Benign Prostatic Hyperplasia

"The Diagnosis and Management of BPH from the Primary Care Perspective"

Daniel Lee, MD
Clinical Professor of Family Medicine,
David Geffen School of Medicine at UCLA

Opening Case

- 60 y.o. male presents for CPE.
- Has chronic medical conditions of HTN, Dyslipidemia, and Obesity.
- He has several urinary complaints.

- Do you know what questions to ask him?
- Do you know the differential diagnosis for his urinary symptoms?
- Do you know what work-up you should consider?
- Do you know the treatment options available, medications, surgery, etc., and what you should try first?

Three Objectives

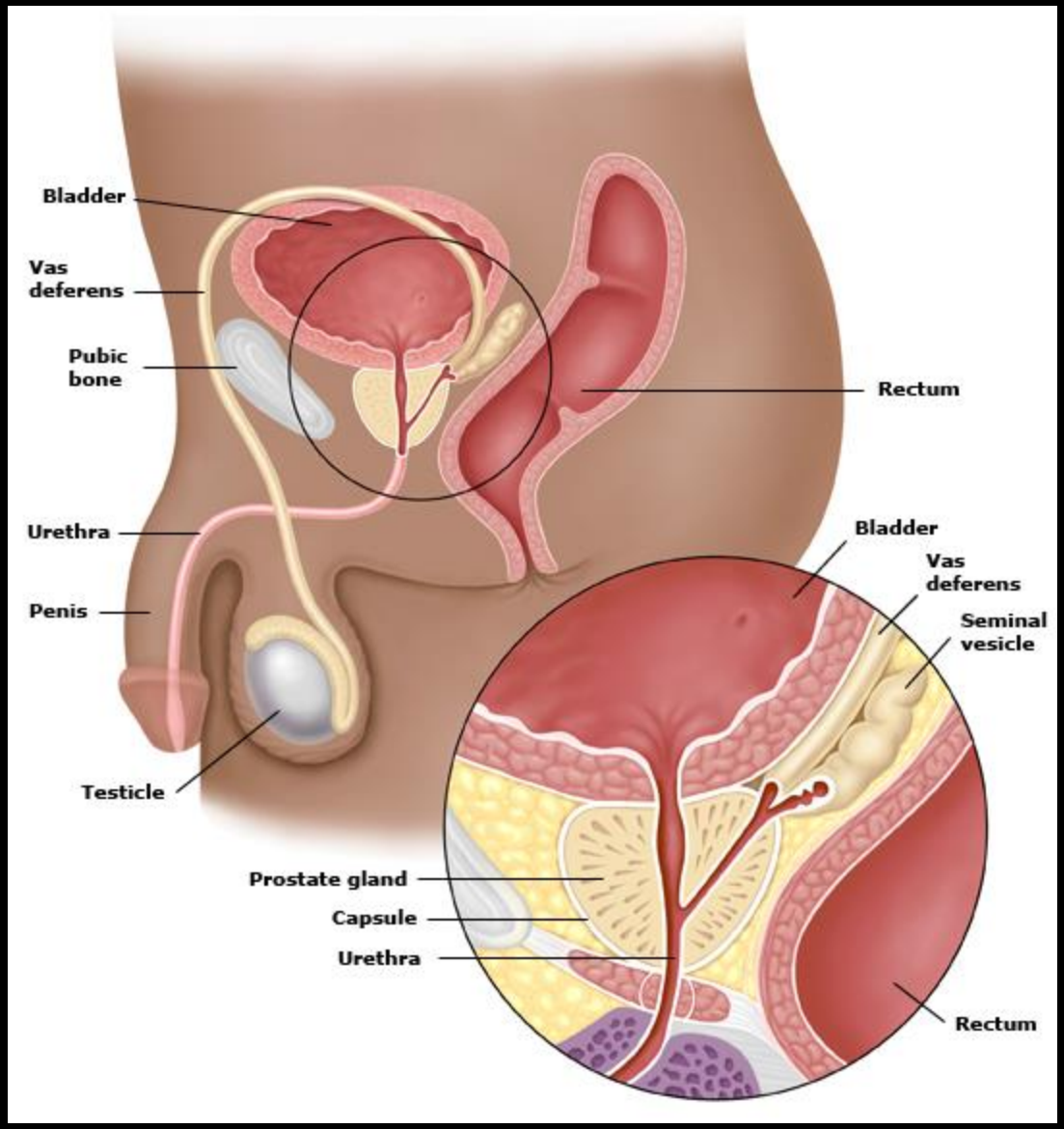
- Learn how to evaluate a patient who presents with LUTS/BPH symptoms
- Learn how to utilize the IPSS questionnaire
- Understand the various treatment options for BPH

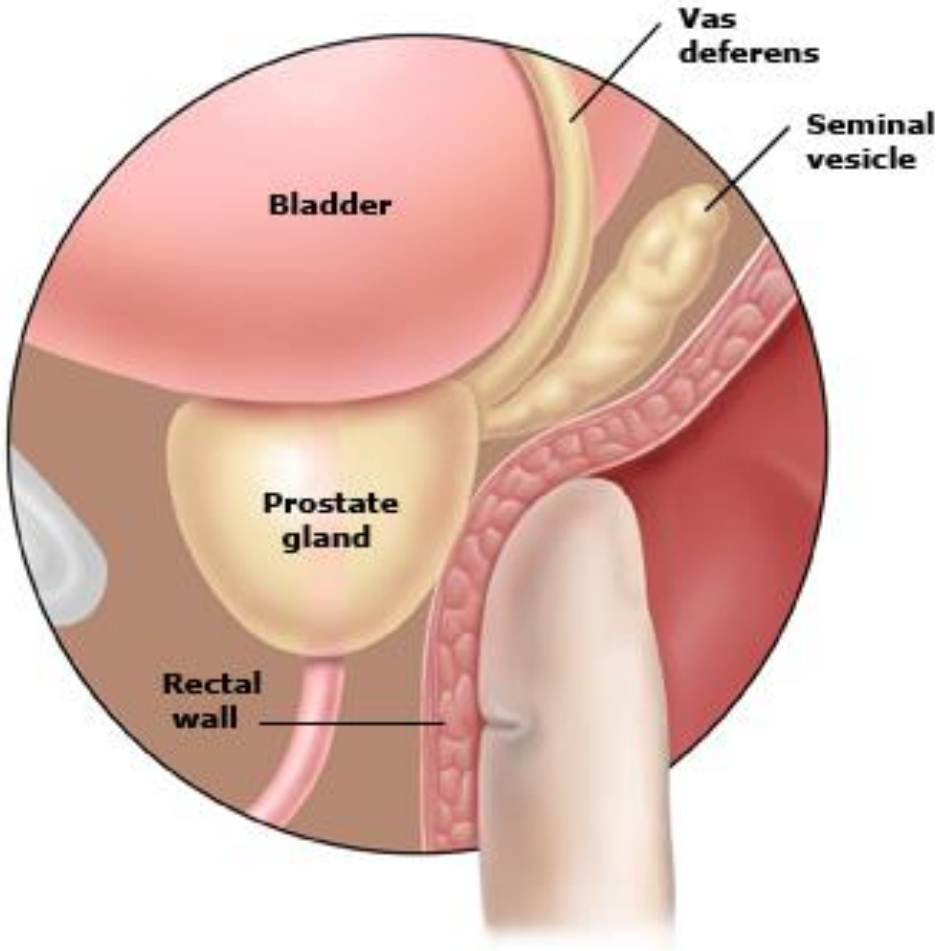
BPH

- Common clinical problem in middle-aged to elderly men
- Causes a myriad of bothersome urinary symptoms
- Can lead to serious disorders including, bladder dysfunction, pyelonephritis, hydronephrosis, urinary obstruction, and acute and chronic kidney disease.

Anatomy

- The prostate is the size of a walnut weighing about 20 grams.
- It surrounds the urethra just below the urinary bladder and can be felt during a rectal exam.
- It’s the only exocrine organ located in the midline in humans.


Bladder
Vas deferens
Pubic bone
Rectum
Urethra
Penis
Testicle
Bladder
Vas deferens
Seminal vesicle
Prostate gland
Capsule
Urethra
Rectum


Vas deferens
Seminal vesicle
Bladder
Prostate gland
Rectal wall

Definitions

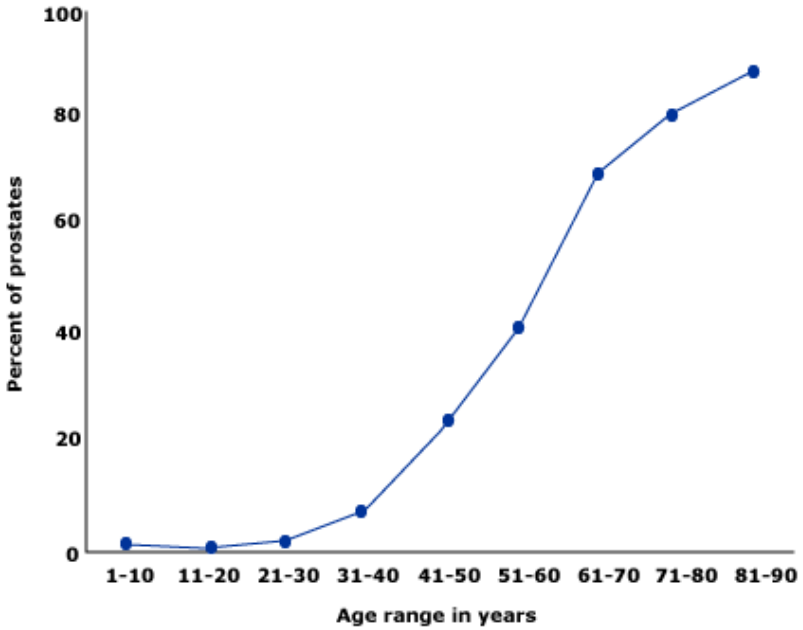
- **BPH**—Benign prostatic hyperplasia
- Is a histologic diagnosis showing increase in the stromal, epithelial, and glandular components of the prostate.
- Terms often used synonymously, include
  - BPE—Benign prostatic enlargement
  - BPO—Benign prostatic obstruction
  - BOO—Bladder outlet obstruction

Definitions

- **LUTS**—Lower Urinary Tract Symptoms
- Is a general term used to refer to any combination of urinary symptoms.
- Not all causes of LUTS are a result of BPH.
  - Overactive Bladder
  - Urethral or bladder neck stricture
  - Prostate Cancer
  - Bladder Cancer
  - Bladder Calculi
  - Neurogenic Bladder
  - UTI's and Prostatitis
  - Medication or other substance side effects

Prevalence of Histologic BPH

Prevalence of benign prostatic hyperplasia pathology with age



Age-associated increase in pathologic evidence of benign prostatic hyperplasia in 1075 men at autopsy. The percentage with benign prostatic hyperplasia was determined during 10-year intervals from five different studies; the mean values are shown.

Data from Berry, SJ, Coffey, DS, Walsh, PC, et al. The development of human benign prostatic hyperplasia with age. J Urol 1984;132:474.

UpToDate

Prevalence of Moderate-Severe LUTS

- Age 40-49 – 26%
- Age 50-59 – 33%
- Age 60-69 – 41%
- Age 70-79 – 46%

If BPH is so common, how come we don't diagnose or treat it more?

- Two general reasons:
  - Patients' side
  - Physicians' side

Patients' Side

- Too embarrassed or afraid to bring it up
- Think it's a typical part of aging
- Symptoms are not severe enough to disrupt their life
- Don't realize there are good treatment options

Physicians' Side

- Underestimate the prevalence of the disease
- Forget to ask the patient
- "Don't ask, won't tell."
- Don't have a good grasp on diagnosis and treatment of BPH

Illustrative Case

- 60 y.o. male comes in for a CPE.
- After spending 30 minutes:
  - Taking a history
  - Going over P,F,SHx., Meds
  - Physical Exam
  - Discuss medical problems, HTN, Dyslipidemia, and obesity.
  - Prevention counseling on various screening tests and immunizations, etc.
  - You have yet to fill out all the forms
- He says… "by the way doc".

Illustrative Case

- "I've been having some urinating problems"
- What do you say next?

Potential responses from the physician…

- "Are you kidding me, I've taken care of too many things already."
- "If it isn't completely blocked, don't worry about it."
- "You're just getting older, don't worry about it."
- "Just cut down on the caffeine and alcohol."
- "I'll refer you to my friendly urologist."

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1. Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
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Total score _____

Quality of Life Due to Urinary Symptoms

If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?

Delighted	Pleased	Mostly satisfied	Mixed—about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
0	1	2	3	4	5	6

FIGURE 3. The International Prostate Symptom Score, as developed by the American Urological Association and adopted by the International Consensus Committee of the World Health Organization. Patients with a symptom score ≤7 have mild symptoms, those with scores 8 to 19 have moderate symptoms and those with scores ≥20 have severe symptoms. Because BPH is treated primarily for symptoms, the degree of the patient's need for relief is probably the best predictor of the need for treatment.

AUASI or IPSS

- American Urological Association Symptom Index

Or

- International Prostate Symptom Score

- The AUASI and IPSS are the same thing except for one difference.
- Great way to quantitate the symptom severity of the BPH/LUTS and monitor the symptom progression over time.

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The IPSS result helps guide treatment

- Mild—7 or less
- Moderate—8-19
- Severe—20 or greater

- Quality of life score

Take a History

- **Symptoms, when did they start, how severe, how often?
- ROS: Hematuria, fever, weight loss, dysuria, pain?
- PMHx—CVA, Spinal cord injury, Parkinson's, Multiple Sclerosis, Cataracts
- SHx—Tob, ETOH, caffeine intake
- FHx—BPH, Prostate CA
- Meds—anticolinergics, antihistamines, pseudoephedrine, diuretics, opioids, PDE-5 inhibitors, etc.

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Next step?

- After reviewing the IPSS questionnaire and taking a history, what is the next step?

PE and Labs

- PE—Rectal exam—sphincter tone, estimate prostate size, feel for nodules, tenderness, etc.
- Send UA and UCx
- Labs—BMP, CBC, PSA

Treatment Options

1. Behavioral Modification
2. Medications
3. Surgery

Behavioral Modification

- Avoid fluids after dinner or before going out when restroom not readily available

Behavioral Modification

- Reduce or stop caffeine and alcohol

Caffeine check

It takes as little as 15 minutes for caffeine to give your system a jolt. Good news for those days you just *caaan't* get out of bed. Experts say drinking a few cups a day is no problem for most people; the not-fun, jittery, heart-racing effects of caffeine kick in when you start consuming more than 300 mg a day. Here's how popular hits stack up.

Chocolate milk, 8 oz
5 mg

Mountain Dew, 12 oz
54 mg

Jolt Energy Gum, 2 pieces
55 mg

Pepsi Max, 12 oz
69 mg

Coffee, 6 oz
71–135 mg

Red Bull, 8.4 oz
80 mg

Crystal Light Energy, 16 oz
120 mg

Espresso, 2 oz
128–150 mg

EBoost, 2-oz shot
150 mg

Monster Energy, 16 oz
184 mg

Arizona Energy, 16 oz
200 mg

5-Hour Energy, 1.9-oz shot
215 mg

NOS High Performance Energy drink, 16 oz 224 mg

Sources: Consumer Reports; manufacturers' labeling; USDA

Caffeine Content

Beverage	Size (oz.)	Caffeine Content (mg)	Cafeeine Per Ounce (mg/oz.)
Espresso shot	1	55	55.00
Generic brewed	8	150	18.75
McDonald's brewed	16	100	6.25
Starbucks latte	16	150	9.38
Starbucks Pike Place	16	330	20.63
Black tea	8	45	5.63
Green tea	8	30	3.75
AriZona Iced Tea	8	11	1.38
5-Hour Energy	2	207	103.50
Monster	8	80	10.00
Red Bull	8.4	80	9.52
Coca-Cola Classic	12	30	2.50
Diet Coke	12	45	3.75
Mountain Dew	12	50	4.17

Behavioral Modification

- Limit fluids after dinner
- Avoiding caffeine and alcohol
- Double voiding
- Avoid meds that can exacerbate symptoms or induce urinary retention such as anticholinergic meds (sedating antihistamines, tricyclic antidepressants), adrenergic meds such as decongestants, opioids.

Medications

- The outlet obstruction of BPH has two components:
- Structural component: Mechanical obstruction of the enlarged prostate impinging upon the urethra
- Dynamic component: Increased tension or tone of prostatic smooth muscle in the prostate and bladder neck.

Two major classes of medications (6 total)

- 5-alpha-reductase inhibitors — target the structural component.
  - 5-alpha-reductase catalyzes the conversion of testosterone to dihydrotestosterone in the prostate.
  - Blocking this conversion results in apoptosis of the prostate and it will shrink.
- Alpha-1-adrenergic antagonists — target the dynamic component.
  - Alpha-1 receptors are abundant in the prostate and base of the bladder.
  - Blocking these receptors decreases smooth muscle tone.

Alpha-1-adrenergic antagonists

- Six alpha-1-antagonists
- Terazosin (Hytrin)
- Doxazosin (Cardura, Cardura XL)
- Silodosin (Rapaflo)
- Alfuzosin (Uroxatral)
- Tamsulosin (Flomax)

- Prazosin (Minipress)

Alpha-1-adrenergic antagonists

- Three alpha-1 adrenoreceptor sub-types have been characterized (1A, 1B, 1D).
- Alpha-1A and alpha-1D receptors are prevalent in the prostate and certain parts of the bladder
- Alpha-1B are prevalent in vasculature smooth muscle
- Terazosin (Hytrin), doxazosin (Cardura), alfuzosin (Uroxatral) antagonize all three receptor subtypes.
- Tamsulosin (Flomax) has selectivity for alpha-1A and -1D receptors.
- Silodosin (Rapaflo) is a relatively selective 1A receptor antagonist.

Alpha-1-adrenergic antagonists

- Terazosin (Hytrin) and Doxazosin (Cardura) will lower blood pressure and cause side effects of orthostatic hypotension and dizziness.
- Start at lowest dose 1mg. qhs and titrate up slowly. Take the very first dose while in bed.
- However, alfuzosin (Uroxatral), tamsulosin (Flomax), silodosin (Rapaflo) have minimal hypotensive effects.
- Tamsulosin (Flomax) and Silodosin (Rapaflo) can cause decreased ejaculate volume and retrograde ejaculation

Alpha-1-adrenergic antagonists

- All alpha blockers can cause asthenia, nasal congestion and other URI symptoms, headaches, and dizziness.
- The hypotensive effects of terazosin and doxazosin can be potentiated by concomitant use of the phosphodiesterase-5 (PDE-5) inhibitors sildenafil (Viagra) and vardenafil (Levitra). The risks of tadalafil (Cialis) is less clear.
- Men on lower does of alpha blocker and not experiencing orthostatic hypotension can use the PDE-5 inhibitors but the dosing must be separated by four hours.

Alpha-1-adrenergic antagonists

- Efficacy among alpha-blockers for BPH are about equal allowing for individual differences.
- If you want your patient's BP to be lower, use doxazosin or terazosin.
- If your patient's BP is low or normal, consider newer generation alpha-blockers.

5-alpha-reductase inhibitors

- Finasteride (Proscar) 5 mg. daily
- Dutasteride (Avodart) 0.5 mg. daily

- Effective with larger prostates
- No dose titration needed
- 6-12 months of treatment is needed before prostate is sufficiently reduced to improve symptoms
- Can add on to alpha blockers

5-alpha-reductase inhibitors

- Serum PSA levels should decrease by ~50%.
- The corollary is one should correct the PSA evaluation by a factor of 2
- Side effects include decreased libido, decreased ejaculate volume, erectile dysfunction (4-13% risk), and gynecomastia.
- May grow back hair for those with androgenic alopecia.

5-alpha-reductase inhibitors

- Pregnancy category X medicine.
- Pregnant aged women should not be taking or even handling these medications.
- Men on these medications cannot donate blood.
- I also advise against taking these meds if trying to conceive or during a partner's pregnancy

5-alpha-reductase inhibitors

- They seem to lower risk of less aggressive prostate CA (Gleason 6 or lower), but increase the risk of more aggressive CA (Gleason 8-10). The trade off equates to 1 additional case of high grade CA to prevent 3-4 lower-grade cases
- Give informed consent before starting this med
- No change overall in morbidity or mortality in reference to prostate cancer so far on these meds

Antimuscarinic (Anticholinergic) Agents

- Work by decreasing involuntary detrusor (bladder smooth muscle) contractions.
- Can:

1. Decrease the sensation of urgency
2. Decrease episodes of frequency
3. Increase voided volume
4. Decrease episodes of urge incontinence.

Antimuscarinic (Anticholinergic) Agents

- Tolterodine—Detrol, Detrol LA
- Oxybutynin—Ditropan XL
- Darifenacin—Enablex
- Solifenacin—Vesicare
- Fesoterodine—Toviaz
- Trospium—Sanctura XR
- Side effects: Dry mouth, blurry vision for near objects, tachycardia, drowsiness, decreased cognitive function, inhibition of gut motility, constipation.
- Contraindicated in angle closure glaucoma and severe gut motility problems

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Antimuscarinic (Anticholinergic) Agents

- In studies, Tolterodine (Detrol) when combined with alpha-blocker was more effective than alpha-blocker alone.
- Consider in patients with predominance of more irritative or overactive bladder (OAB) symptoms of frequency, urgency (question 2 and 4 on IPSS and maybe 7) and/or incontinence.
- Generally safe but be aware of urinary retention.
- Should be restricted to men with low post-void residual (PVR) volumes
- Send to Urologist to check PVR before starting these meds

Beta-3 Adrenergic Agonists

- Mirabegron (Myrbetriq)—may raise blood pressure
- Vibegron (Gemtesa)

- Stimulate detrusor beta-3 adrenergic receptors to promote relaxation without compromising bladder contractility.
- Much less urinary retention or dry mouth compared to anticholinergics

Phoshpodiesterase-5 (PDE-5) inhibitors

- PDE-5 inhibitors have shown improvement in IPSS after >12 weeks on therapy
- Tadalafil (Cialis) is FDA approved for use in BPH
- Consider with patient with both ED and BPH
- Contraindicated if creatinine clearance <30
- Can use alone or in combination with other BPH meds
- PDE-5 inhibitors can potentiate the hypotensive effects of alpha blockers
- Consider taking 4 hours apart and/or combining with the non-blood pressure lowering alpha blockers

Herbal Therapies

- Used more widely in Europe
- No herbal therapies are FDA approved in US
- Saw palmetto—berries from the dwarf palm tree

Do herbal therapies work?

- Studies using Saw Palmetto show conflicting results.
- Most rigorous placebo controlled trials showed no benefit over placebo.
- (There is a significant placebo effect for BPH)
- Side effects are mild, including headache, nausea, and dizziness.
- Doctor's Best Saw Palmetto Extract (Doctor's Best)
- CVS Pharmacy Saw Palmetto (CVS Corporation)
- GNC Herbal Plus Standardized Saw Palmetto (General Nutrition Corporation)
- Solgar Saw Palmetto Berry Extract (Solgar Vitamin and Herb)

Other Herbal products

- Cernilton prepared from the rye grass pollen
- Pygeum africanum-extract of bark from the African plum tree
- Cucurbita pepo--pumpkin seeds
- Urtica dioica or Urtica urens—nettle root
- Bee pollen (particularly that from the rye plant)
- African potato (tubers of Hypoxis rooperi)

Surgical Treatments

- Transurethral resection techniques:
  - Transurethral resection of the prostate (TURP)
  - Transurethral laser enucleation
- Transurethral ablation techniques:
  - Transurethral electrovaporization prostate (TUVP)
  - Photoselective vaporization prostate (PVP)
  - Water vapor thermal therapy (WVTT)
  - Transurethral microwave therapy (TUMT)
  - Transurethral incision prostate (TUIP)
- Prostatectomy

Case 1

- 44 yo new patient. His insurance switched and seeing you for the first time. He has diagnosis of BPH and has been on an alpha-blocker for months but it hasn't helped.

- What do you do now?

Case 1

- Go through the systematic approach.
  - Take a history—PMHx, SHx, Meds, etc.
  - IPSS questionnaire to quantitate his LUTS
  - PE—rectal exam
  - Labs

Case 1

- Rectal exam—normal.
- You do an IPSS and his score is 19.
- Check CBC, BMP, PSA, U/A, UCx

Case 1

- His glucose comes back in the 400's.
- You diagnose him with DM and treat it.
- His IPSS score goes down to 1
- Take home message: Not all LUTS due to BPH

Case 2

- 42 yo with recent onset of urinary symptoms.
- History is benign
- His IPSS score is 15.
- The rectal exam shows tender, boggy prostate.

- What do you do?

Case 2

- Treat him for prostatitis.
- Do not check the PSA as it can go through the roof.
- Repeat the IPSS in several months.

Case 3

- 50 yo presents with worsening urinary symptoms over the past year.
- History--benign
- IPSS is 9
- Rectal reveals mildly enlarged prostate.
- Labs, urine testing is WNL.
- What do you do?

Case 3

- Check his quality of life score
- In this case it is good.

- Behavioral Modification
- Saw Palmetto? Sure go for it.
- Follow up 6-12 months
- Can follow the IPSS over time

Case 4

- 60yo with chronic urinary symptoms. Patient has HTN, dyslipidemia, and obesity.
- IPSS score is 26
- Prostate is moderately enlarged
- Labs/Urine WNL

- What do you do now?

Case 4

- Behavioral modification
- Start alpha blocker. Which one?

His IPSS goes down to 12.

What do you do now?

Case 4

- Check his quality of life score.
- Use this to guide your treatment.

Case 5

- 65 yo. presents fairly healthy patient with years of LUTS but becoming more bothersome recently. Only med is sildenafil (Viagra) prn.

- Rectal exam shows moderate to severely enlarged prostate.
- IPSS is 25
- PSA is 3
- What do you do now?

Case 5

- Behavioral modification
- You start alpha-blocker. Which one?

Case 5

- He returns in a couple of months
- His IPSS goes to 20.
- What do you do now?

Case 5

- You start a 5-alpha reductase inhibitor.
- What must you warn him about?

- He returns in one month and there is no change in IPSS. It's still 20. But no side effects to the med
- What do you do now?

Case 5

- It's too early to see improvement.
- But the lack of side effects is encouraging. Plan is continue with treatment.

- He returns 12 months later.
- His IPSS score zooms down to 10.
- What do you do now?

Case 5

- Check PSA.
- His PSA is now 2.1
- What do you do now?

Case 5

- Refer the patient to Urology
- The PSA did go down, but less than the 50% expected.

Case 6

- 67 yo here for pre-op H&P for cataract surgery.
- PMHx: BPH
- PSHx: TURP BPH symptoms resolved and doing well
- Meds: None
- ROS and PE—WNL
- You clear him for surgery.
- Anything else you need to do?

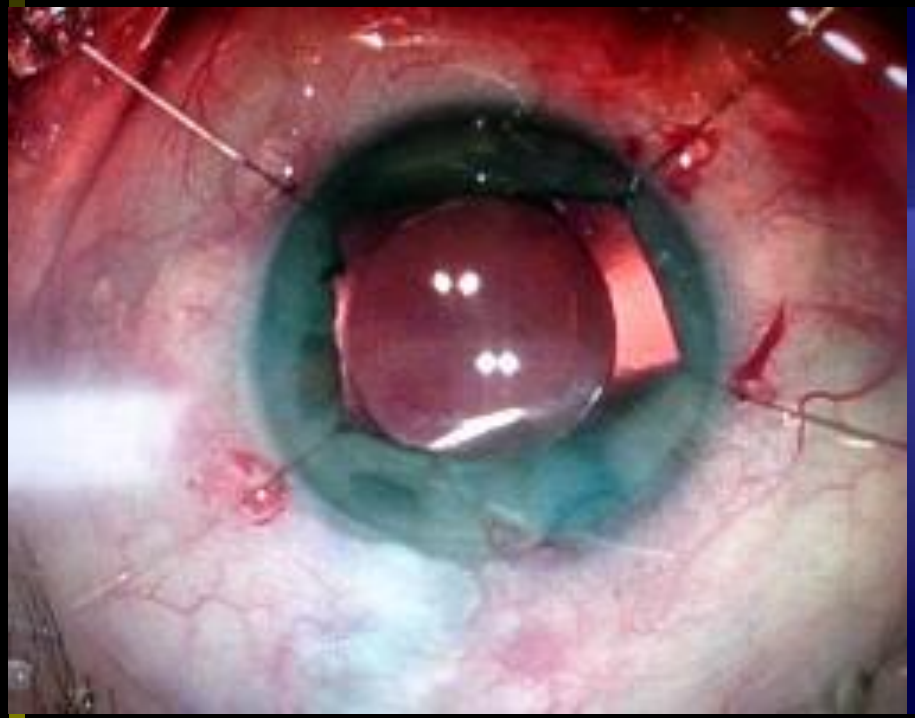
Case 6

- Get history if he took alpha-blocker in the past
- In fact this patient did take tamsulosin (Flomax) in the past
- Need to explicitly document and inform ophthalmologist that this patient took alpha-blocker in the past and tell patient to inform ophthalmologist of this too

Alpha-1A receptors also found in:

- The iris.
- Intraoperative Floppy Iris Syndrome (IFIS), which occurs during cataract surgery, happens at a significantly higher rate in patients who have taken alpha blockers and most specifically tamsulosin (Flomax).

Intraoperative Floppy Iris Syndrome



Case 7

- 50 yo. in for complete physical exam.
- He has heard that some of the prostate medications have been shown to decrease the incidence of prostate cancer.
- His father had prostate cancer diagnosed at age 75 but didn't die of it.

- He wants your opinion if he should take them.

Case 7

- 5-alpha reductase inhibitors have been shown to decrease the incidence of prostate cancer detection.
- However, in the patients whom prostate cancer is detected, there is an increase in high-grade lesions.
- Bottom line, not ready for “Primetime” usage today for this indication.

QUESTIONS

Three Objectives

- Learn how to evaluate a patient who presents with BPH symptoms
- Learn how to utilize the IPSS questionnaire
- Understand the various treatments options for BPH

References:

- Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE https://www.auanet.org/guidelines-and-quality/guidelines/non-oncology-guidelines
- Up To Date: 1) Epidemiology and pathophysiology of benign prostatic hyperplasia 2) Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia 3) Medical treatment of benign prostatic hyperplasia

- Doxazosin may not be the most appropriate agent to manage BPH symptoms in patients with HTN, based on results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized double-blind , controlled trial in 24,335 hypertensive patients. Patients who received doxazosin experienced a significantly higher risk of stroke and combined cardiovascular disease compared with those treated with the diuretic chlorthaladone. These results prompted the discontinuation of the doxazosin arm of the study in 2000.

- The first generation alpha blockers such as phenoxybenzamine (Dibenzyline) which are non-specific for the alpha receptors, are not indicated for the treatment of BPH due to the profound vasodilatory side effects

- There are 2 types of 5-alpha reductase, type I and type II. Finasteride selectively inhibits type II 5-alpha-reductase, which is found in the prostate, seminal vesicles, epididymides, and liver. Type II 5-alpha reductase is responsible for up to two-thirds of circulating DHT. The recommended dosing for finasteride is 5mg once a day. Dutasteride inhibits type I (primarily found in the skin and liver) and type II 5-alpha reductase, thereby relieving symptoms and reducing bladder outlet obstruction. The recommended dosing for dutasteride is 0.5mg once daily.

- The thought of how BPH can cause overactive bladder is the strain on the bladder causes ischemia, hypoxia leading to scarring, thickening, hypertrophy leading to dysfunction.

- Some with BPH/LUTS may also have irritative symptoms such as frequency, urgency, and incontinence related to an overactive bladder. Bladder contractions are stimulated by acetylcholine effects on muscarinic receptors in smooth muscle of the bladder. A randomized trial in patients with moderate to severe irritative symptoms, as least a mod. Bother score, and urgency found that combination therapy with an anticholinergic agent with antimuscarinic effects (tolterodine) plus an alpha-1-adrenergic antagonist (tamsulosin--Detrol) was reasonably safe with few episodes of urinary retention. Combination therapy was more effective than tamsulosin alone. Use of antimuscarinic agents should be restricted to men with low post-void residual volumes.

- At the same time, other Western herbs were investigated, with most attention falling to pumpkin seeds (*Cucurbita pepo*), nettle root (*Urtica dioica* or *Urtica urens*), bee pollen (particularly that from the rye plant), African potato (tubers of Hypoxis rooperi), and the large high-altitude African tree *Pygeum africanum*, also known as *Prunus africanum* (13, 14). In most cases, but particularly with pumpkin seeds and African potato, the main active components are understood to be the sterols, such as beta-sitosterol, which has been used as a therapeutic agent for BPH by itself (18). Triterpenoids in pygeum have also been proposed to be active components, reducing the swelling of the prostate (17).
- Among the Chinese herbs recommended for BPH, the iridoid glycosides may be the active components: these include aucubin from plantago seed, catalpol from rehmannia, and morroniside from cornus (an ingredient in the rehmannia formulas). Iridoids have not been found in the Western herbal therapies for BPH and represent a potential new area for future investigation. Iridoids are the recognized active constituents of the Western herb chaste tree berry, *Vitex agnus costus*, which has been shown to reduce prolactin levels in women (20); elevated prolactin may be a risk factor for prostate enlargement in men. Triterpenoids found in vaccaria and alisma (an ingredient in rehmannia formulas) could contribute to their therapeutic effects, in a manner similar to those suggested for pygeum.

- Recent studies show that PDE-5 is present in prostate and bladder tissue. This coupled with the observation that erectile function declines in men with increasing severity of LUTS prompted an initial evaluation of PDE-5 inhibitors as a treatment for LUTS. McVary and colleagues showed that both the IPSS and the BPH Impact Index were improved in men receiving tadalafil.

- **Effect of Dutasteride on the Risk of Prostate Cancer**
- *Gerald L. Andriole, M.D., David G. Bostwick, M.D., Otis W. Brawley, M.D., Leonard G. Gomella, M.D., Michael Marberger, M.D., Francesco Montorsi, M.D., Curtis A. Pettaway, M.D., Teuvo L. Tammela, M.D., Claudio Teloken, M.D., Ph.D., Donald J. Tindall, Ph.D., Matthew C. Somerville, M.S., Timothy H. Wilson, M.S., Ivy L. Fowler, B.S.N., Roger S. Rittmaster, M.D., for the REDUCE Study Group*
- *Background* We conducted a study to determine whether dutasteride reduces the risk of incident prostate cancer, as detected on biopsy, among men who are at increased risk for the disease.
- *Methods* In this 4-year, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, we compared dutasteride, at a dose of 0.5 mg daily, with placebo. Men were eligible for inclusion in the study if they were 50 to 75 years of age, had a prostate-specific antigen (PSA) level of 2.5 to 10.0 ng per milliliter, and had had one negative prostate biopsy (6 to 12 cores) within 6 months before enrollment. Subjects underwent a 10-core transrectal ultrasound-guided biopsy at 2 and 4 years.
- *Results* Among 6729 men who underwent a biopsy or prostate surgery, cancer was detected in 659 of the 3305 men in the dutasteride group, as compared with 858 of the 3424 men in the placebo group, representing a relative risk reduction with dutasteride of 22.8% (95% confidence interval, 15.2 to 29.8) over the 4-year study period (P<0.001). Overall, in years 1 through 4, among the 6706 men who underwent a needle biopsy, there were 220 tumors with a Gleason score of 7 to 10 among 3299 men in the dutasteride group and 233 among 3407 men in the placebo group (P=0.81). During years 3 and 4, there were 12 tumors with a Gleason score of 8 to 10 in the dutasteride group, as compared with only 1 in the placebo group (P=0.003). Dutasteride therapy, as compared with placebo, resulted in a reduction in the rate of acute urinary retention (1.6% vs. 6.7%, a 77.3% relative reduction). The incidence of adverse events was similar to that in studies of dutasteride therapy for benign prostatic hyperplasia, except that in our study, as compared with previous studies, the relative incidence of the composite category of cardiac failure was higher in the dutasteride group than in the placebo group (0.7% [30 men] vs. 0.4% [16 men], P=0.03).
- *Conclusions* Over the course of the 4-year study period, dutasteride reduced the risk of incident prostate cancer detected on biopsy and improved the outcomes related to benign prostatic hyperplasia. (ClinicalTrials.gov number, NCT00056407 [ClinicalTrials.gov] .)

- **Dutasteride Gives Mixed Results in Preventing Prostate Cancer**
- Dutasteride lowers the incidence of prostate cancer, but not high-grade tumors, according to a *New England Journal of Medicine* study.
- In a double-blind study designed by dutasteride's manufacturer, some 6700 high-risk men underwent randomization to either daily dutasteride or placebo. At entry, subjects were 50 to 75 years old, had PSA levels between 2.5 and 10 ng/mL, and had had a negative biopsy.
- During 4 years' follow-up, the incidence of biopsy-detected cancer was lower in the treatment group than in controls (20% vs. 25%). The number of high-grade tumors, however, was significantly higher in the treatment group during the last 2 years of follow-up.
- An editorialist concludes that the 5-alpha-reductase inhibitors like dutasteride "do not prevent ... but merely temporarily shrink tumors that have a low potential for being lethal." He adds that, because the drugs suppress PSA levels, "men may have a false sense of security," thus delaying diagnosis.

- Risk of TURP—ED is ~10-20% but can be up to 70% in some trials. Retrograde ejaculation 57%.
- The risk of sexual dysfunction is much less with other surgical procedures that are less invasive.

- Discovering the association between the alpha-1 antagonist tamsulosin (Flomax) and a new complication called intraoperative floppy iris syndrome (IFIS) solved a troublesome mystery for cataract surgeons.Characterized by sudden intraoperative iris prolapse and pupil constriction, IFIS causes a significant increase in surgical complications, particularly when it is not recognized, understood, or anticipated. Some complications have been sight-threatening, including severe iris defects associated with permanent pupil deformity, glare, and photophobia.
- A recent Canadian study of nearly 100,000 men undergoing cataract surgery during a five-year period found that those taking tamsulosin had 2.3 times the risk of severe postoperative complications, such as retinal detachment and lost lens fragments.[6] There was no increased risk associated with nonselective alpha-1 antagonists in this study.
- Of the three alpha-1 receptor subtypes (A, B, and D), the 1A receptor predominates in the iris dilator and prostatic smooth muscle. Among alpha-1 antagonists commonly used to treat benign prostatic hyperplasia (**BPH**), including terazosin (formerly Hytrin), doxazosin (Cardura), and alfuzosin (Uroxatral), only tamsulosin is subtype selective and demonstrates the highest affinity for the alpha-1A receptor.
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- In October 2008, the U.S. Food and Drug Administration approved a new alpha-1 antagonist, silodosin (Rapaflo), for the treatment of **BPH** symptoms. Compared with others in this drug class, it most resembles tamsulosin because it is also highly selective for the alpha-1A receptor subtype. However, its relative propensity to cause IFIS is unknown at this time.
- Another unexpected and remarkable finding is that IFIS can occur more than one year after tamsulosin has been discontinued

- Considering the prevalence of cataracts and **BPH**, many ophthalmologists worry about the prospect of increasing numbers of challenging IFIS cases as the population ages. Cataract surgery has long been the most frequent operation performed in the United States, and even before direct-to-consumer advertising, tamsulosin was the most widely prescribed medical treatment for **BPH**.
- Since intraoperative floppy iris syndrome (IFIS) was first described in 2005, its association with the systemic alpha-1 adrenergic antagonist, tamsulosin (Flomax®, Boehringer-Ingelheim Pharmaceuticals, Inc., Ridgefield, CT), has become well established [1-7]. The clinical manifestations of IFIS complicating cataract surgery are poor preoperative pupil dilation, iris billowing and prolapse, and progressive intraoperative miosis [1]. In one prospective study, 90% of 167 eyes from patients taking tamsulosin exhibited some degree of IFIS during cataract surgery [5]. Tamsulosin is the only systemic alpha-1 antagonist which is selective for the alpha-1A receptor subtype [8]. IFIS has also been reported with non-subtype specific alpha-1 adrenergic antagonists, such as terazosin (Hytrin®; Abbott Laboratories, Inc., North Chicago, IL), doxazosin (Cardura®; Pfizer Inc, New York, NY), and alfuzosin (Uroxatral®; Sanofi-Aventis, Paris, France). However, several prospective and retrospective studies suggest that IFIS is more likely to occur with tamsulosin than with the non-specific alpha-blockers [1-3, 6, 9]. Tamsulosin and alfuzosin are considered to be uroselective and less likely to cause postural hypotension [7].
- A number of studies confirm that cataract surgical complications are increased when IFIS is not anticipated or recognized by the

- The AOA has been asked by the American Society of Cataract & Refractive Surgery (ASCRS) and the American Academy of Ophthalmology (AAO) to cooperate in the education of health care providers who may be involved in this issue.
- In a patient with a known diagnosis of cataract, prescribing physicians may wish to consider involving the patient's cataract surgeon prior to initiating non-emergent, chronic tamsulosin or alpha blocker treatment. Options might include an eye exam or having either the patient or the prescribing MD communicate with the cataract surgeon. Patients should also be encouraged to report any prior or current history of alpha-1 antagonist use to their ophthalmic surgeon prior to undergoing any eye surgery.

- surgeon [1, 4, 5-7]. The same prospective study of 167 consecutive eyes from tamsulosin patients undergoing cataract surgery showed that when the surgeon was forewarned by a history of tamsulosin use, surgical risks were reduced by using a variety of alternative small pupil management strategies [5]. However, because only experienced high-volume surgeons participated in this multi-center trial, the results may not be representative of the global ophthalmic surgical community at large. Discontinuing tamsulosin prior to cataract surgery did not reduce the severity of IFIS in this prospective trial. Surprisingly, IFIS can occur up to several years after discontinuation of tamsulosin [1, 5].
- According to a 2008 online survey sent to ASCRS members, 95% of the nearly 1000 respondents believe that tamsulosin makes cataract surgery more difficult and 77% believe that it increases the risks of surgery [10]. Specifically, cataract surgeons reported an increased rate of significant iris damage (52% of respondents) and an increased rate of posterior capsule rupture (23% of respondents) in eyes with IFIS during the past two years. Of those respondents with sufficient experience to judge, 90% believe that IFIS is more likely to occur with tamsulosin than with non-specific alpha blockers. Many ophthalmologists (59%) would recommend an ophthalmic evaluation for patients with a history of cataracts or decreased vision prior to initiating treatment with tamsulosin. Nearly two thirds of the respondents would either avoid taking tamsulosin if they themselves had cataracts (41%) or would have their cataract removed first (23%). The former sub-group includes 17% who would still defer cataract surgery, but would take a non-specific alpha-1 blocker instead of tamsulosin.

- December 03rd 2007 Posted to Dr. Brian Lewy- Dr. Jay Stockman
- Television watching has become a national pass time in the United States, and along with it commercial exposure. We often hear, and see new products and drug manufacturers now use this medium to advertise their pharmaceuticals. The problem that often arises is that the viewer does not know what the new drug is used for, or what the drug's side affects are. The commercials, by law must include disclaimers about potential problems with the drug, but the layperson doesn't understand what they mean.
- One such drug is Flomax, which always instructs the viewer to inform his/her eye doctor about the use prior to cataract surgery. What on earth would a prostate drug have to do with a cataract? The answer is Floppy Iris Syndrome.
- Flomax, and drugs like it such as Uroxatrol, Hytrin, Cardura, Proscar and even Saw Palmetto which is over the counter all will cause the Floppy Iris Syndrome. They are all work by blocking Alpha-1A receptors in patients with enlarged prostates. The drugs minimize contraction of the muscle fibers in the prostate. The issue that arises is that these drugs also block these same receptors in the dilating muscles in the iris. This pharmacological reaction prevents the eye from dilating, and results in very poor muscle tone in the iris. Since the constrictor muscles are still functioning well the pupil remains small with a billowing iris body.
- This affected iris then demonstrates a triad of findings. The first is a fluttering iris that billows back and forth in response to the normal aqueous humor flow. It looks like a sail on a boat blowing in the wind. The second is the progressive pupillary constriction during surgery. This requires the use of special iris retractors during surgery. This may also permanently damage the iris and pupil. Special care must be employed during this procedure. The final part of the triad is the most serious. Due to the lack of muscle tone in the iris, when surgery is performed it always gets sucked out the the surgical wound. This is called iris pr0lapse. When it occurs it substantially complicates the procedure. It can lead to disaster if not handled correctly immediately.
- While making the surgeon aware of this drug use is very important, discontinuing its' use prior to surgery does not eliminate the complication. Once the Flomax has been used, the affect on the dilating muscles is permanent. When the drug has been used, special care and preparations must be made prior to any eye surgery. It may also bring with it an increased rate of surgical complications such as vitreous loss, and parts of the natural lens remaining in the eye post surgically.
- In short, any drug that one is taking must always be told to the surgeon during the initial consultation. It can, and often does affect preparation and performance of a surgery.

2248. Grant H. Kenyon Prostate Cancer Detection Act

(a) If a physician and surgeon, during a physical examination, examines a patient's prostate gland, the physician and surgeon shall provide information to the patient about the availability of appropriate diagnostic procedures, including, but not limited to, the prostate antigen (PSA) test, if any of the following conditions are present:

(1) The patient is over 50 years of age.

(2) The patient manifests clinical symptomatology.

(3) The patient is at an increased risk of prostate cancer.

(4) The provision of the information to the patient is medically necessary, in the opinion of the physician and surgeon.

(b) Violation of subdivision (a) constitutes unprofessional conduct and is not subject to Section 2314.