1) Failure to initiate
   (psychogenic, endocrinologic, or neurogenic)

(2) Failure to fill
   (arteriogenic)

(3) Failure to store blood within lacunar network
   (venoocclusive dysfunction)
Erectile stimuli increase blood flow into the cavernosal spaces, causing erection. Blood collects in the corpus cavernosum, increasing ‘cavernous pressure’

Drainage occurs via surrounding veins. Vein compression against tunica albuginea during erection prevents this drainage.
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Erectile Dysfunction

- cavernosal arteries
- cavernosal spaces
- helicine arteries
- venules
- shunt
- cavernosal artery

Flow shunt to:
- cavernosum

Sympathetic tone ($\alpha_1$) → vasoconstriction

Parasympathetic innervation → vasodilation

Relative amount of blood flow

FLACCID

- shunt

ERECT

- shunt
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Erectile Dysfunction

Parasympathetic innervation of the corpus cavernosum

NANC
“non-adrenergic, non-cholinergic”

arginine $\rightarrow$ NOS $\rightarrow$ NOS

NET RESULT:
Hyperpolarization, Relaxation

Pelvic ganglia

Nerve ending

NO $\rightarrow$ sGC

GTP $\rightarrow$ cGMP

PDE5

K$^+$

myosin light chain phosphatase
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Erectile Dysfunction

**Therapeutic Approaches:**

**Phosphodiesterase type 5 inhibitors** (for ED)

- **Avanafil** (Stendra®) - 2012
- **Sildenafil** (Viagra®) - 1998
- **Tadalafil** (Cialis®) - 2003
- **Vardenafil** (Levitra®) - 2003

**Typical response rate:** 60-80%
(20-40% show no improvement)

*FDA approval for pulmonary hypertension:*
- **Sildenafil** (Revatio®)
- **Tadalafil** (Adcirca®)

**Diagram:**

- GTP → NO → SGC → cGMP → PDE5 → Inhibitor → SMC relaxation
- GMP → PDE5 → Inhibitor

- Typical response rate: 60-80%
(20-40% show no improvement)
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Erectile Dysfunction

PK Properties

**Avanafil (Stendra®)**
- Bioavailability: Not report.
- HALF-LIFE: 5 hr
- Onset: 10 min-0.5 hr
- Duration: 4-6 hr

**Tadalafil (Cialis®)**
- Bioavailability: 35%
- HALF-LIFE: 15-18 hr
- Onset: 1-2 hr
- Duration: up to 36 hr

**Sildenafil (Viagra®)**
- Bioavailability: 20-60%
- HALF-LIFE: 4 hr
- Onset: 0.5-1 hr
- Duration: 4-12 hr

**Vardenafil (Levitra®)**
- Bioavailability: 15%
- HALF-LIFE: 4-5 hr
- Onset: 0.5-1 hr
- Duration: 4-6 hr
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Erectile Dysfunction

PK Properties

FOOD:

**Sildenafil, Vardenafil**: ONSET (absorption rate) SLOWED by food (especially fatty meals) – food does NOT affect AUC

**Avanafil, Tadalafil**: take without regard to food

METABOLISM:

All drugs are **MAJOR CYP3A4 substrates**
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Erectile Dysfunction

Common Side Effects (5-20%):

• Headache
• Facial flushing
• Dyspepsia
• Congestion

More common with Tadalafil:
• Myalgia, back pain

Precautions:

• Do NOT take with NITRATES (may cause severe hypotension, MI)
• Use Caution in elderly
• Use Caution with $\alpha_1$ blockers

Sildenafil also inhibits PDE6 (retina) and may cause visual disturbances:
Blue hue (Cyanopsia), brightness, blurriness
Also possible (but more rare) with Vardenafil
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Urinary Incontinence

Involuntary loss of urine that is *sufficient to be a problem*

- 13 million Americans affected
- More frequent in elderly persons
- Women are affected twice as often as men

**Detrusor muscle**
- Parasympathetic
- $M_2, M_3$ - VOIDING

**Internal sphincter**
- Sympathetic
- $\alpha_1$ - STORAGE

**External sphincter**
- Skeletal
- nACh - STORAGE

**Trigone muscle**
- Sympathetic
- $\alpha_1$ - STORAGE
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Urinary Incontinence

Therapeutic Approaches:

**Antimuscarinics,**
**Indirect anticholinergics** (botulinum toxin A, Botox®)

**GOAL:** Relax detrusor muscle (INHIBIT VOIDING)

α₁ agonists – antihypotensives (off-label)
Midodrine

**Antidepressants** (off-label)
Imipramine (Tofranil®)
Duloxetine (Symbalta®)

**GOAL:** Contract internal sphincter, trigone muscles
(ENHANCE STORAGE)
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ANTIMUSCARINICS

Darifenacin (Enablex®)
*Fesoterodine (Toviaz®)
Flavoxate (Urispas®) - also used as anti-spasmotic
Oxybutynin (Ditropan®) - also used as anti-spasmotic
Propantheline (Pro-Banthine®) - anti-spasmotic for GI and GU
Solifenacin (Vesicare®)
Trospium (Sanctura®)
Tolterodine (Detrol®)

*Newest drug (2008) Pro-drug (hydrolyzed in body to SAME active metabolite as tolderodine) = 5-hydroxymethyl tolterodine (BOTH are Pfizer drugs) Tolterodine = 1998
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Urinary Incontinence

$M_3$-selective:
- **Darifenacin** (Enablex®)
- **Solifenacin** (Vesicare®)

**Side effects** of antimuscarinics

Common ($M_3$):
- Dry mouth (xerostomia) - common reason to quit
- Cough
- Constipation

For the ‘nonselective’ antimuscarinic drugs
- Tachycardia ($M_2$, Vagus nerve)
- Drowsiness, confusion – in elderly! ($M_1$, CNS)
  (except trospium, has + charge, no access to CNS)
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Urinary Incontinence

PK Properties

- **Darifenacin** $t_{1/2} = 16$ hr; Bioavailability = 20%; CYP3A4
- **Fesoterodine** $t_{1/2} = 7$ hr; Bioavailability = 52%; (prodrug Activated by nonspecific esterases; Eliminated by CYP3A4)
- **Solifenacin** $t_{1/2} = 45-68$ hr; Bioavailability = 90%; CYP3A4
- **Trospium** $t_{1/2} = 20$ hr; Bioavailability = 10%; RENAL (60% unchanged)
- **Tolterodine** $t_{1/2} = 10$ hr; Bioavailability = 77% ([take with food](#)); Activated by CYP2D6, Eliminated by CYP3A4)
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**Urinary Incontinence**

**Botulinum toxin A (Botox®)**

- Indirect mechanism: inhibits release of ACh
- **Paralyzes** muscle
- Local injections into detrusor muscle
- **CAUTION:** Overdose may cause urinary retention
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Urinary Incontinence

ADRENERGIC AGONISTS

Midodrine – $\alpha_1$ selective
Increases tone of trigone muscle and internal sphincter

Adverse effects: insomnia, elevated blood pressure, exacerbation of myocardial ischemia, cardiac arrhythmias

ANTIDEPRESSANTS

Mechanism: Block NE reuptake

- Enhance urine storage reflex
- Increase sympathetic tone of the trigone muscle and internal sphincter

Imipramine: tricyclic antidepressant, multiple effects (including NE) (double mechanism: is also antimuscarinic!)

Duloxetine – SNRI: blocks the reuptake of NE and serotonin
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Urinary Retention

For post-surgical, post-partum, and diabetic (neuropathic) inability to urinate voluntarily

**Bethanechol** (Urecholine®)
Oral tablets
or
CHOLINERGIC AGONIST
(Unlike ACh, bethanechol is NOT hydrolized by cholinesterases)

**Side Effects:**
- Hypotension, reflex tachycardia
- Headache (cerebral vasodilation)
- GI cramps
- Bronchoconstriction
- Lacrimation, Myosis

May cause painful spasms, treat with Anticholinergics:

**Flavoxate** (Urispas®)
**Oxybutynin** (Ditropan®)
**Propantheline**