Pharmacology Pearls: Prostate Cancer and BPH

Mechanisms, Side Effects, and More

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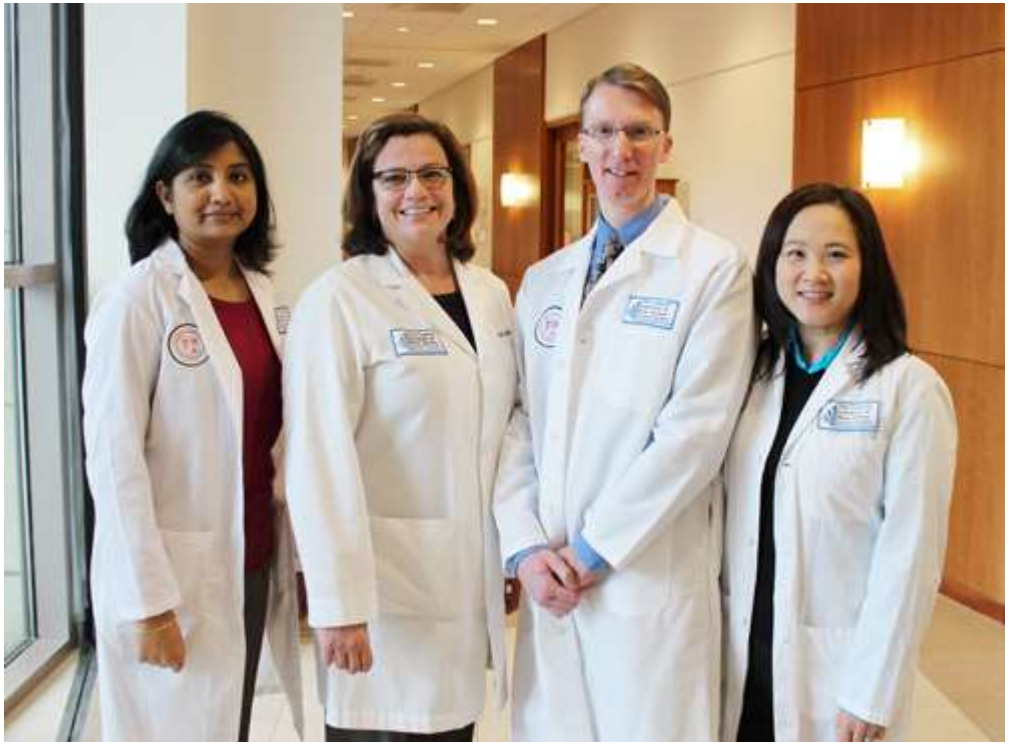
About Me


PURDUE UNIVERSITY

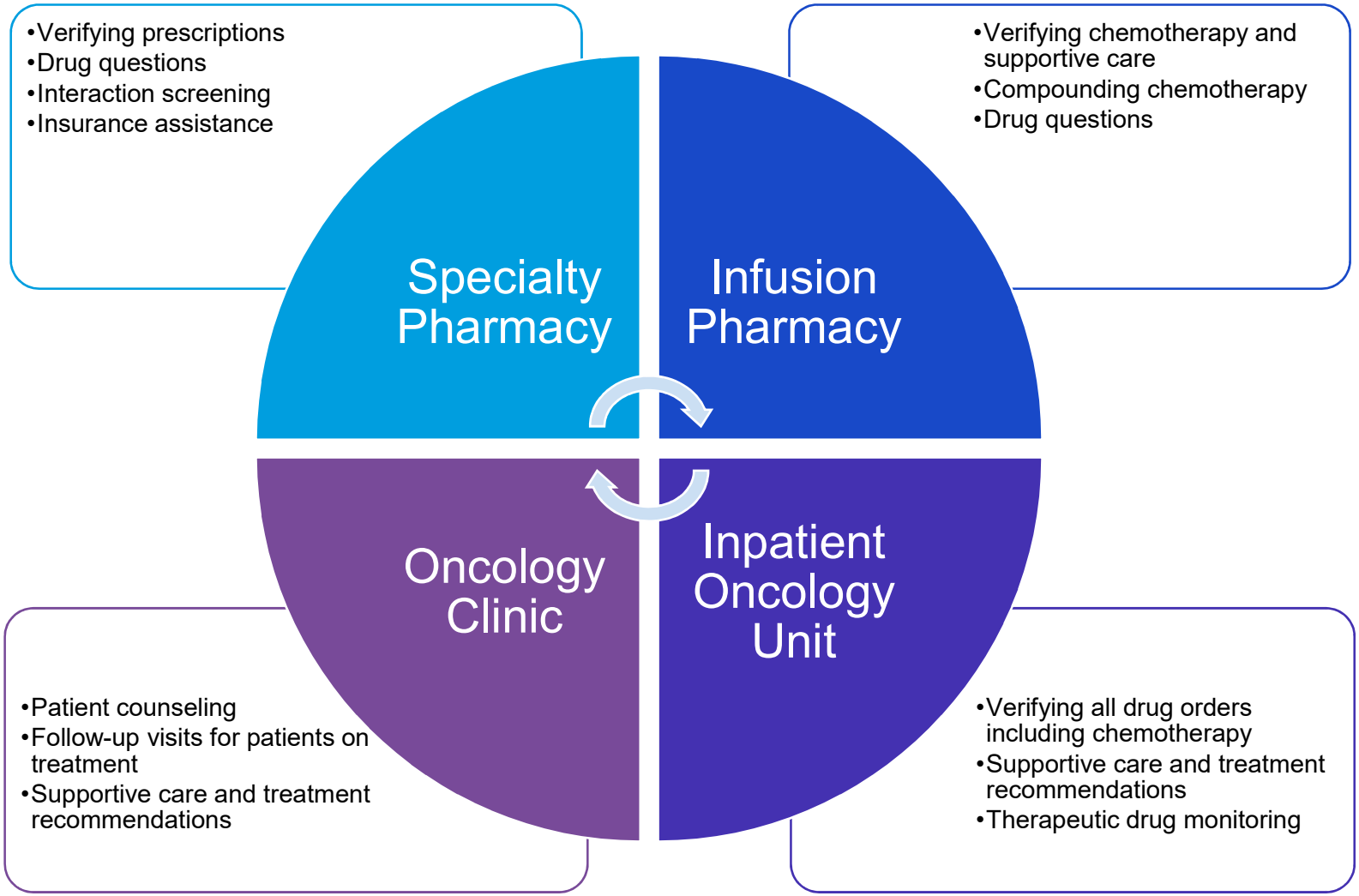

Froedtert & Medical College of Wisconsin

Oncology Pharmacists

- Expert on oncology-related medications and supportive care
- Typically have advanced training (residency) in oncology



Oncology Pharmacy Settings



Embedded Clinic Oncology Pharmacist

New Treatment Counseling

- What the medication does
- How to take the drug
- Side effects
- Storage/handling/missed doses
- Drug interaction check

Follow Up On Treatment

- Side effect assessment and recommendations
- Tips for remembering to take the medication

Insurance and Pharmacy Assistance

- Ensuring prior authorizations and copay assistance completed
- Coordinating prescriptions between patients, oncologists, pharmacies, and insurance plans

Overview

Prostate Cancer

- ADT options
- Androgen receptor signaling inhibitors
- Targeted therapy
- Chemotherapy

BPH/LUTS

- Tamsulosin and friends
- Alternative agents
- Drugs to avoid

Prostate Cancer Pharmacology

Androgen Deprivation Therapy (ADT)

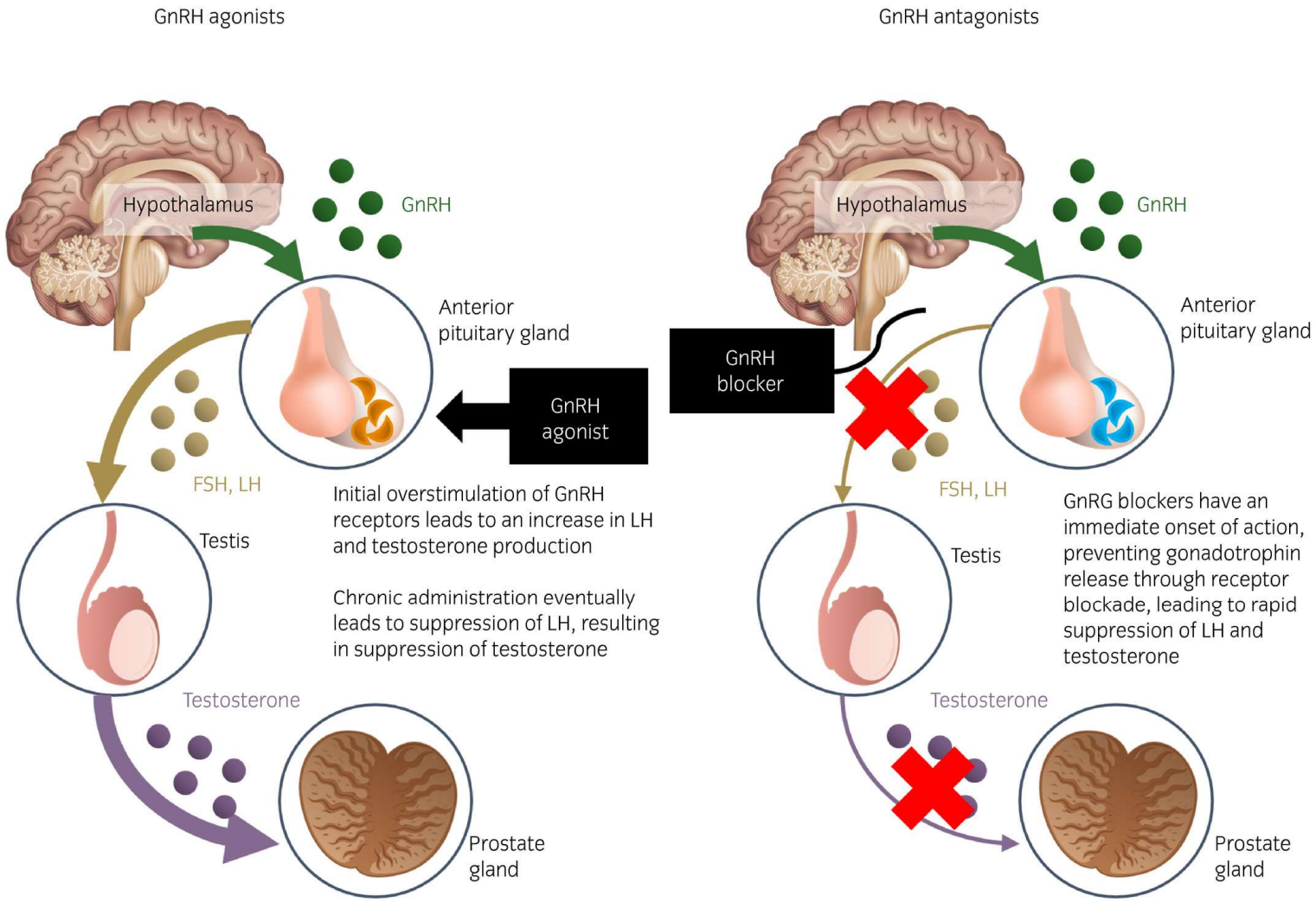
GnRH Agonists

- Leuprolide (Lupron, Eligard)
- Histrelin (Vantas)
- Goserelin (Zoladex)

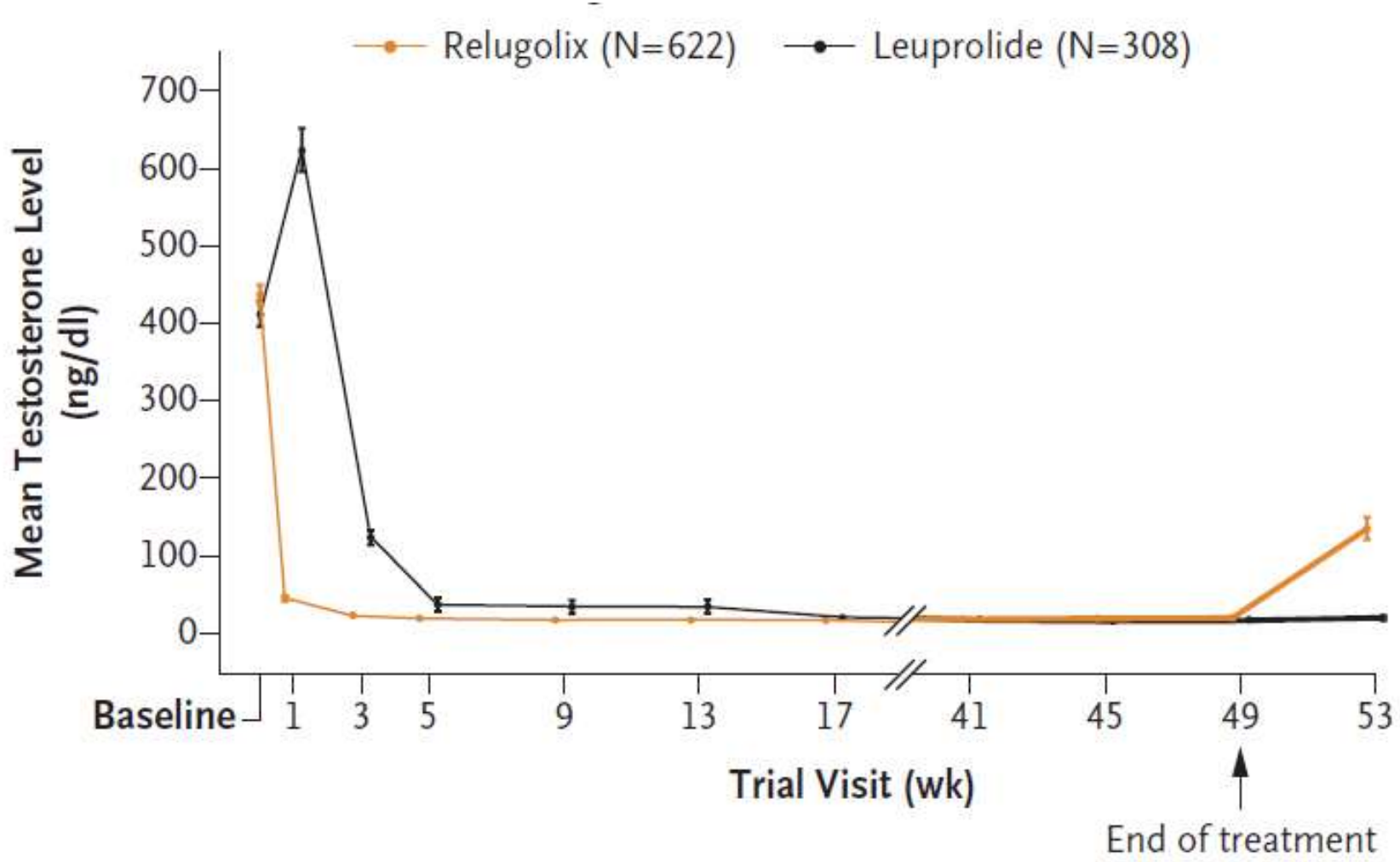
GnRH Antagonists

- Degarelix (Firmagon)
- Relugolix (Orgovyx)

GnRH Analogs



Agonist vs Antagonist – Initial Flare



Relugolix (Orgovyx)

- New oral GnRH antagonist (ADT) approved for advanced prostate cancer
- Taken 3 tablets (360 mg) the first day and 1 tablet (120 mg) daily after that
- Missed doses can be risky – testosterone comes back more quickly after relugolix compared to the injections
- Similar side effects compared to injections
  - May be safer for heart health
  - May cause more high blood sugar

Drug Approvals by Setting

Class	Drug	Very High Risk Localized	Biochem-ically Recurrent	nmCRPC	mCSPC	mCRPC
CYP 17	Abiraterone acetate (Zytiga, Yonsa)	X			X	X
AR Inhibitor	Enzalutamide (Xtandi)		X	X	X	X
	Apalutamide (Erleada)			X	X	
	Darolutamide (Nubeqa)			X	X (+ doce)	
PARP Inhibitor	Niraparib (Akeega)					X*#
	Olaparib (Lynparza)					X*#
	Rucaparib (Rubraca)					X*
	Talazoparib (Talzenna)					X*^
Taxane	Docetaxel (Taxotere)				X	X
	Cabazitaxel (Jevtana)					X

*if certain mutations present ^in combination with enzalutamide #in combination with abiraterone

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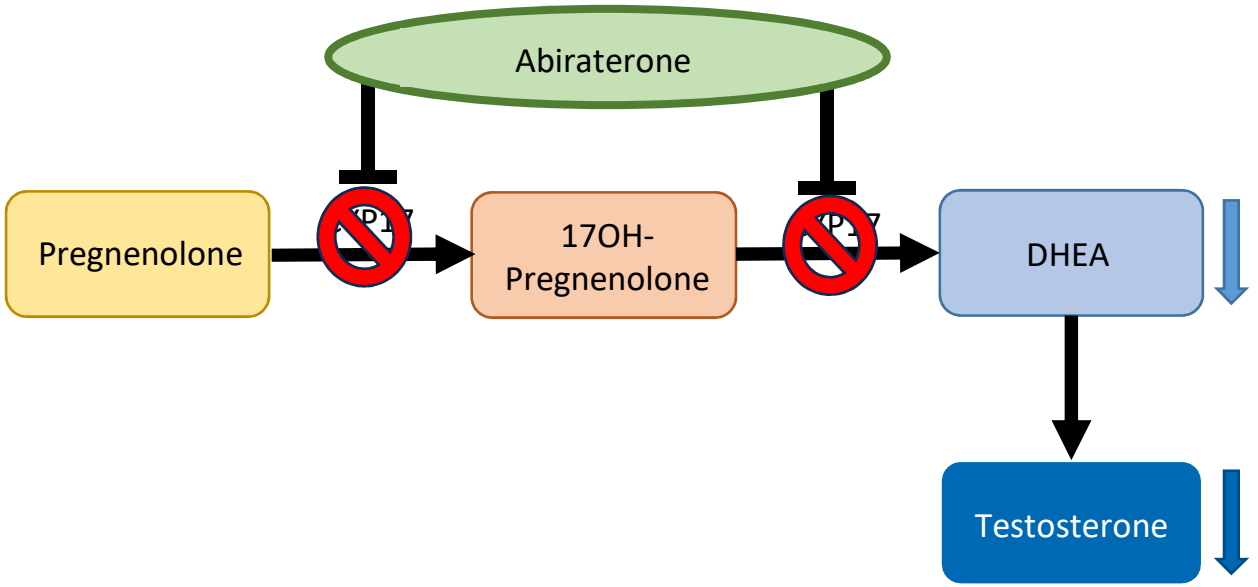
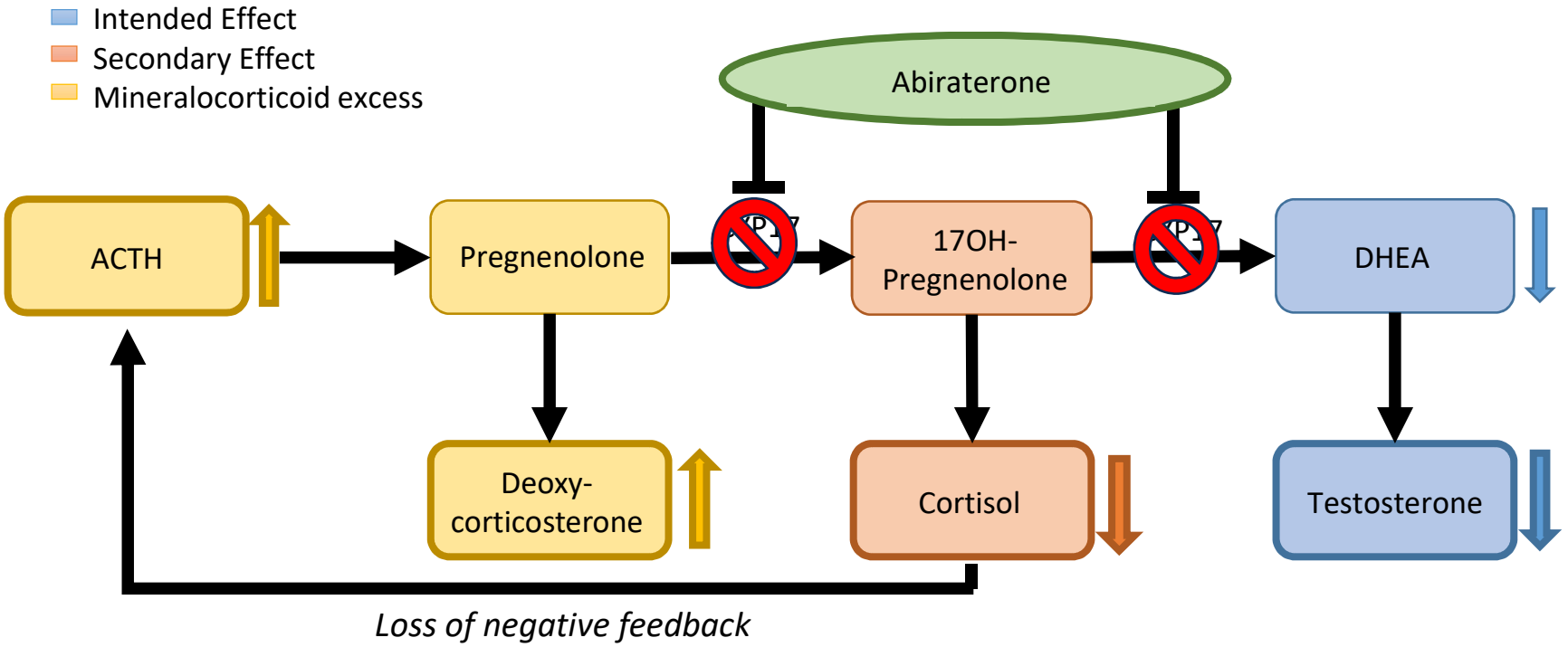
CYP17 Inhibitor – Abiraterone (Zytiga or Yonsa)

- Abiraterone blocks production of testosterone in adrenals and prostate cancer
- Prostate cancer can learn to get around ADT by making its own testosterone
- Can prolong effectiveness of ADT or treat cancer that is ADT resistant



Abiraterone Side Effects

- **Mineralocorticoid Excess Syndrome (MES)**
  - May cause low potassium, high blood pressure, and/or edema
  - Giving abiraterone with prednisone helps prevent this
  - Check blood pressure and look for ankle swelling at home



Abiraterone Pearls

- Other key side effects
  - Liver inflammation
  - Fatigue
  - Hot flashes
  - Increased blood sugar
- Abiraterone typically 1000 mg every day on an empty stomach (1h before food or 2h after) plus prednisone 5 mg once or twice daily
  - 1000 mg = 4 x 250 mg tablets or 2 x 500 mg tablets
  - Due to improved absorption with food, taking 250 mg with low-fat breakfast may be equivalent to 1000 mg on an empty stomach
  - Pre-existing liver dysfunction may require lower starting dose

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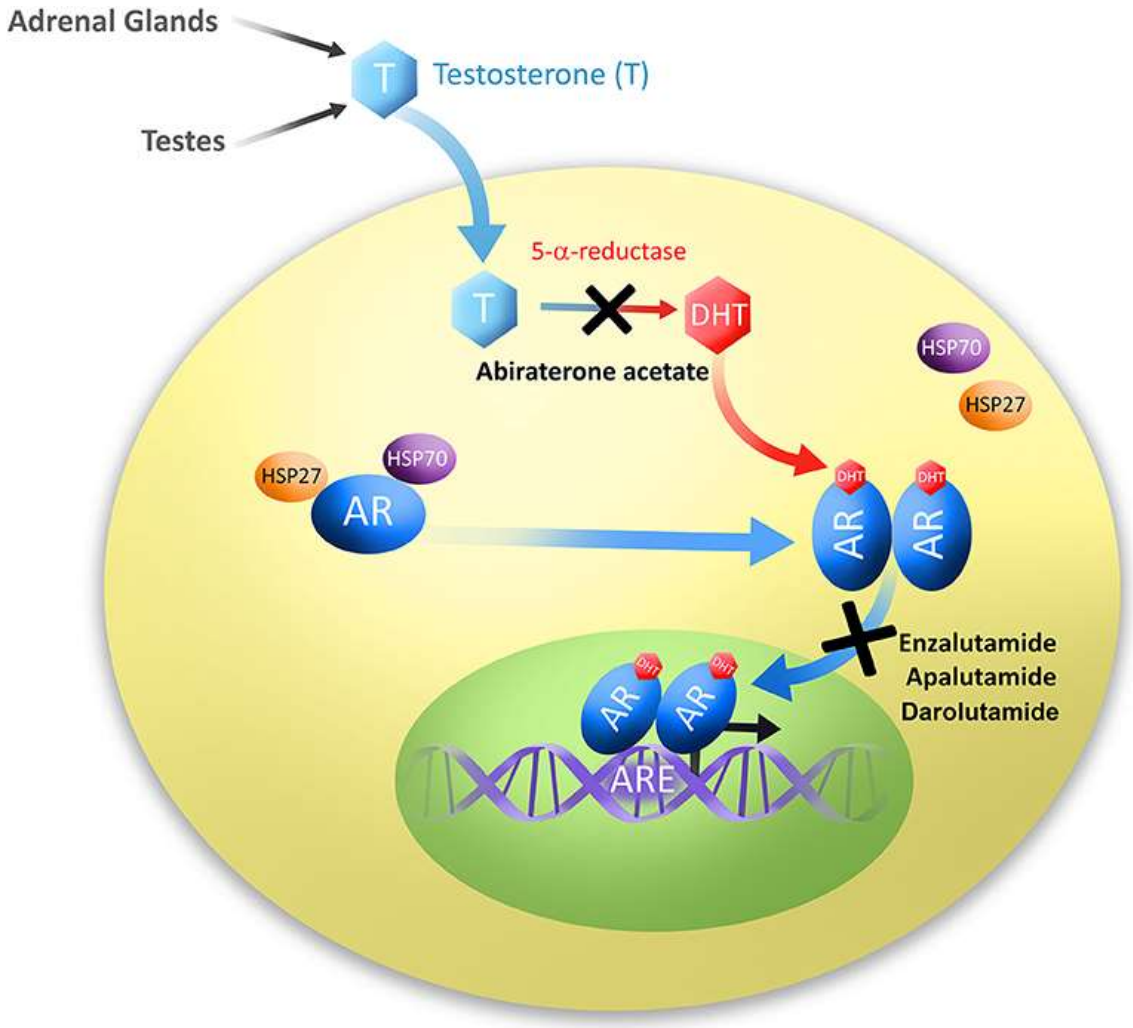
Androgen Receptor (AR) Inhibitors



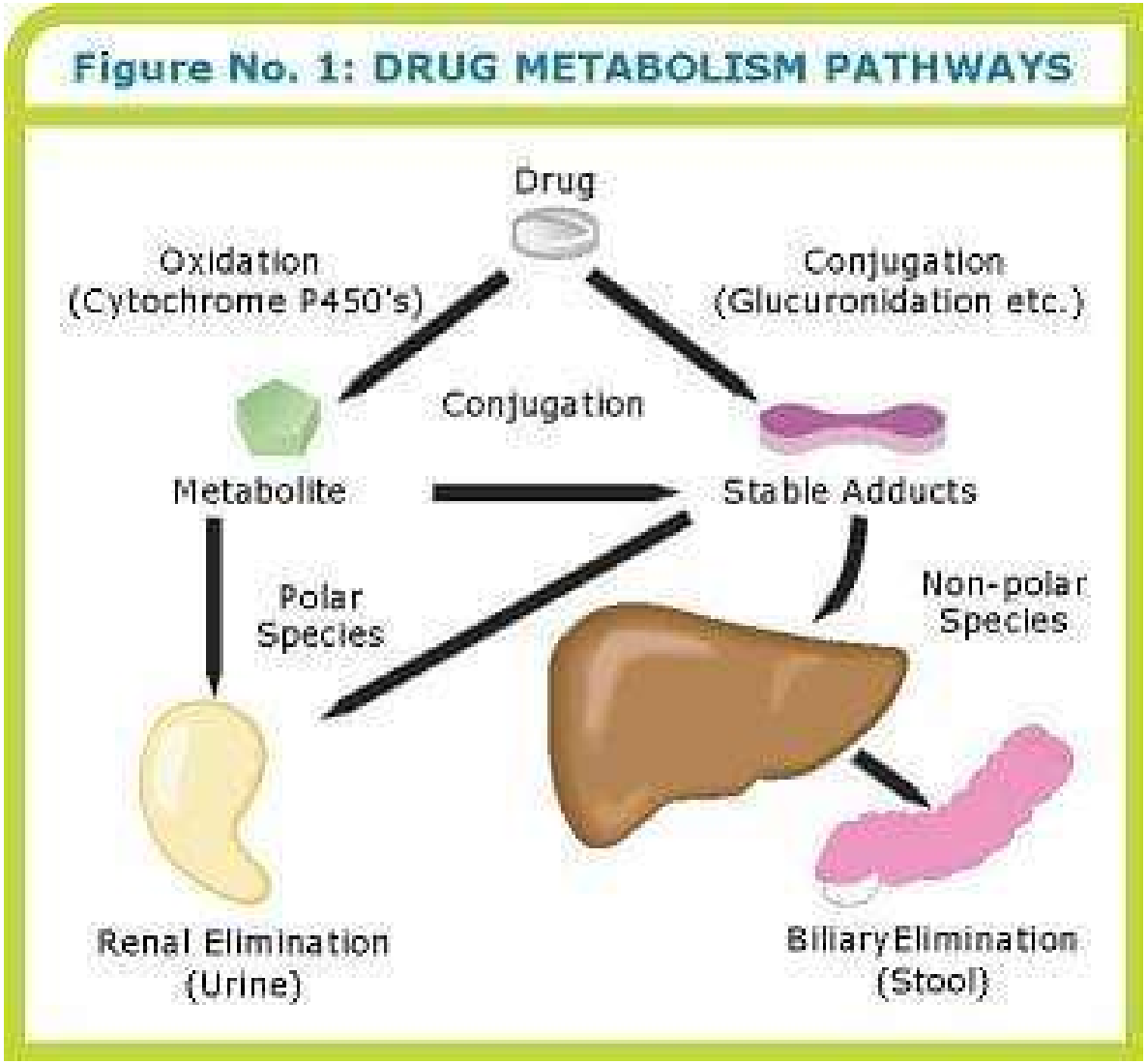
AR Inhibitor Dosing/Administration

- Enzalutamide 160 mg (4 x 40 mg capsules or tablets OR 2 x 80mg tablet), with or without food
- Apalutamide 240 mg (4 x 60 mg tablet or one 240mg tablet) once a day, with or without food
- Darolutamide 600 mg (2 x 300mg tablet) twice a day WITH food
  - Lower dose recommended if significant kidney or liver impairment

AR Inhibitor Side Effects

Common	Enzalutamide (Xtandi)	Apalutamide (Erleada)	Darolutamide (Nubeqa)
Fatigue	+++	++	+
Cognitive Effects	+	-	-
Hot flashes	+	+	+
High blood pressure	+	+	+
Hypothyroidism	-	+	-
Rash	-	+	-
RARE			
Seizure	y	y	n
Stroke or Heart Attack	y	y	y
Falls/Fractures	y	y	n

AR Inhibitor Interactions



AR Inhibitor Interactions

- Both enzalutamide and apalutamide can cause significant decreases in the amount of other medications in your body

Commonly Impacted Medications

- Blood thinners
- Pain medications
- Blood pressure drugs
- Statins
- Drugs for mood and mental health

Ways to Manage Interactions

- Switch medications
- Adjust the dose of the impacted drug
- Monitor for symptoms of decreased effectiveness

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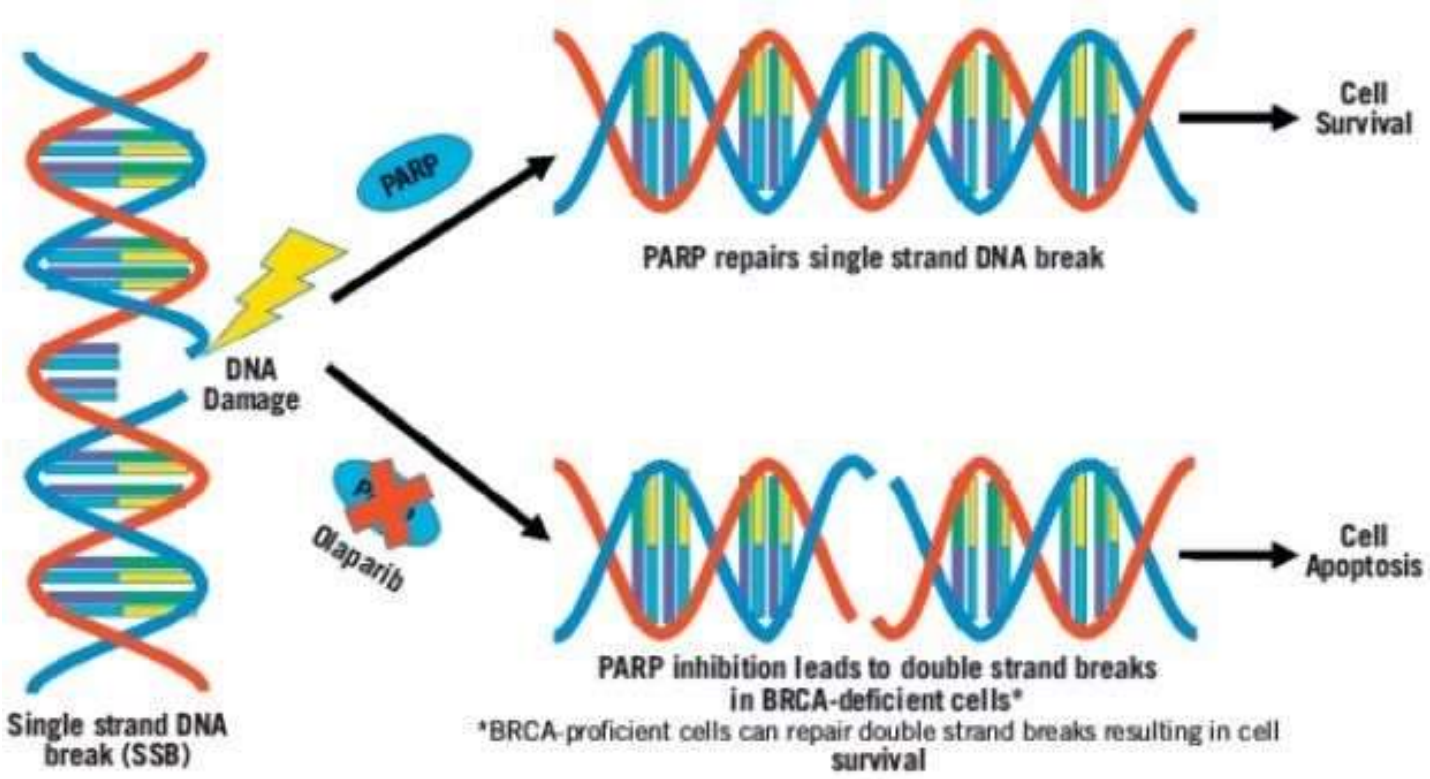
PARP Inhibitors (Olaparib, Rucaparib, Niraparib, Talazoparib)

- Effective in mCRPC if lacking certain DNA repair enzymes (BRCA1/2, CDK12)
- Kill cells through accumulation of DNA damage



PARP Side Effects

- Most common
  - Low blood counts
  - Increase in creatinine (may not reflect actual kidney injury)
  - Fatigue
  - Upset stomach (nausea, indigestion)
  - Increased cholesterol or liver irritation (rucaparib)
- RARE side effects (≤1%)
  - Lung injury (pneumonitis)
  - Leukemia (MDS/AML)

Drug Approvals by Setting

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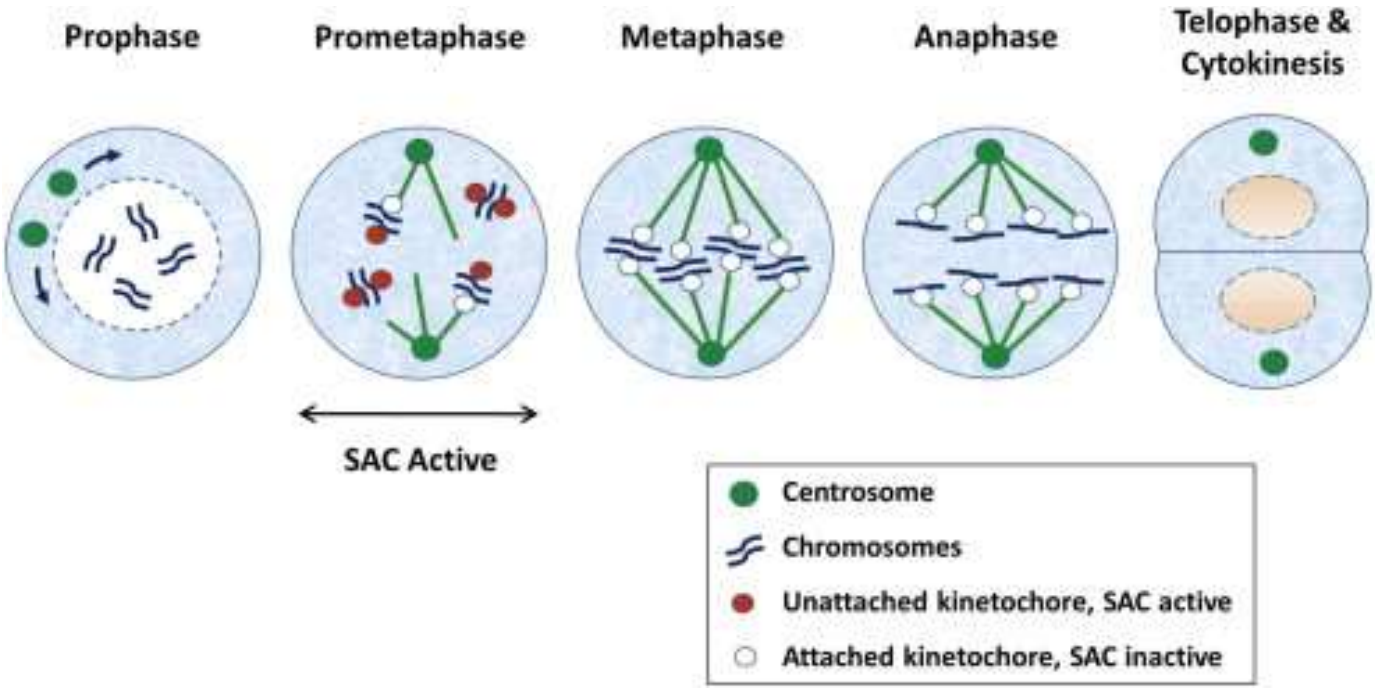
Taxanes

- Considered chemotherapy because taxanes kill growing cells
- Prevent cell growth by interfering with “metaphase” of the cell cycle
- Only active against replicating cells



Taxane Side Effects

- Low blood counts, especially white blood cells and platelets
  - May require white blood cell support – filgrastim or pegfilgrastim injection
- Water retention and swelling
- Infusion reactions (aka hypersensitivity reactions)
- Neuropathy
- Hair loss
- Nail changes
- Fatigue
- Relatively low risk of nausea/vomiting

Taxane Dosing/Administration

- IV medications, infused over 1 hour and dosed based on height and weight
- Docetaxel typical initial dose 75 mg/m^2 IV every 3 weeks
  - Lower dose recommended if liver impairment
  - Dexamethasone typically given day before, day of, and day after to prevent water retention and infusion reactions
  - Diphenhydramine and famotidine also given prior to dose
- Cabazitaxel typical initial dose 20-25 mg/m^2 IV every 3 weeks
  - Lower dose recommended if liver impairment
  - Diphenhydramine, dexamethasone, and famotidine given prior to dose to prevent infusion reactions. Ondansetron may also be added.

Dosing and Side Effects – Pearl

Sola dosis facit venenum

The dose makes the poison

- Prostate cancer drugs historically dosed to the “maximum tolerated dose” rather than the dose required to treat prostate cancer
- Lower doses can be effective and often better-tolerated, as most side effects are dose-related
- Clinical trials all allowed dose reductions for side effects
- Discuss dose reductions and/or supportive care with your team if you have side effects affecting your quality of life or ability to function

Drugs for BPH

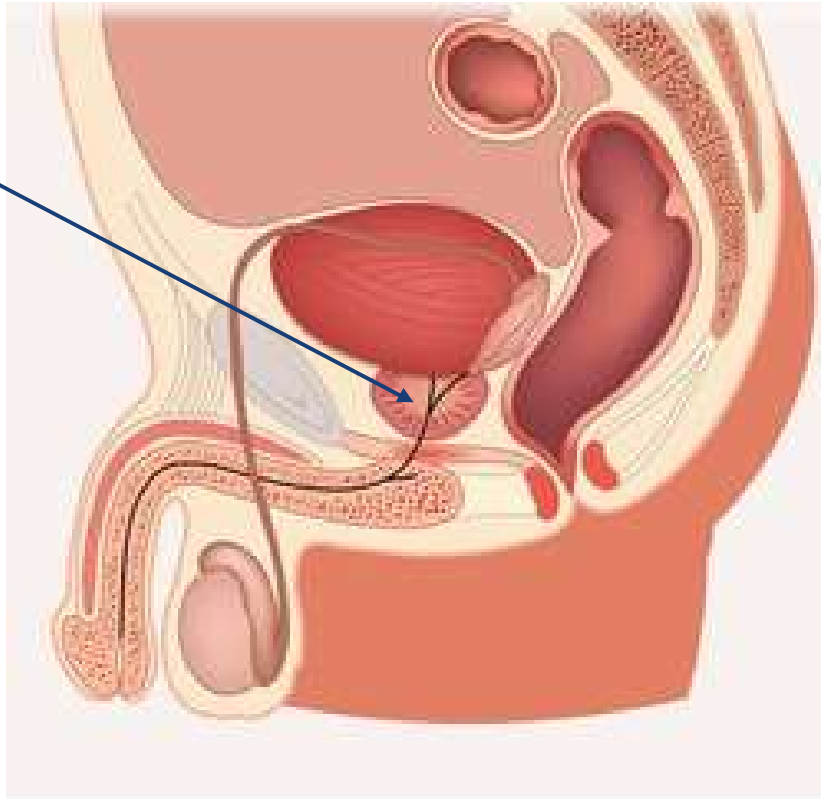
Autonomic Nervous System in GU

Sympathetic
Ligand: norepinephrine

α1A
urethral contraction

β3
detrusor relaxation

α1
ejaculation



Parasympathetic
Ligand: acetylcholine

M3
detrusor contraction

M3
erection

Abreu-Mendes P, et al. Pharmacology of the lower urinary tract: update on LUTS treatment. *Ther Adv Urol* 2020; 12:1-16.

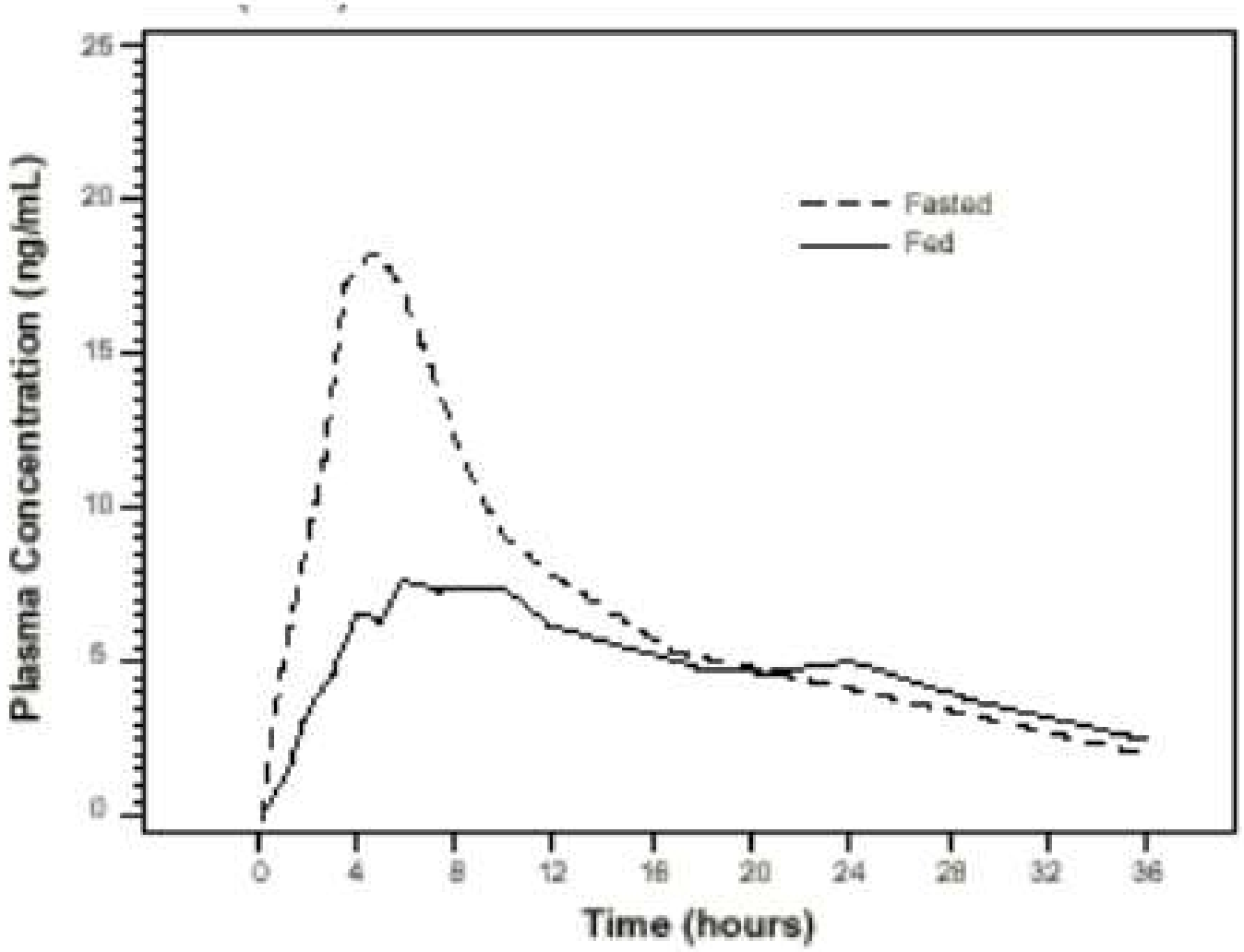
Alpha Blockers (tamsulosin, doxazosin)

- First-line agents for LUTS related to BPH
- Relaxes urethra
- Onset is rapid, days
- Side effects
  - α1 in vasculature → orthostatic hypotension/dizziness
  - α1 in iris → floppy iris syndrome, blurred vision
  - α1 in corpus cavernosum → ejaculatory dysfunction
- Class DDI:
  - Increased orthostatic hypotension: blood pressure medications, nitrates, PDE-5 (Viagra, Cialis)

Alpha-1 Antagonists – Class Members

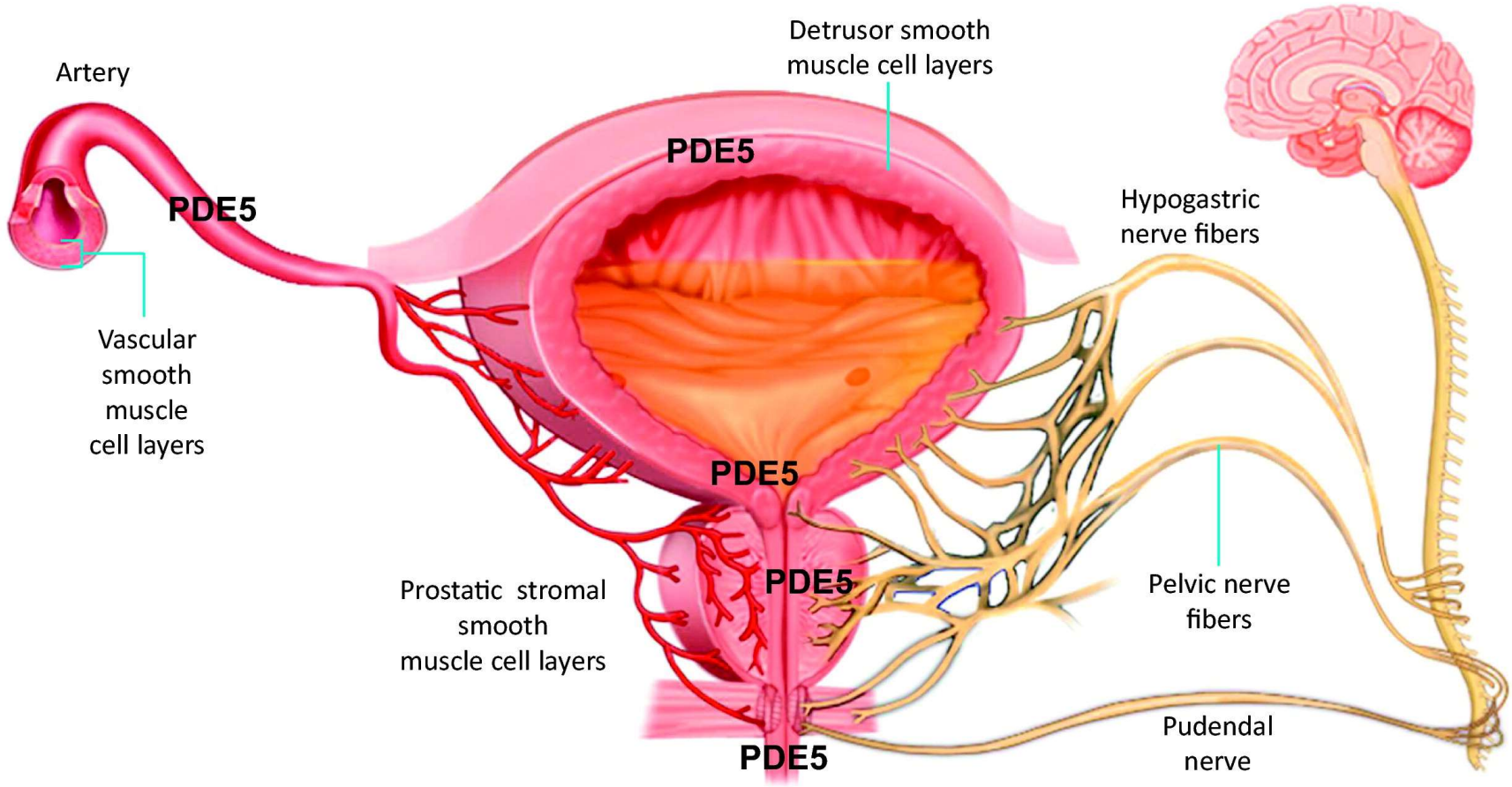
	Drug	Formulation	Dosage	Notes
α1A selective ↓ orthoHTN, ↑ IFIS, ↑ ejac dysfunction	Tamsulosin (Flomax)	0.4 mg 24h ER capsule	Initial: 0.4 mg daily Maint: 0.4 – 0.8 mg daily	Take 30 minutes after same meal each day Do not chew/ crush/open
	Silodosin (Rapaflow)	4 mg or 8 mg capsule	Initial: 4 mg daily Maint: 4 – 8 mg daily	Take with food Capsules can be opened, mixed with food
Nonselective α1 ↑ orthoHTN, ↓ IFIS, ↓ ejac dysfunction	Alfuzosin (Uroxatrol)	10 mg 24h ER tablet	10 mg daily	Take with food Do not chew/crush
	Doxazosin (Cardura)	1, 2, 4, and 8 mg IR tablets 4 and 8 mg 24h ER tablet	IR: 1 mg initial, up to 8 mg maint ER: 4 mg initial, up to 8mg maint	IR: either AM or PM, with/without food ER: take with AM meal. Do not chew/crush.
	Terazosin (Hytrin)	1, 2, 5, and 10 mg tablets	Initial: 1 mg qHS Maint: 10 – 20 mg qHS	Least DDI Can crush/chew Titrate up slowly over weeks

Tamsulosin Release Characteristics



Alternative and Combination Options for BPH

Phosphodiesterase (PDE) Inhibitors in BPH



Giuliano F, et al. The Mechanism of Action of Phosphodiesterase Type 5 Inhibitors in the Treatment of Lower Urinary Tract Symptoms Related to Benign Prostatic Hyperplasia. *Eur Urol* 2013; 63(3):506-516.

PDE-5 Inhibitors (tadalafil, sildenafil, vardenafil)

- Option for LUTS from BPH, regardless of concurrent erectile dysfunction
- Onset is rapid, 1-2 weeks
- Side effects
  - Hypotension
  - Priapism
  - Visual disturbances – PDE6
  - Hearing loss
- Class DDI
  - **Nitrates** (contraindicated) -> delay nitrate for 48hr after tadalafil
  - **Alpha blockers** – do not combine, no symptomatic benefit, orthostatic hypotension risk

Class Members – PDE5 for BPH

Drug	Formulation	Dosage	Notes
Tadalafil (Cialis)	5 mg tablet (2.5, 10, and 20 mg also exist)	5 mg daily	With/without food
Finasteride + tadalafil (Entadfi)	5 mg / 5 mg capsule	One capsule daily	Take on an empty stomach

**Tadalafil not well covered by Medicare part D even if prescribed for BPH

5α-Reductase Inhibitors (finasteride, dutasteride)

- Inhibit testosterone conversion to potent dihydrotestosterone (DHT)
- Typically an additive agent for BPH in men with enlarged prostates
  - AUA: >30cc prostate, PSA > 1.5ng/dL, or palpable prostate enlargement
- Onset very delayed, 6-12 months
- Likely not helpful for men on who have low T from ADT
- Side Effects
  - Decreased libido
  - Erectile dysfunction
  - Decreased ejaculate volume
  - Gynecomastia

Lerner LB, et al. Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE PART I. *J Urol* 2021; 206(4):806-817

5α-Reductase Inhibitors – Class Considerations

- Reduce risk of urinary retention and need for prostate-related surgery
- Reproductive Risk
  - In utero exposure to 5-ARI may cause fetal harm
  - Finasteride and dutasteride both present in semen
- Minimal drug interactions
- Impact on prostate specific antigen (PSA)
  - PSA declines by 50% within 6 months on 5-ARI
  - Increase in PSA while on 5-ARI concerning even if value is WNL

5α-Reductase Inhibitors – Class Members

Drug	Formulation	Dosage	Notes
Finasteride (Proscar)	1 and 5 mg tablets	5 mg daily	With/without food Type II selective
Dutasteride (Avodart)	0.5 mg capsule	0.5 mg daily	With/without food Both Type I/II Do not open/chew/crush
Dutasteride + tamsulosin (Jalyn)	0.5 mg / 0.4 mg capsule	One capsule daily	Take 30 mins after same meal daily Do not open/crush/chew

Drugs to AVOID in BPH

- Anticholinergics in patients with urinary retention
  - Anti-allergy: Diphenhydramine (or any 1 gen)
  - Antiemetics: Meclizine, scopolamine, promethazine
  - Muscle relaxants: Orphenadrine, tizanidine
  - Mood-altering: Paroxetine, clozapine, quetiapine, amitriptyline, nortriptyline, doxepin
  - Parkinsons: Benztropine, trihexyphenidyl
  - Antispasmodics: Hyoscyamine, dicyclomine, belladonna
- Alpha agonists
  - Pseudoephedrine
  - Midodrine

Cost Pearls

- Mark Cuban CostPlusDrugs pharmacy
  - Online, mail-order pharmacy that makes low-cost but reputable generic drugs
  - Does NOT take insurance (alternative option if insurance isn't working for you)
  - Prostate cancer drugs: abiraterone, bicalutamide
  - BPH drugs: tamsulosin, silodosin, alfuzosin, doxazosin, dutasteride, finasteride, dutasteride-tamsulosin
  - ED/BPH drugs: sildenafil, tadalafil, vardenafil
- Copay assistance options for brand drugs (specialty drugs) may be available through copay cards, manufacturer patient assistance programs, prostate cancer foundation grants, or hospital-based programs

BPH with Predominant OAB/Storage Symptoms

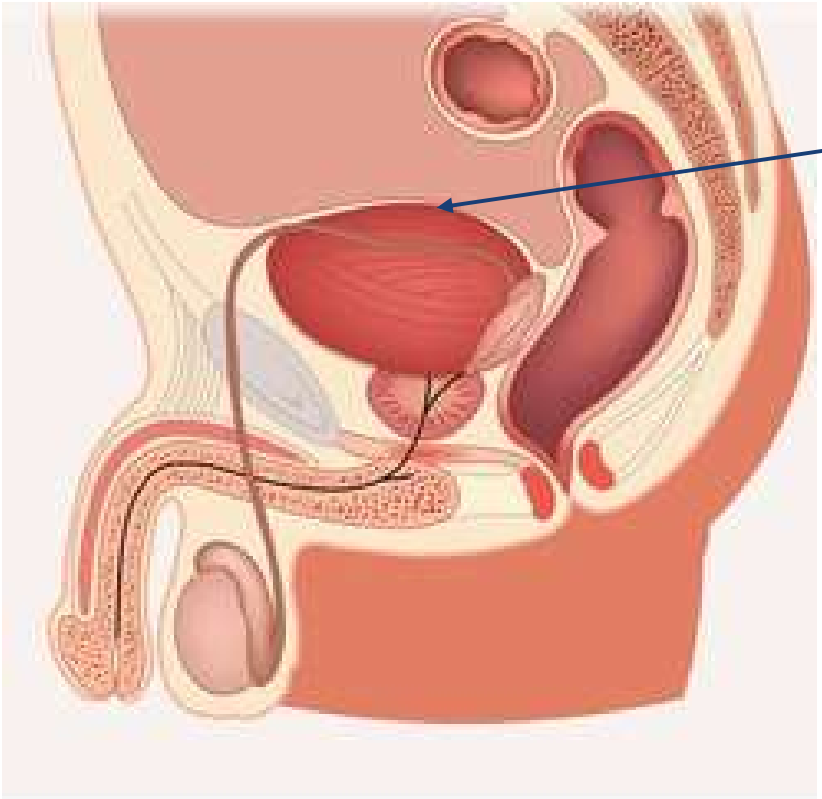
Autonomic Nervous System in GU

Sympathetic
Ligand: norepinephrine

α1A
urethral contraction

β3
detrusor relaxation

α1
ejaculation



Parasympathetic
Ligand: acetylcholine

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detrusor contraction

M3
erection

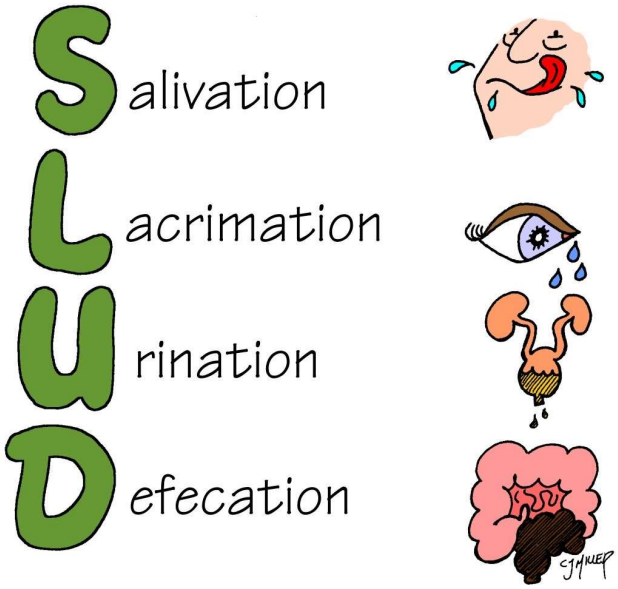
Abreu-Mendes P, et al. Pharmacology of the lower urinary tract: update on LUTS treatment. *Ther Adv Urol* 2020; 12:1-16.

Antimuscarinics (Anticholinergics)

- May be useful alone or combo with alpha blocker for storage symptom-predominant LUTS
- Obtain PVR prior to prescribing and monitor at follow-up
- Drug interactions:
  - Acetylcholinesterase inhibitor (donepezil, galantamine, rivastigmine) – decreased effectiveness
  - Botulinum toxins – additive anticholinergic effects

Antimuscarinic Side Effects

- Dry mouth
- Dry eyes and/or blurred vision
- Urinary retention
- Constipation
- Dizziness
- Fatigue
- Cognitive effects/dementia risk
- Avoid in untreated narrow-angle glaucoma and myasthenia gravis



Antimuscarinic Class Members

	Drug	Formulation	Dosage	Notes
M3	Darifenacin (Enablex)	7.5 mg 24h ER tablet	Initial 7.5 mg daily Max 15 mg daily	CYP2D6 inhibitor
	Solifenacin (Vesicare)	5 and 10 mg tablet	Initial: 5 mg daily Max: 10 mg daily	Renally eliminated Don't chew/crush
Nonselective	Festoterodine (Toviaz)	4 and 8 mg 24h ER tablet	Initial: 4 mg daily Max: 8 mg daily	Renally eliminated Don't chew/crush
	Oxybutynin (Ditropan XL)	5, 10, and 15 mg 24h ER tablet Topical gel, oral solution, and patch also available	ER: 5 – 10 mg daily initial, max 30mg daily IR: 5 mg BID-TID initial, max 20 mg/day	ER preferred With/without food Don't chew/crush ER
	Tolterodine (Detrol/Detrol LA)	2 and 4 mg 24h ER capsule 1 and 2 mg IR tablet	ER: 4 mg daily (may lower to 2mg) IR: 2 mg BID	Renally eliminated
	Trospium (Trosec)	60 mg 24h ER capsule 20mg IR tablet	ER: 60 mg daily in the AM IR: 20 mg BID	Renally eliminated Take on empty stomach

Autonomic Nervous System in GU

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Ligand: norepinephrine

α1A
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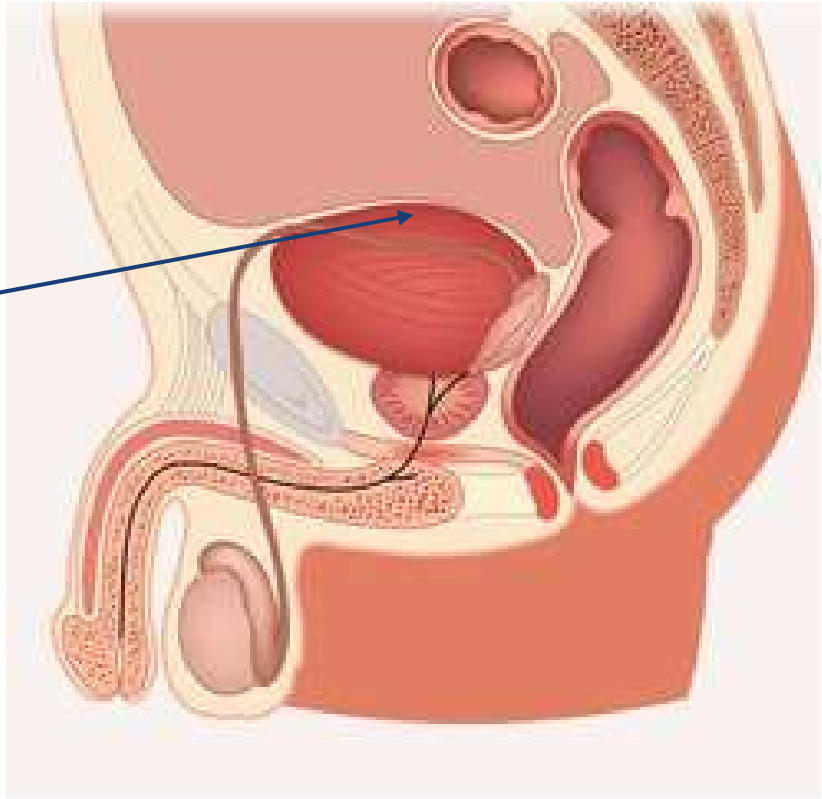

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β3 Agonists

- Combination therapy with alpha blockers for storage symptom-predominant LUTS
- Side Effects
  - β1 activity
    - Avoid in severe controlled HTN (>=180/>=110)
    - Tachycardia
  - Urinary retention – monitor PVR
  - Angioedema (rare)
- Class DDIs: none

β3 Agonists - Class Members

Drug	Formulation	Dosage	Notes
Mirabegron (Myrbetriq)	25 and 50 mg 24h ER tablet ER solution	Initial: 25 mg daily Max: 50 mg daily	With/without food Swallow whole Renally cleared CYP2D6 inhibitor
Vibegron (Gemtesa)	75 mg tablet	75 mg daily	With/without food Swallow whole or crushed in applesauce

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