TEXAS A&M
HEALTH SCIENCE CENTER
IRMA LERMA RANGEL COLLEGE OF PHARMACY

Benign Prostatic Hyperplasia (BPH)

IPT VI

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Overview

1. Introduction and background of BPH
2. Causes and common symptoms
3. Treatment options

Learning objectives

After completing this topic students should be able

1. Discuss causes and symptoms of BPH
2. Discuss several treatment options available for BPH
3. Classify drugs used in treating BPH
4. Discuss mechanism of action, pharmacokinetics, adverse effects & metabolism of α_1-adrenergic antagonists and 5α-reductase inhibitors

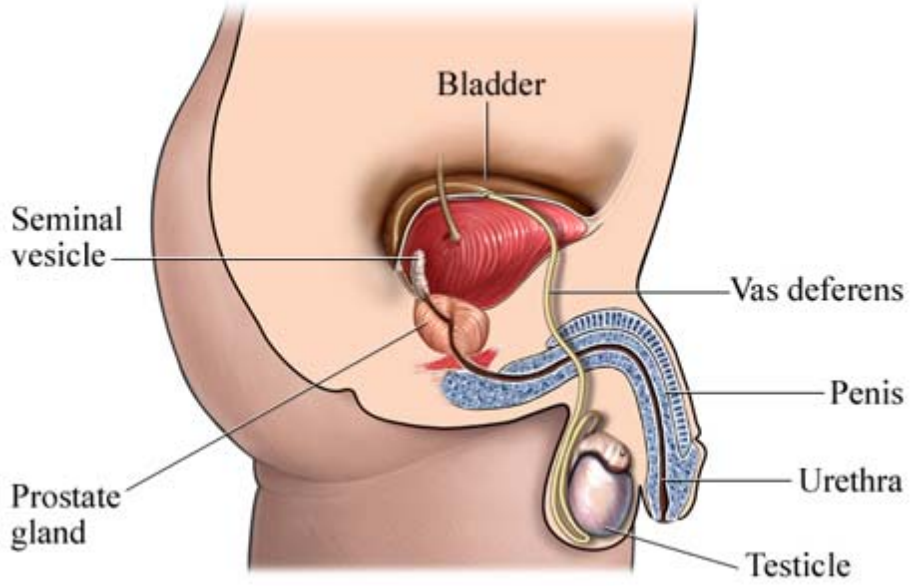
What is BPH?

- **B**enign **P**rostatic **H**yperplasia
- It is NOT cancer (benign)
- Enlargement of the prostate gland

Who develops ?

- Half of all men over the age of 60 will develop an enlarged prostate
- By the time men reach their 70's and 80's, 80% will experience urinary symptoms

What is Prostate ?



- Walnut-shaped gland that forms part of the male reproductive system
- Surrounds the urethra - the tube that carries urine from the bladder out of the body

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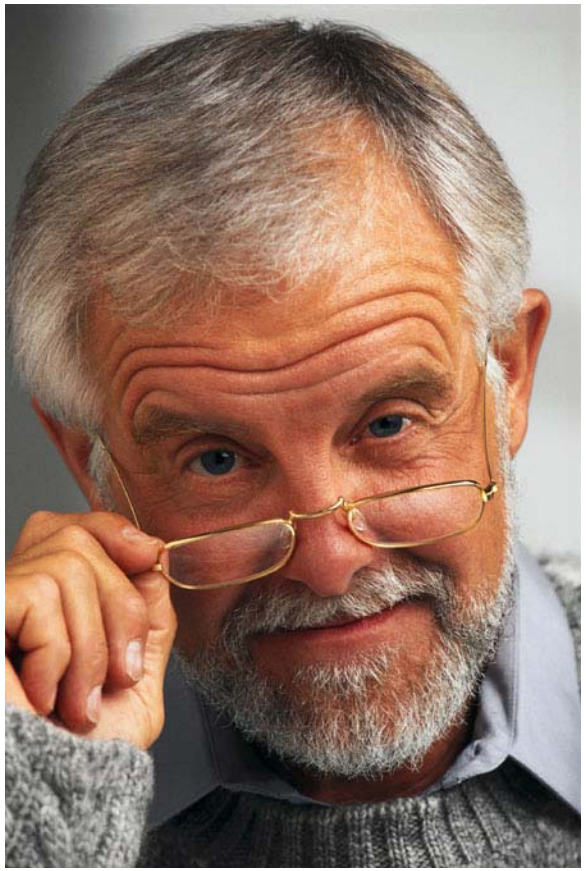
What does it do ?

- Secretes semen which carries sperm
- During orgasm, prostate muscles contract and propel ejaculate out of the penis

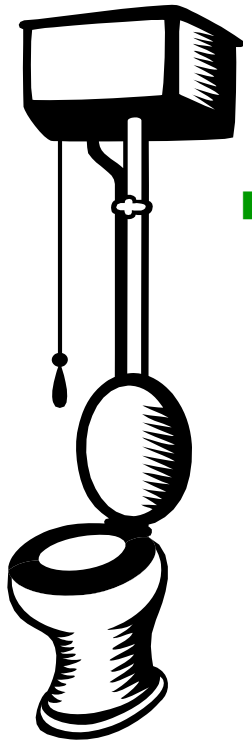
What causes BPH?

- BPH is part of the natural aging process, like getting gray hair or wearing glasses
- BPH **cannot** be prevented
- BPH **can** be treated



Common symptoms

- Frequent and urgent need to urinate, especially at night
- Dribbling or leaking after urination
- Intermittent or weak stream



- Straining to urinate
- Pain or burning during urination
- Feeling that the bladder never completely empties

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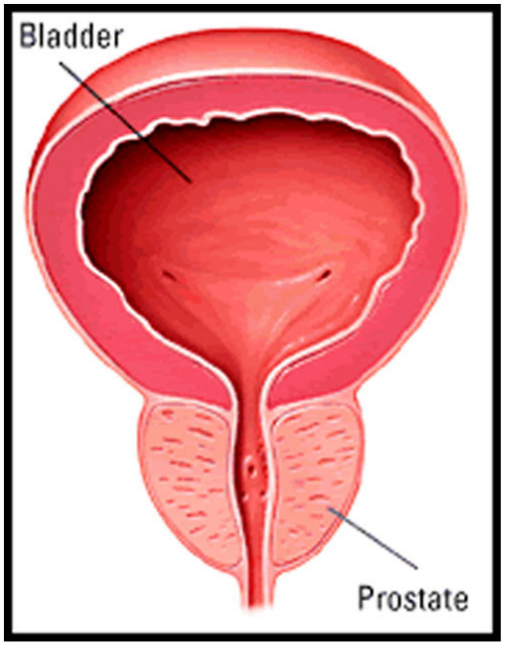
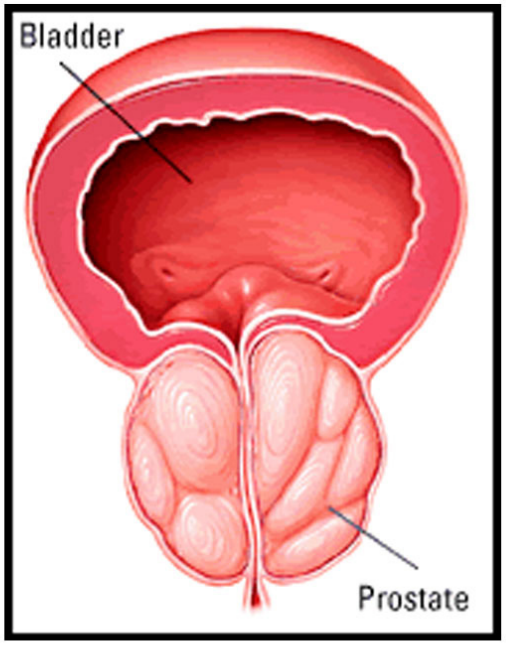
What causes these symptoms?



Normal Prostate



Enlarged Prostate (BPH)

- Prostate grows with age and time
- Pressure on the urethra restricts urine flow similar to a clamp on a garden hose

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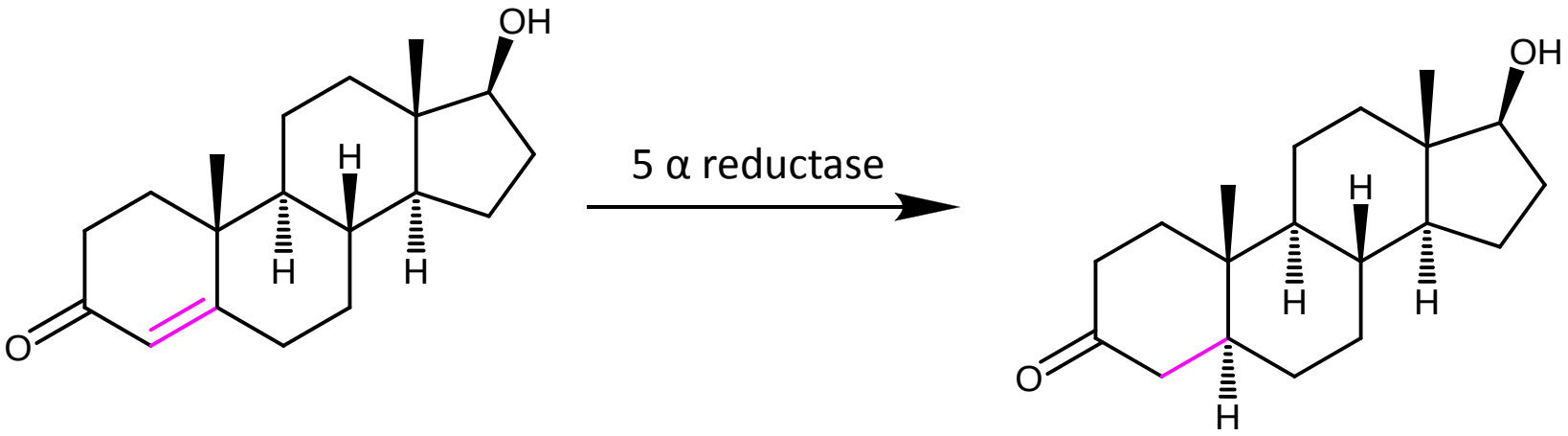
Why does prostate enlarge?

- Results from increased concentration of estradiol and DHT in prostate, which promotes cell growth.

- DHT plays critical role in determining the prostate size.

Testosterone to DHT



Testosterone

Dihydrotestosterone (DHT)

- DHT plays a critical role in determining prostate size
- Type 2 5α-reductase inhibitor (e.g., finasteride) induces apoptosis of epithelial cells, which in turn significantly decreases the volume of the prostate

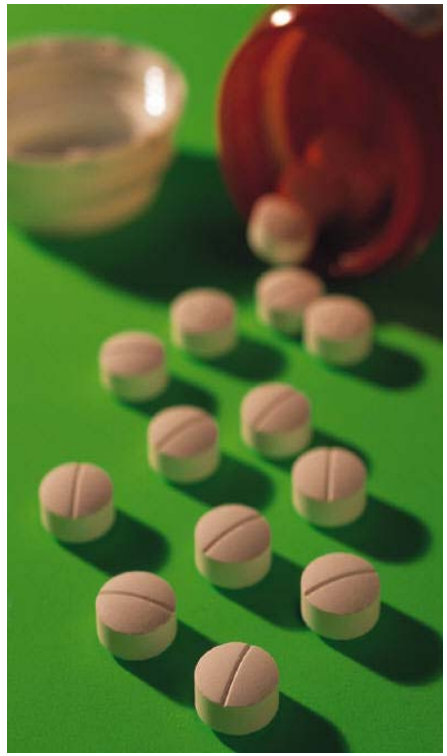
Treatment options

1. “Watchful waiting”
2. Medication
3. Heat therapies
4. Surgical approaches
    a. Invasive “open” procedures (TURP)
    b. New laser treatment

Medications

1. α_1-adrenergic antagonists

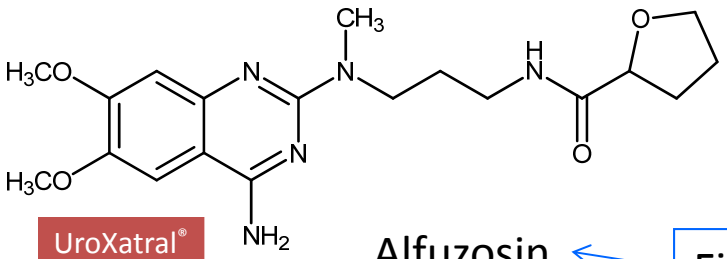
2. 5 α-reductase inhibitors



α_1-adrenergic antagonists

- α_1-adrenoceptor subtypes (α_{1A}, α_{1B}, α_{1D})
- α_{1A}-adrenoceptor subtype is concentrated in prostate and urethral smooth muscle cells responsible for muscle contraction
- Blocking this receptor leads to smooth muscle relaxation in the urethra and prostate region
- Alfuzosin (an aminoquinozoline)
- Tamusulosin (an N-substituted, catecholamine related sulfonamide)
- They do not cure BPH, can only alleviate some of the symptoms.

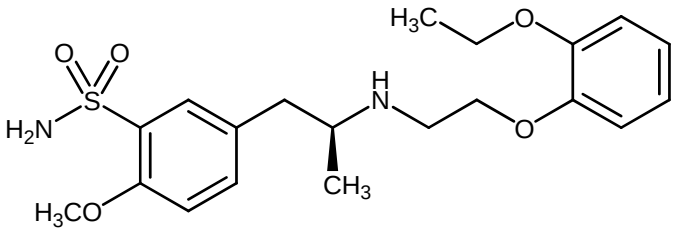
α_1-adrenergic antagonists



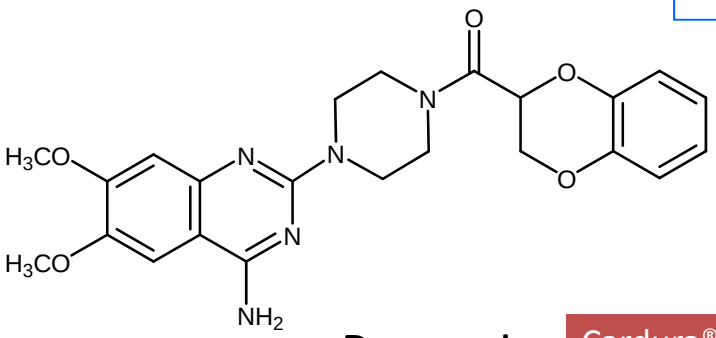
UroXatral®

Alfuzosin

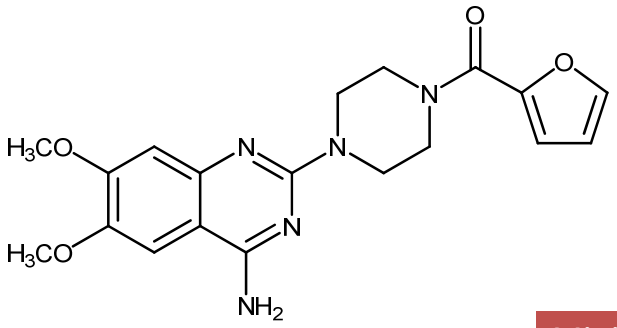
First line agents



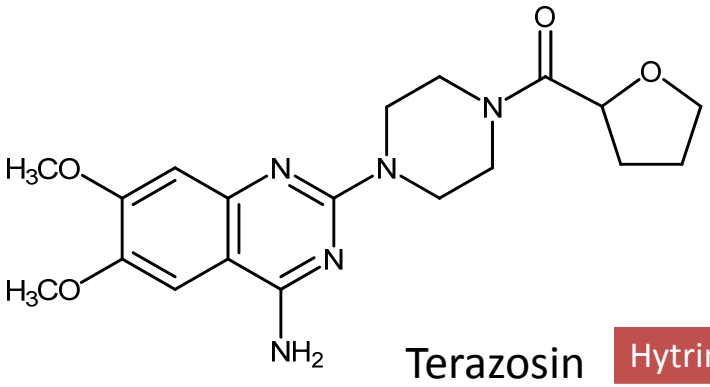
Tamsulosin Flomax®



Doxazosin Cardura®



Prazosin Minipress®



Terazosin Hytrin®

Doxazosin, Prazosin and Terazosin were used as antihypertensives but found to be effective in the treatment of BPH due to common mechanism of action.

Adverse effects

- Vasodilation, including dizziness, orthostatic hypotension, headache, and tachycardia, which occurred during the first 2 weeks of treatment
- These cardiovascular side effects are attributed to a nonselective blockade of α_1-adrenoceptors present in vascular smooth muscle in addition to the required blockade of α_1-adrenoceptors in prostate.
- No first-dose effect and fewer vasodilatory adverse events have been reported with the sustained-release formulations, which occur more frequently with the immediate-release formulation.
- At higher doses, orthostatic hypotension occurs more frequently.

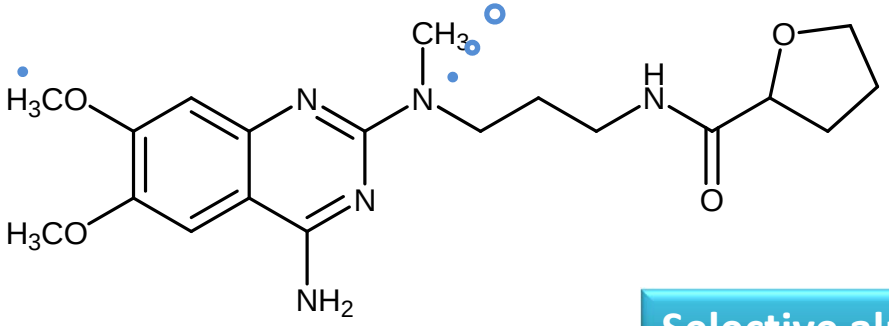
Alfuzosin (Uroxatral®): metabolism

7-O-demethylation

N-dealkylation

CYP3A4

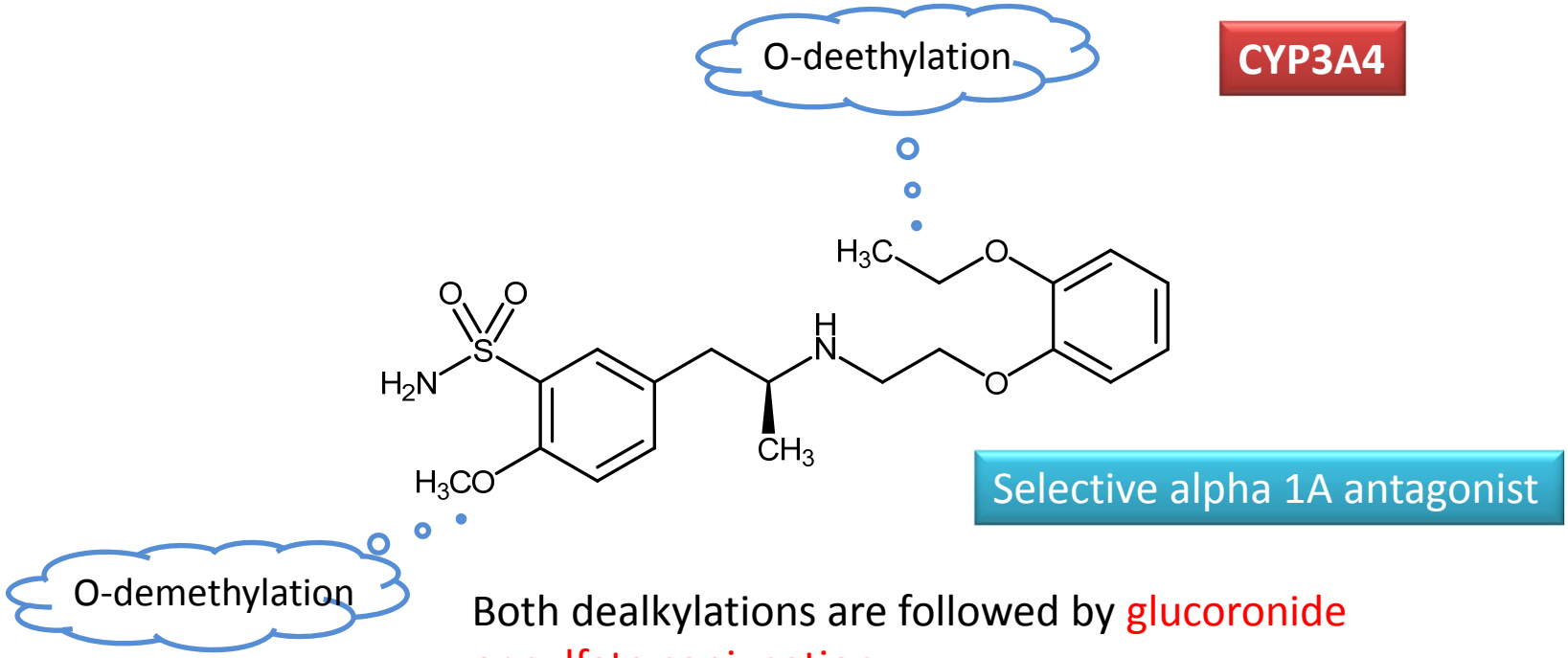
Inactive



Selective alpha 1A antagonist

- Aminoquinozoline designed to treat BPH and no utility in the treatment of hypertension with fewer cardiovascular side effects
- Mainly eliminated by liver, so in patients with hepatic insufficiency dose reduction is recommended.

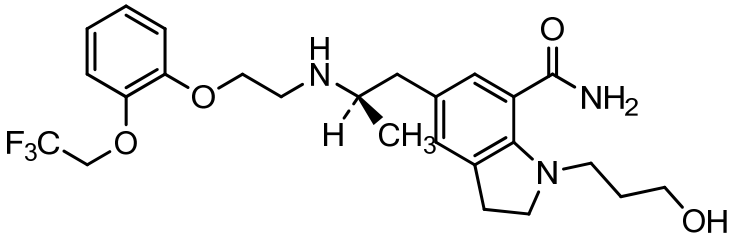
Tamsulosin (Flomax®): Catecholamine-Sulfonamide



Both dealkylations are followed by glucoronide or sulfate conjugation

- Designed to treat BPH and no utility in the treatment of hypertension, therefore have fewer cardiovascular side effects than terazosin and doxazosin.

Silodosin (Rapaflo®)



Selective alpha 1A antagonist

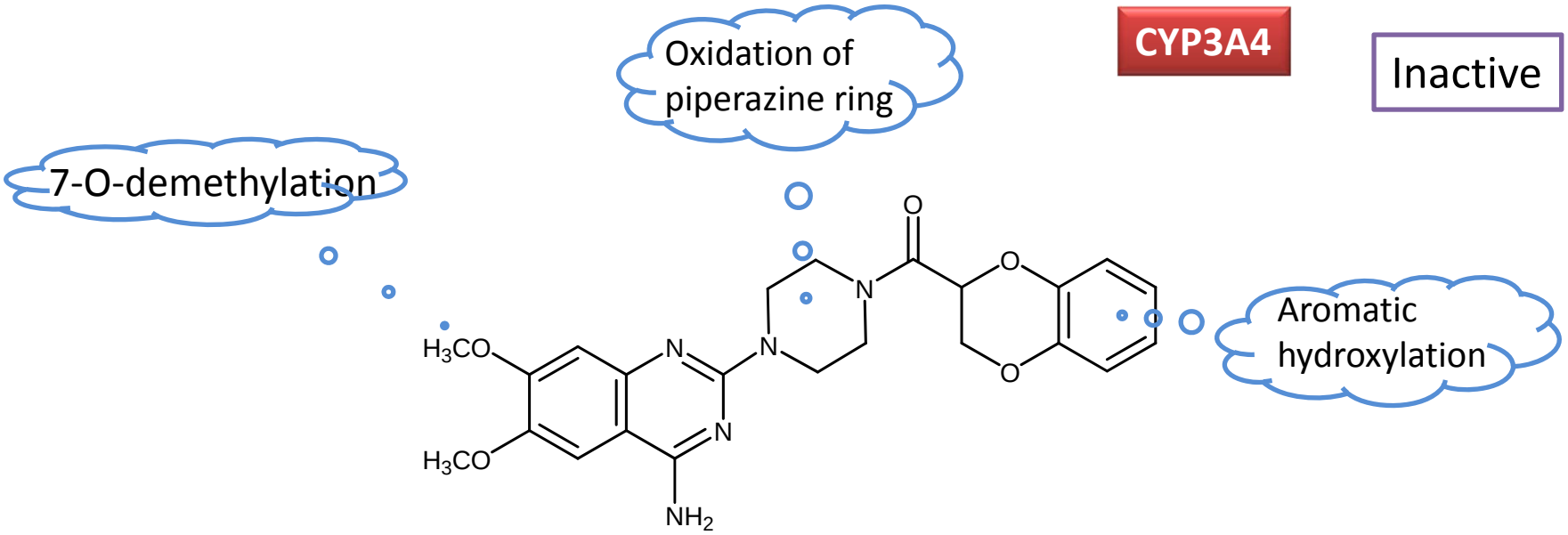
CYP3A4

Metabolism:

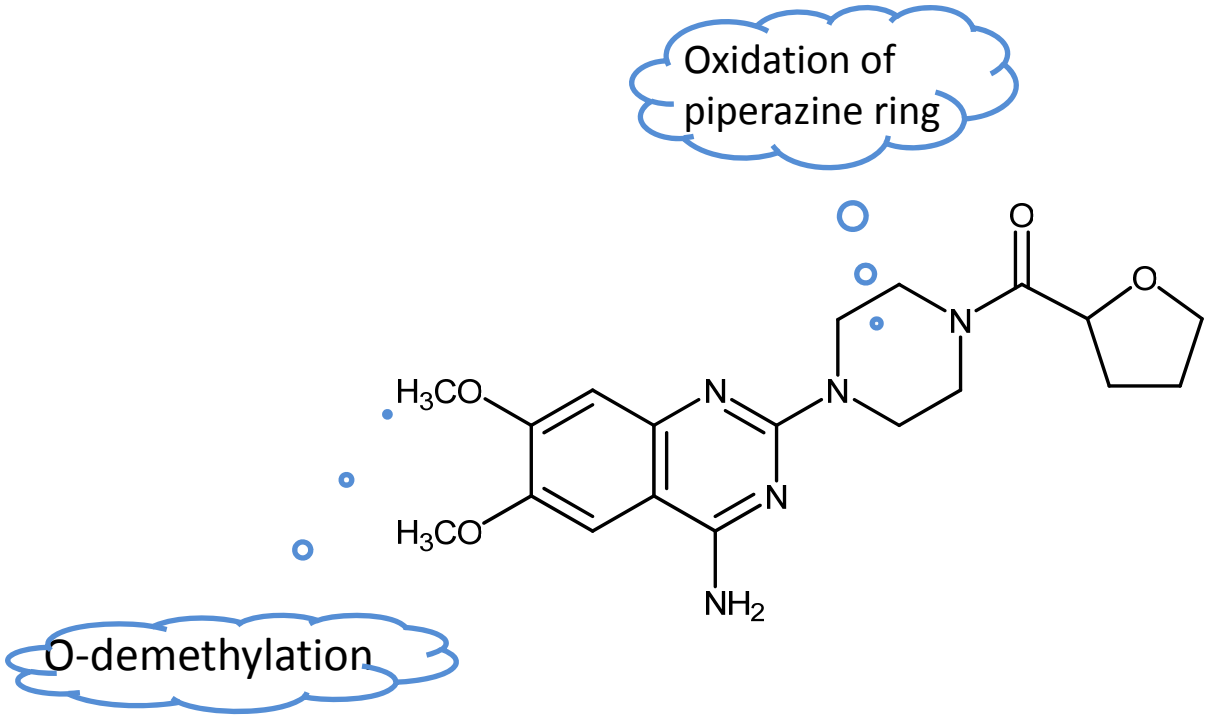
- ❑ Oxidation by alcohol and aldehyde dehydrogenase
- ❑ Glucuronidation

- Can be taken together with other medications for cardiovascular conditions
- Concomitant administration of strong CYP3A4 inhibitors (ketoconazole, itraconazole or ritonavir) and RAPAFLO is contraindicated

Doxazosin (Cardura®): metabolism



Terazosin (Hytrin®): metabolism



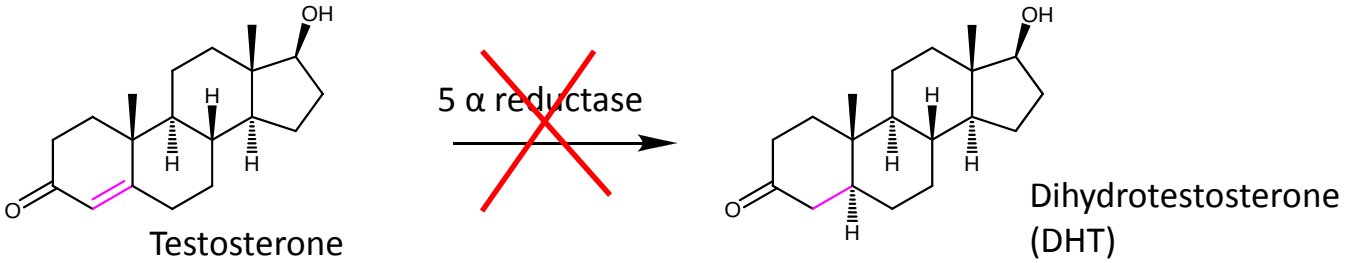
Pharmacokinetics for some of α_1-adrenergic antagonists

Drug	Alfuzosin	Doxazosin	Tamsulosin	Terazosin
Trade Name	Uroxatral	Cardura	Flomax	Hytrin
Oral Bioavailability (%)	65	65 (62–69)	<50 with food >90 fasted	90
Onset of Action (weeks)	<2	1–2	1	2
Duration of Action (hours)	>48	18–36	>24	>18
Protein binding (%)	82–90	98	94	95
Time to Peak Conc. (hours)	1–2	2–5	4–5	1
Volume of Distribution (L/kg)	2.5–3.2	1.0–3.4	18	25–30
Elimination Half-life (hours)	3–10	18–22	9–13 14–15 elderly	9–12
Cytochrome Isoforms	3A4	3A4	3A4, 2D6	—
Excretion (%)	69 feces	63–65 feces	21 feces	55–65 feces
K_i (nmol/L) for α_{1A}	2.4	2.7	0.5	2.5

5 α-Reductase inhibitors

MOA: The 5α-reductase inhibitors work by suppressing the production of intraprostatic DHT, Induces apoptosis of epithelial cells, thereby reducing the size of the prostate

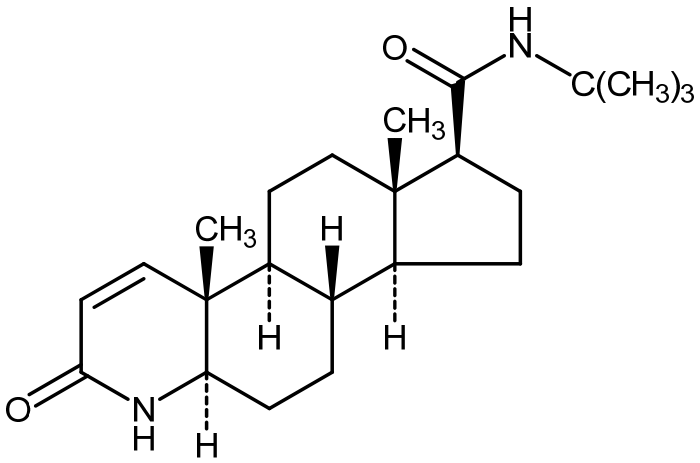
Fenasteride (Proscar®) Dutasteride (Avodart®)



Testosterone

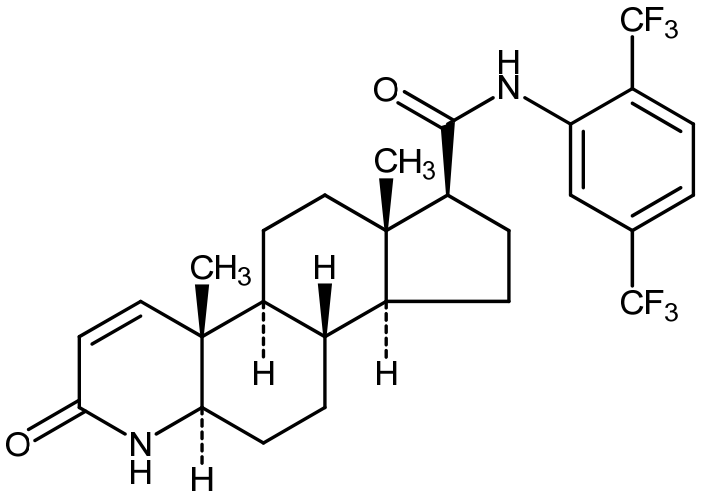
Dihydrotestosterone (DHT)

5 α-Reductase inhibitors



Fenasteride (Proscar®)

•Selective type 2, 5 α-Reductase inhibitor

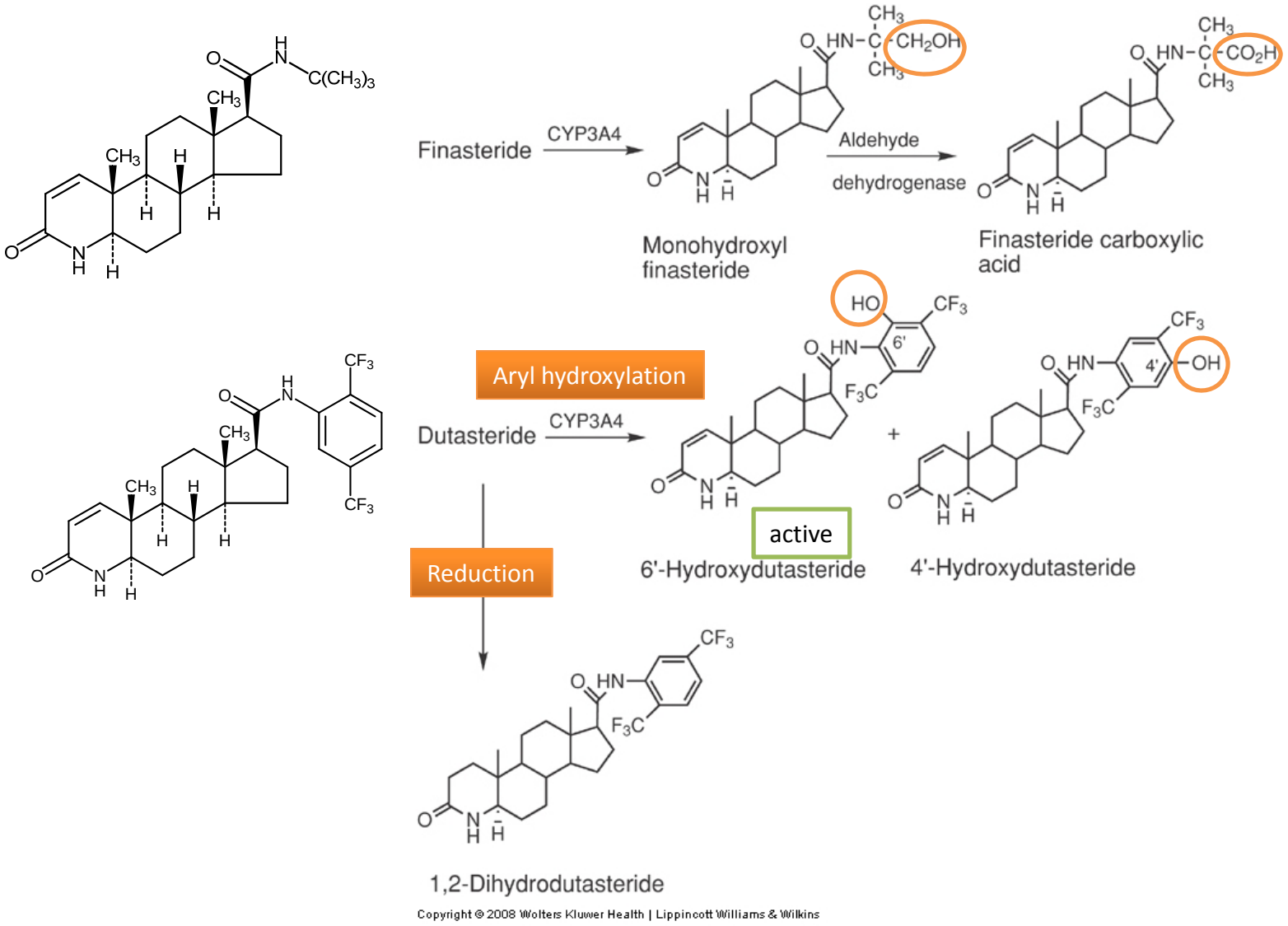


Dutasteride (Avodart®)

•Non-selective type 1 and type 2, 5 α-Reductase inhibitor

MOA: Induces apoptosis of epithelial cells, which in turn significantly decreases the volume of the prostate

Finasteride and Dutasteride: metabolism



Pharmacokinetics of the 5 α-reductase inhibitors

Drugs	Finasteride	Dutasteride
Trade Name	Proscar	Avodart
Oral Bioavailability (%)	65	60
Duration of Action (hours)	—	>5 weeks
Protein binding (%)	90	99
Time to Peak Conc. (hours)	—	2–3
Volume of Distribution (L/kg)	76 (44–96)	300–500
Elimination Half-life (hours)	5–6 (18–60 yr) >8 for 60+ yr	5 weeks
Cytochrome Isoforms	3A4	3A4
Active Metabolites	None	6-*p*-OH
Excretion (%)	57 feces and 40 urine as metabolites	40 feces metabolites 5 unmetabolized urine
IC50 (nmol/L)	313 Type 1 11 Type 2	3.9 Type 1 1.8 Type 2

Drug interactions

- Because finasteride and dutasteride are metabolized primarily by CYP3A4, the CYP3A4 inhibitors, such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, and ciprofloxacin, may increase the drugs' blood levels and, possibly, cause drug–drug interactions.