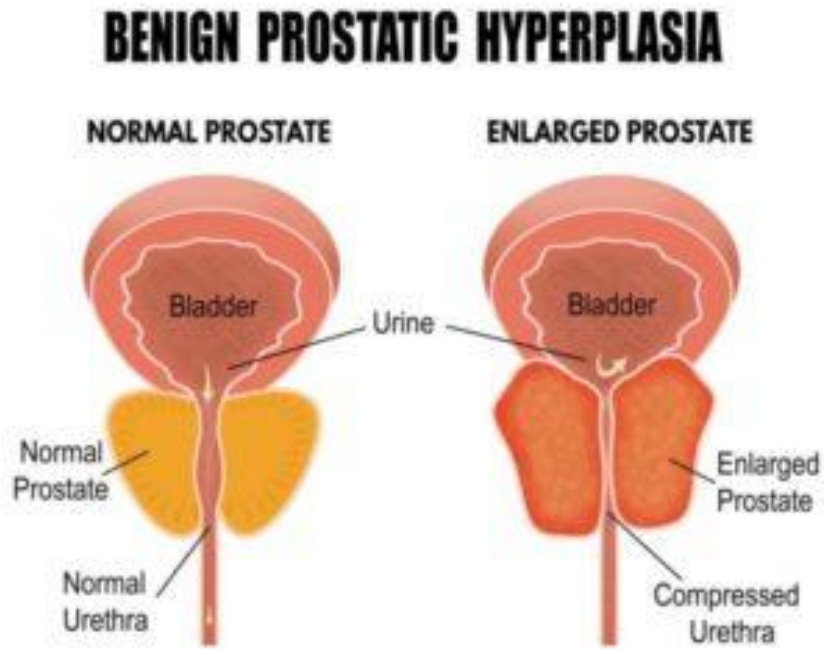
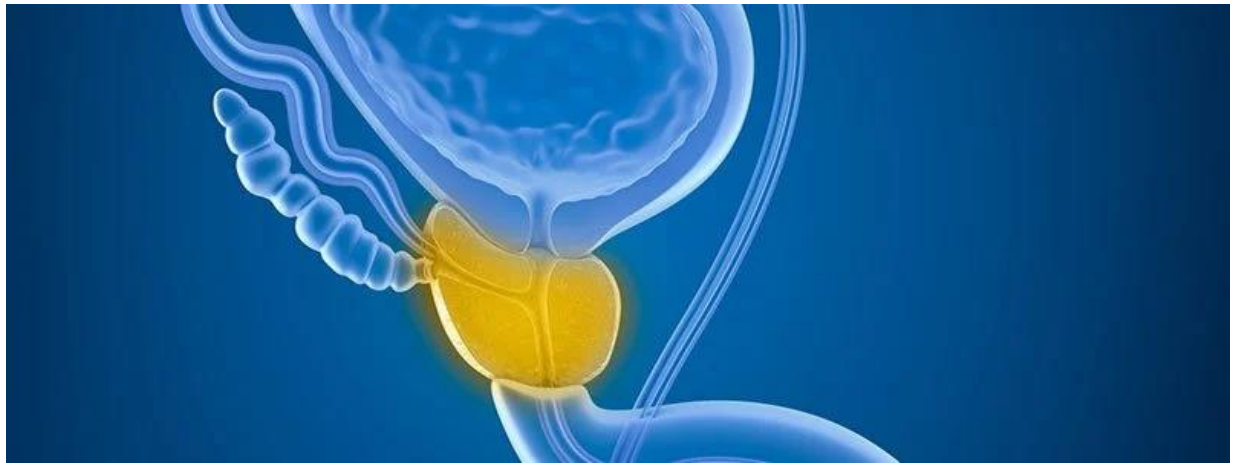
Benign Prostatic Hyperplasia (BPH)





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Objective: Be able to

- Explain pathophysiology and clinical manifestation of BPH
- Explain the mechanism of drug for the treatment of BPH
- Choose appropriate drug for BPH patient

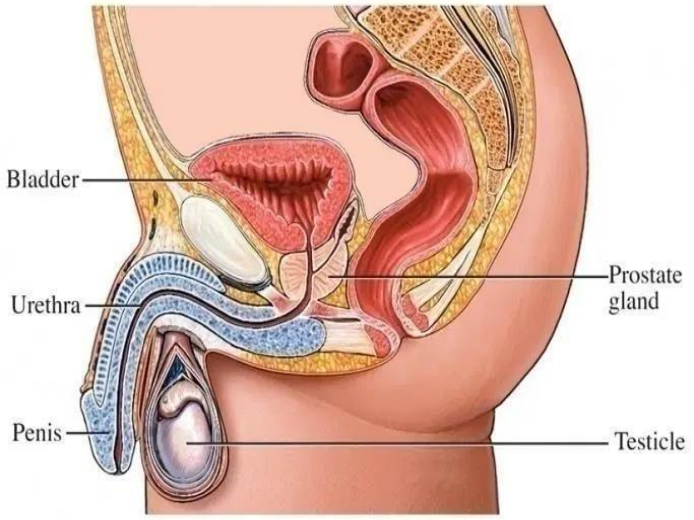
Scope

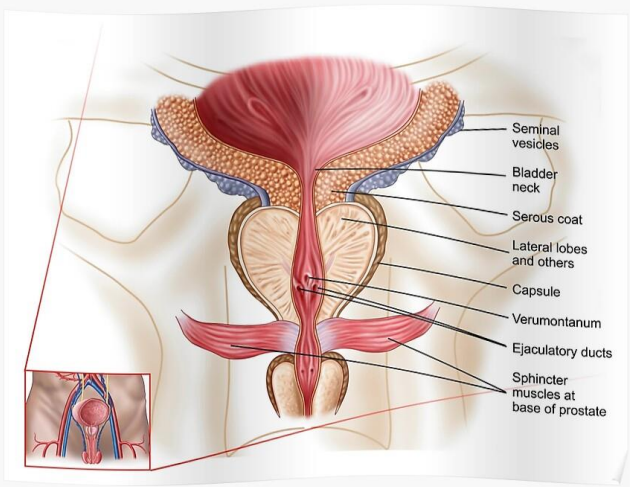
- ❑ Definition and pathophysiology of BPH
- ❑ Clinical manifestation and International prostate symptom score
- ❑ Management for BPH
- ❑ Drug therapy for BPH

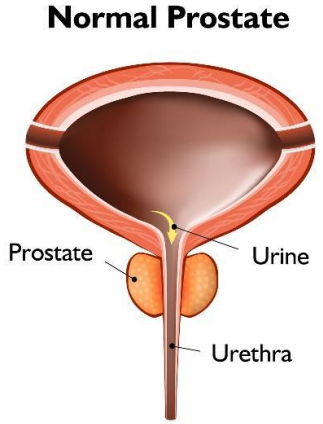
Definition of BPH

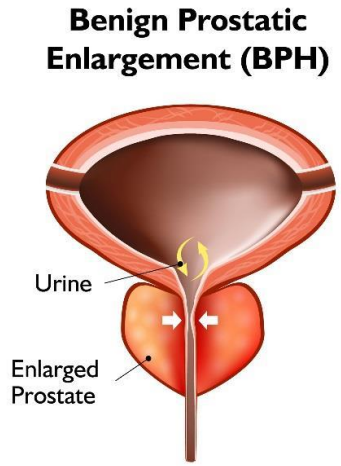
A common, noncancerous enlargement of the prostate gland. The enlarge prostate gland, then, compress the urethra, which courses through the center of the prostate, impeding the flow of urine from the bladder through the urethra to the outside.

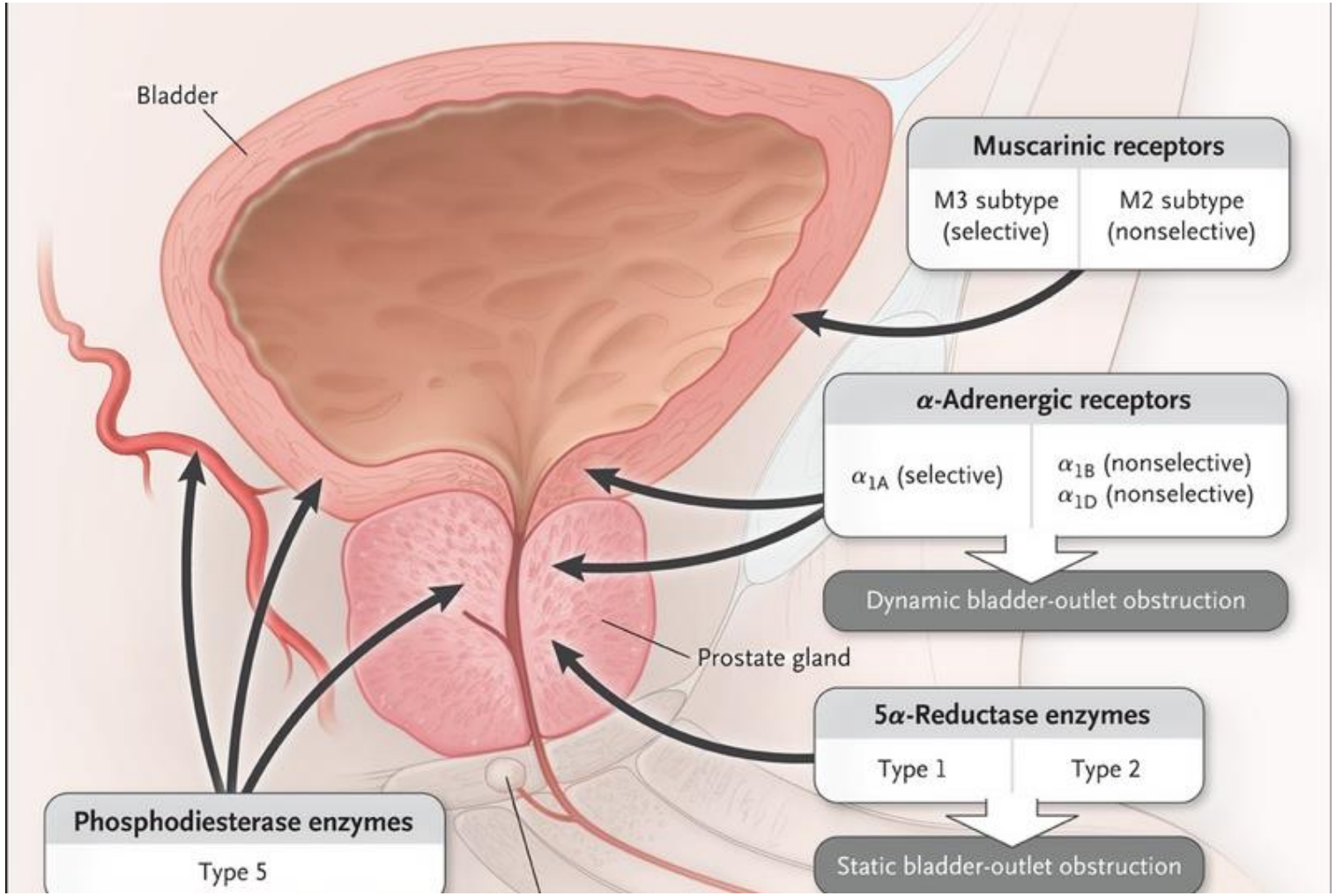
Benign prostatic hyperplasia sometime is called “Benign Prostatic Hypertrophy”





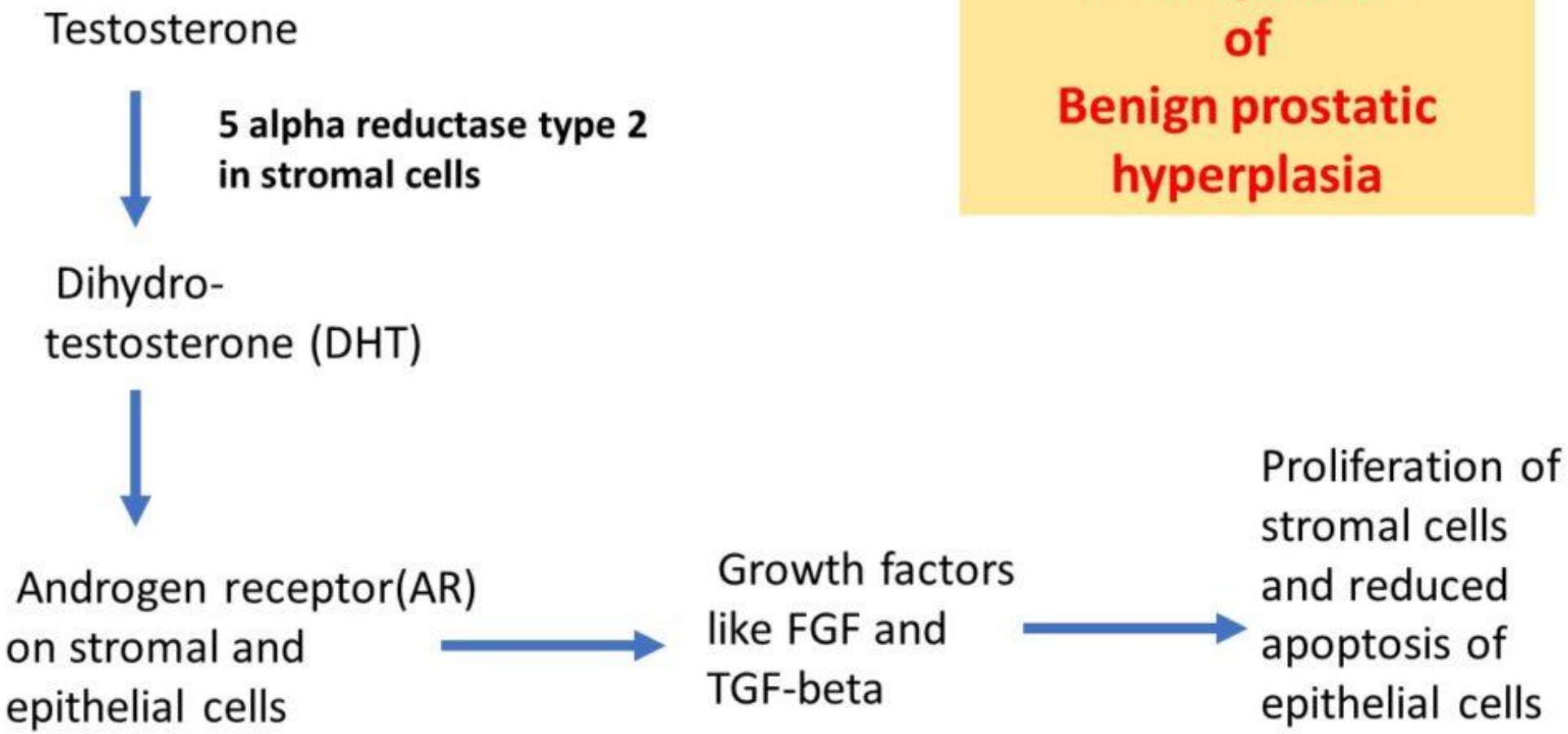






Receptors and Enzyme system in the prostate

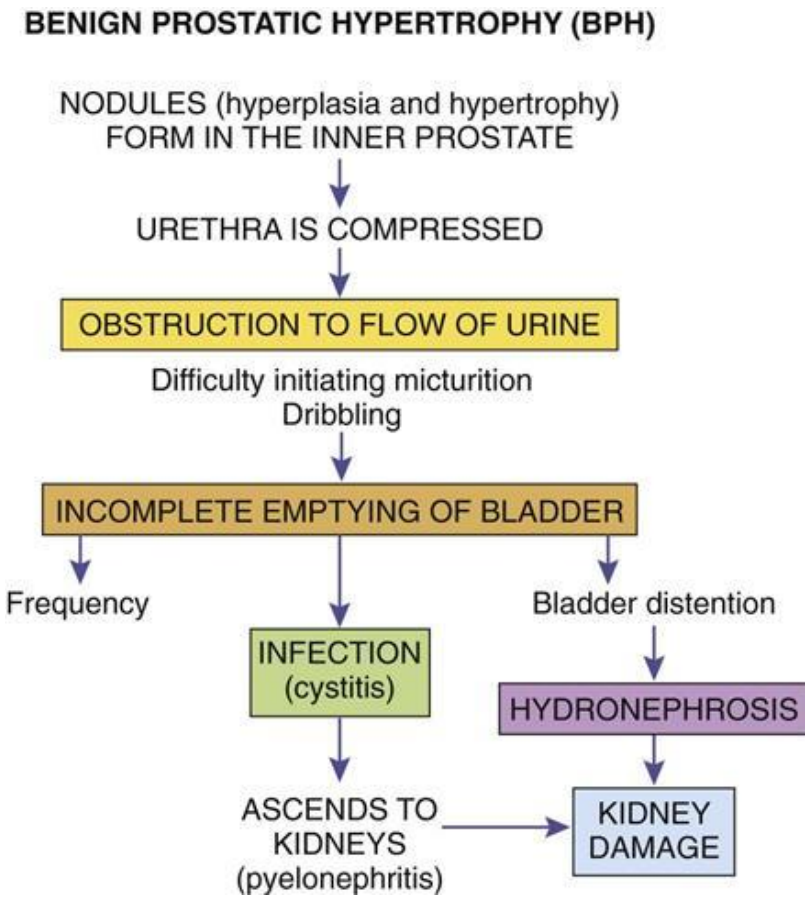
Pathogenesis of Benign prostatic hyperplasia



New Hypothesis

- BPH is caused by malfunction of the valves in the internal spermatic vein manifesting as varicocele
  - Elevated venous pressure causes hypertrophy and exposure to high concentration of free testosterone causes hyperplaisa of prostate
- Involvement of adrenergic nerves in prostatic hyperplasia.
- Cytokines derived from inflammatory cells also induce epithelial growth factors

Consequences and Complications



- **Complications**
  - Hematuria
  - Urinary tract infections
  - Acute urinary retention
  - Urinary incontinence
  - Upper urinary tract deterioration
  - Bladder stone

Clinical Manifestation

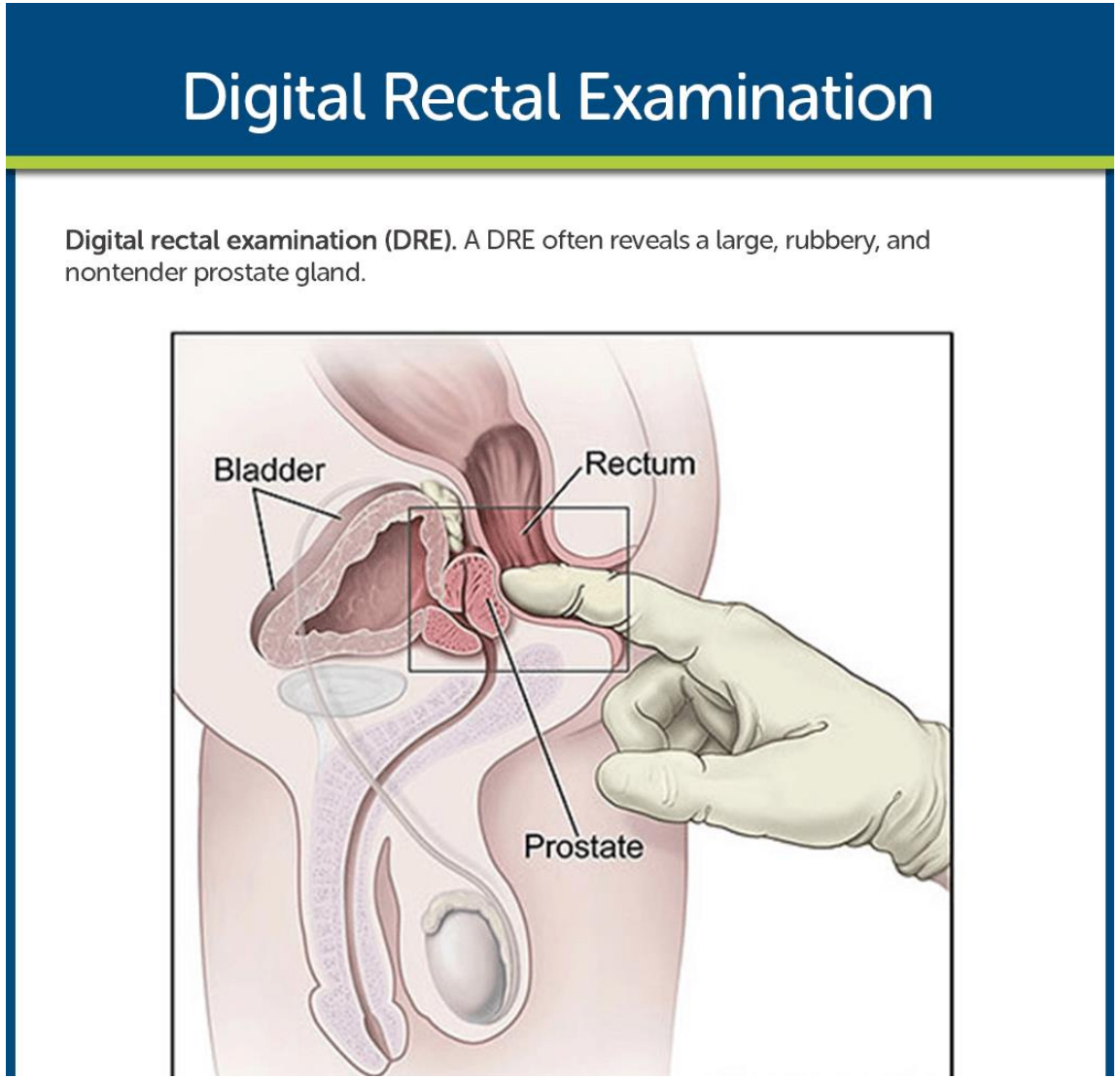
อาการที่แสดงถึงความลำบากในการถ่ายปัสสาวะและอาการที่แสดงออกของการระคายเคืองกระเพาะปัสสาวะ (Obstructive and irritative symptoms)

- Frequent urination (ปัสสาวะบ่อย)
- Urgency (กลั้นปัสสาวะไม่อยู่)
- Hesitancy (ใช้เวลานานในการเริ่ม)
- Dribbling (ปัสสาวะหยด ไม่พุ่ง)
- Nocturia (ปัสสาวะบ่อยตอนกลางคืน)

- Decrease volume & stream of urination (ปัสสาวะออกมาเป็นลำเล็ก)
- Incontinence (ปัสสาวะเล็ดปัสสาวะลอด)
- Intermittency (ปัสสาวะออกไม่ต่อเนื่อง)
- Burning sensation during urination(ปวด แสบ เวลาปัสสาวะ)

Diagnosis of BPH

- Symptom assessment: The international prostate symptom score (IPSS) is recommended as it is used worldwide
- Digital rectal examination
- Ultrasonography
- Urodynamic analysis
- Serum PSA > 4 ng/ml. : Men with larger prostate have higher PSA level (Prostate specific antigen). PSA also a maker for prostate cancer



Name: **Date:**

International prostate symptom score (IPSS)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
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	

	None	1 time	2 times	3 times	4 times	5 times or more	Your score
Nocturia 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	

Interpretation

0-7 = Mild symptomatic
8-19 = Moderate symptomatic
20-35 = Severely symptomatic

Management for BPH

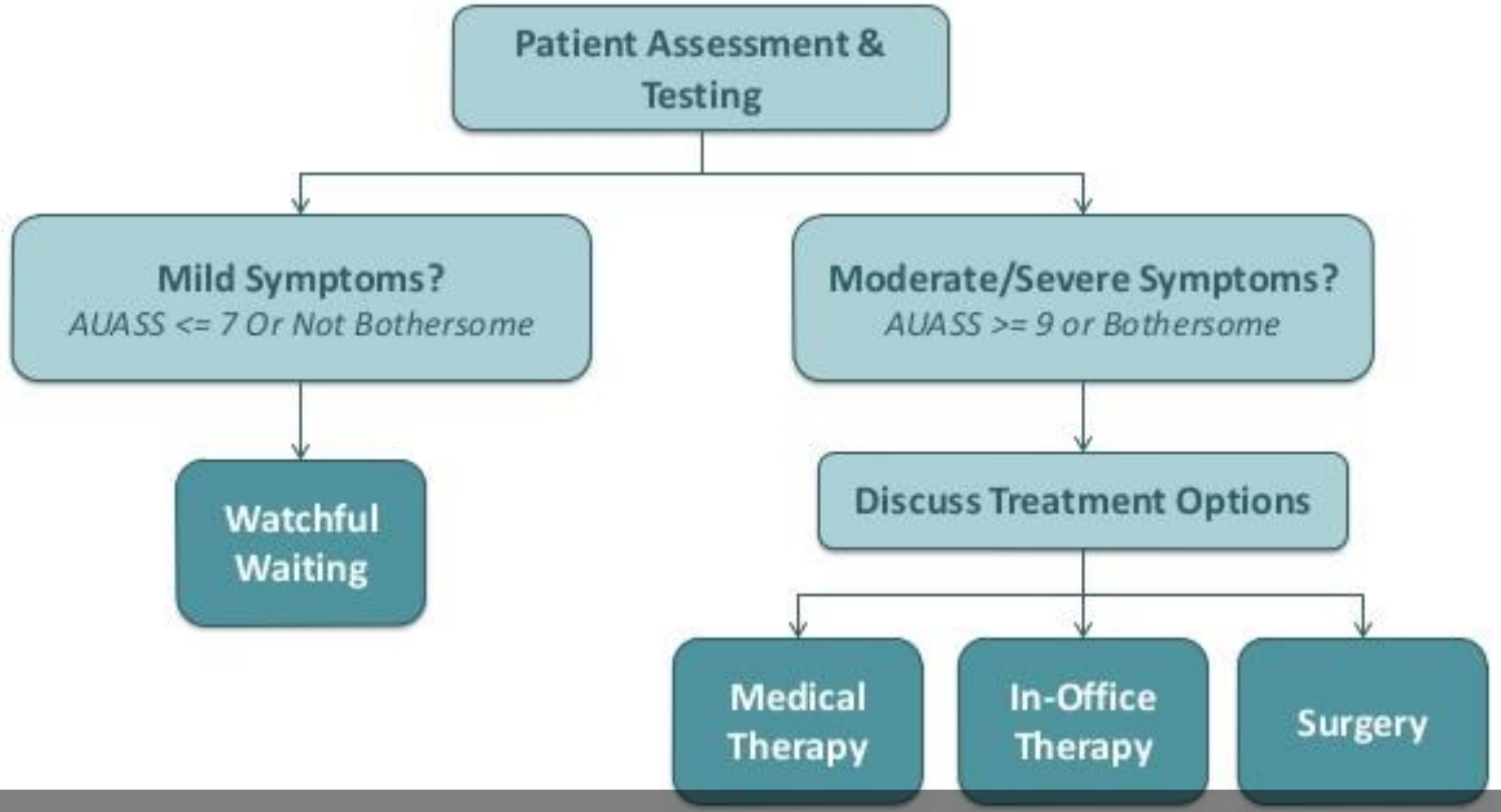
Management

- Watchful waiting
- Pharmacotherapy
- Surgery
- Collaborative care

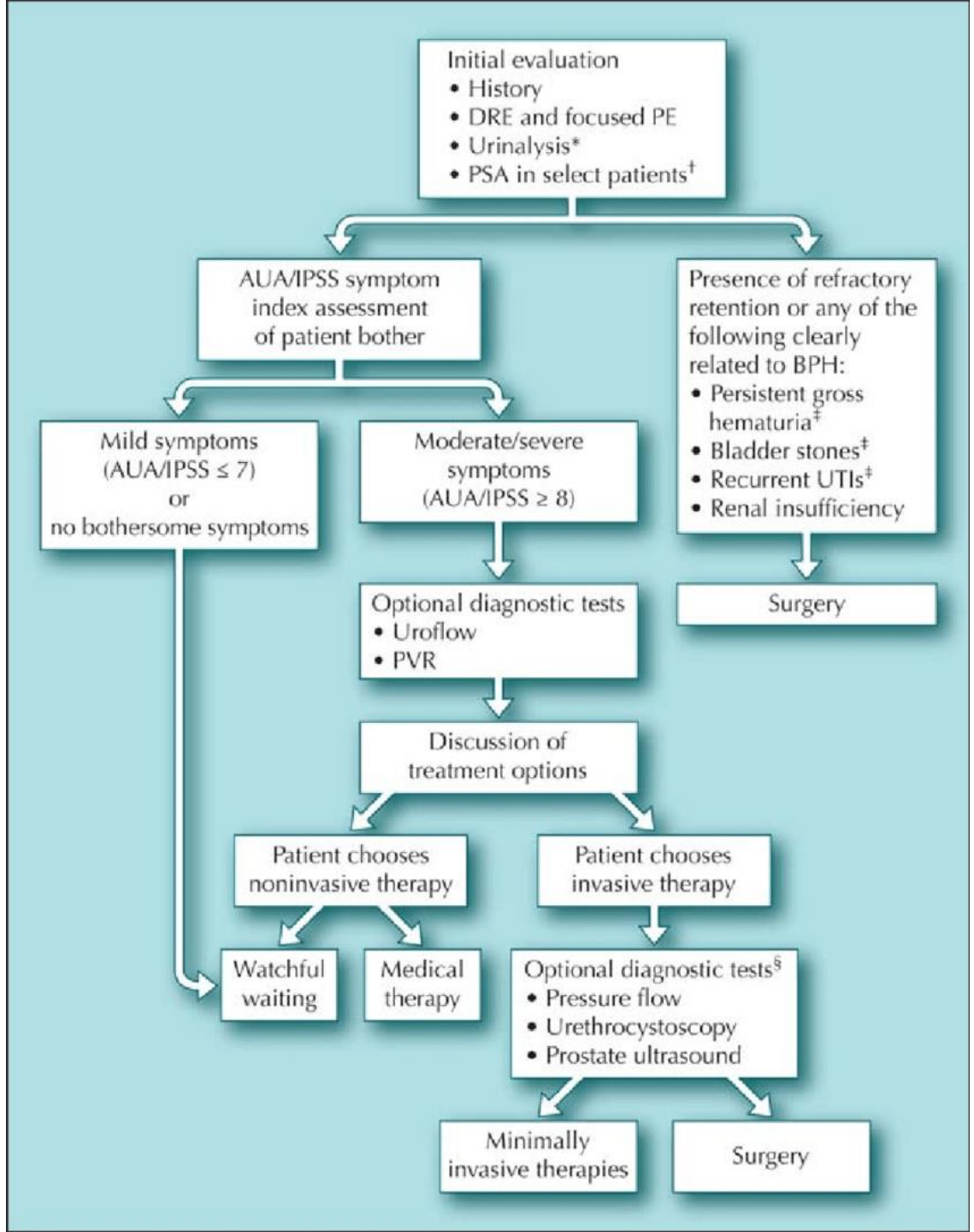
Goals of therapy

- Relief lower urinary tract symptoms and Bladder outlet obstruction
- Restore bladder drainage
- Prevention of complication
- Prevention of disease progression
- Treatment of complication (if any)

AUA Guidelines



AUA = American Urology Association



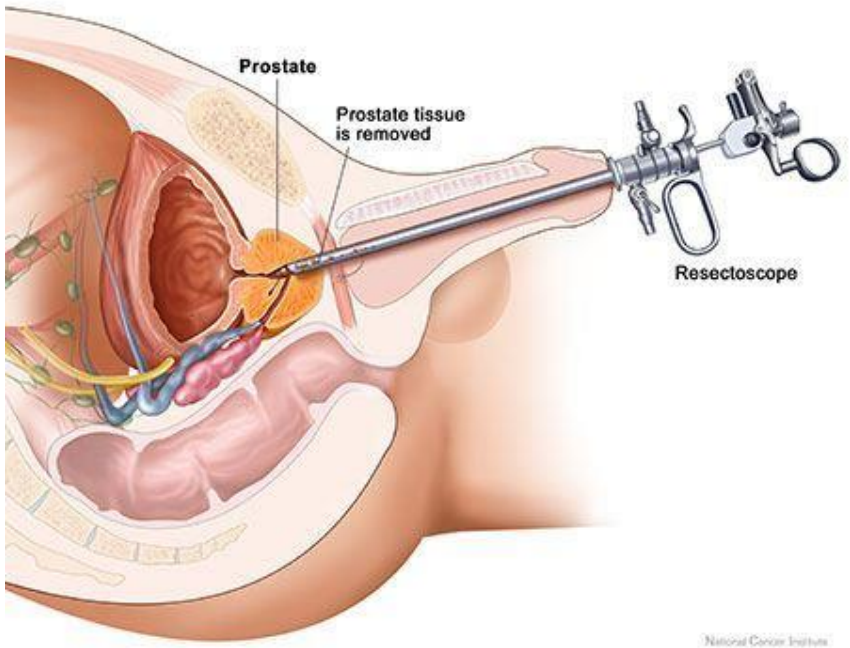
PVR (Post Voidal Residue)

- When voiding function of bladder is impaired it will be manifested as residual urine
- Normal person with no significant obstruction should have residual urine 0 ml
- Any patient with a persistent PVR > 100 ml with no obvious neurogenic cause and association with poor flow rate of 10ml/sec or less, would be suspected to have significant obstruction

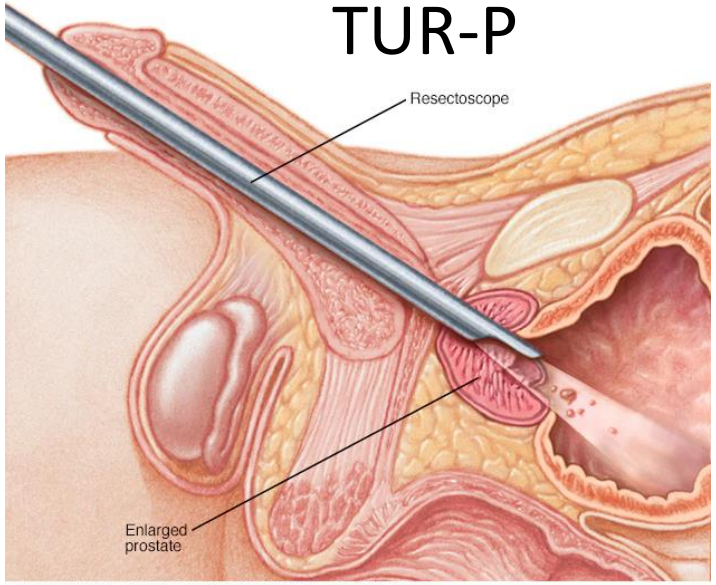
Surgical Treatments

- Transurethral Prostatectomy (TUR-P) ผ่าตัดโดยใส่เครื่องมือเข้าทางท่อปัสสาวะและใช้เครื่องมือตัดชิ้นเนื้อต่อมลูกหมากออก
- Transurethral Incision of the prostate (TUI-P) หัตถการโดยใส่เครื่องมือเข้าทางท่อปัสสาวะแล้วกรีดต่อมลูกหมาก 2-3 รอย โดยไม่มีการตัดชิ้นเนื้อต่อมลูกหมาก ใช้ในกรณีที่ต่อมลูกหมากไม่โตมาก
- Open Prostectomy ใช้กรณีที่ต่อมลูกหมากโตมาก โดยการผ่าตัดผ่านทางหน้าท้องแล้วเอาต่อมลูกหมากออก
- Minimally Invasive Surgery

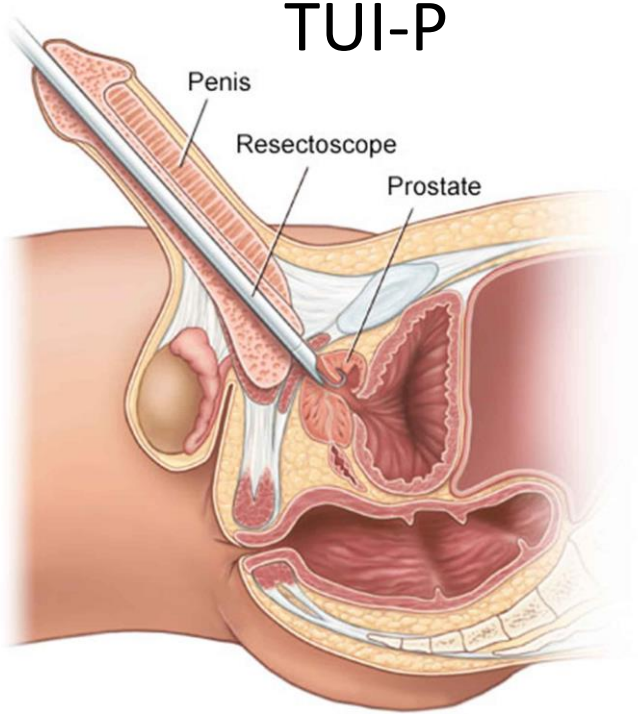
Transurethral resectoscope



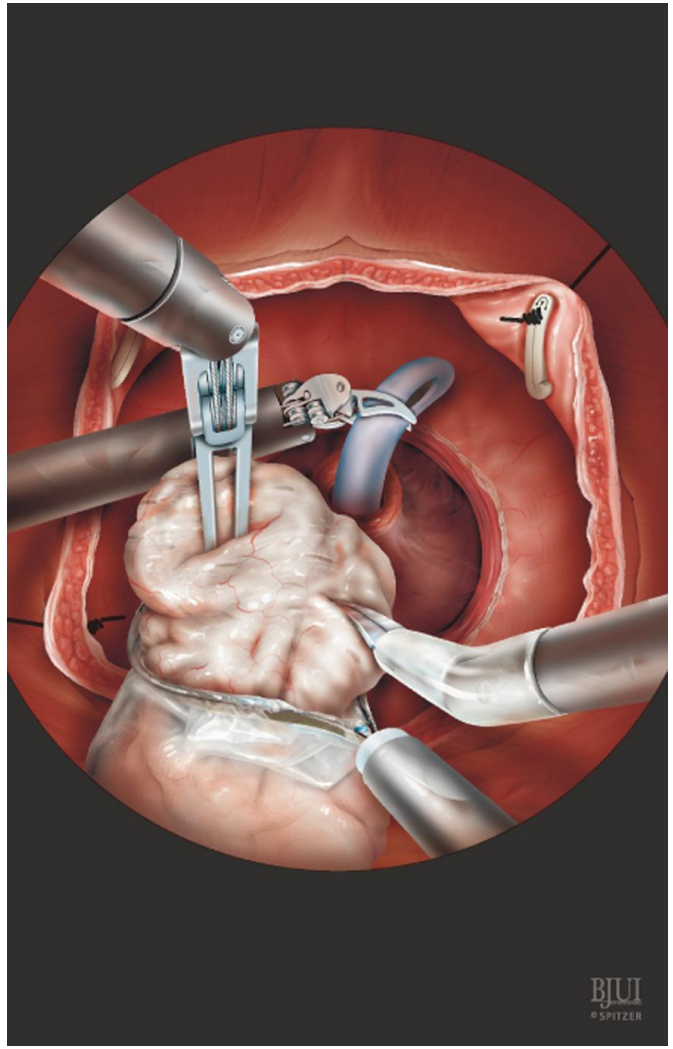
TUR-P



TUI-P



Open prostectomy

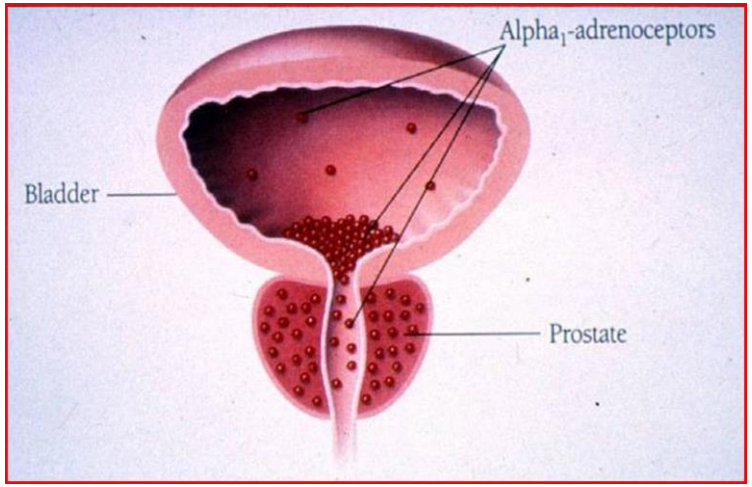


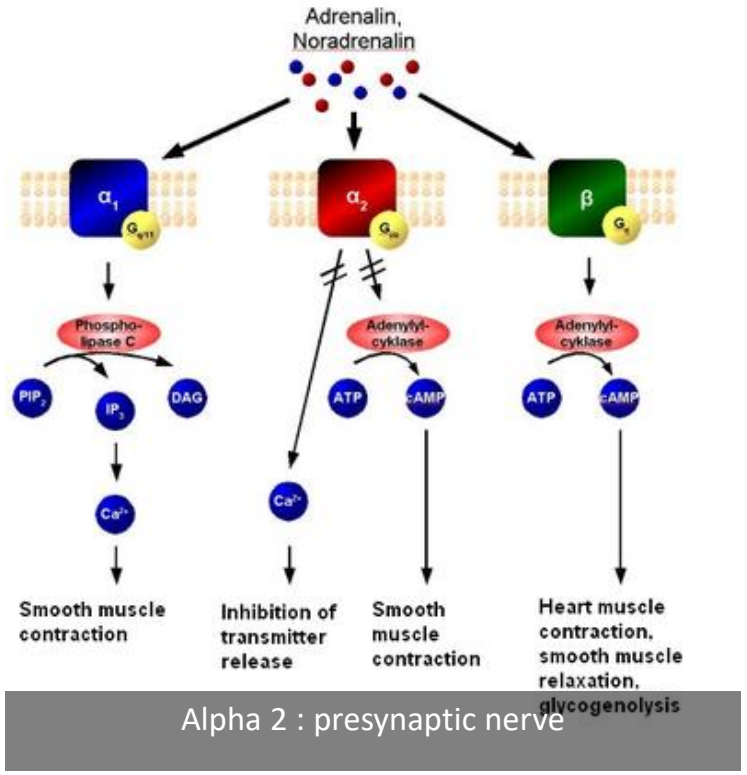
Surgical Treatments

- Minimally Invasive Surgery
  - Prostatic urethral stent เป็นการใส่ตัวค้ำถ่างขยาย (บอลลูน) ให้ปัสสาวะออกได้สะดวกขึ้น เหมาะกับผู้ที่มีอัตราเสี่ยงสูงต่อการผ่าตัด
  - Transurethral microwave thermotherapy (TUMT) ใช้ความร้อนจากพลังงาน microwave ไปทำลายเนื้อ prostate
  - Transurethral needle ablation (TUNA) ใช้พลังงานคลื่นวิทยุ (radio-frequency wave) โดยแทงเข็มผ่าน prostatic urethra ไปทำลายเนื้อ prostate
  - Visual laser ablation of the prostate (VLAP) ใช้พลังงานจาก laser ผ่านทาง probe ที่สอดผ่านท่อปัสสาวะเข้าไปทำให้เกิด coagulation necrosis ของเนื้อเยื่อ prostate
  - Transurethral electrovaporization of the prostate (TVP) ใช้พลังงานจากเครื่องจี้ไฟฟ้ากำลังสูงไปทำลายเนื้อเยื่อ prostate จนเกิด Vaporize

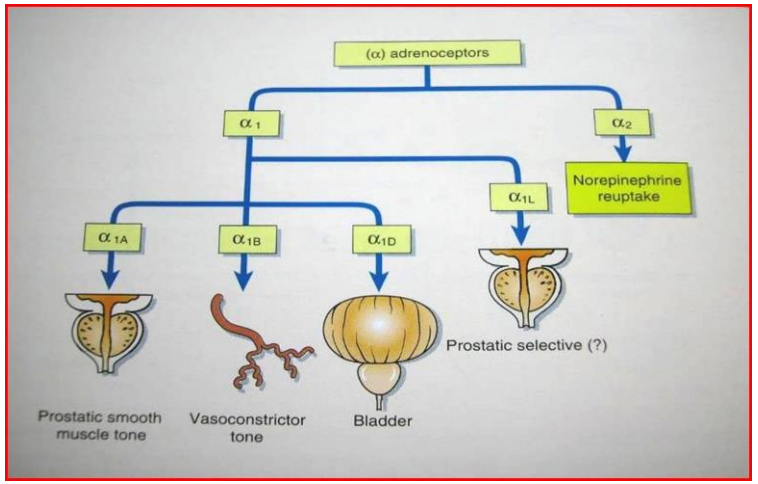
Pharmacotherapy

- Alpha adrenergic blockers: Smooth muscle relaxation → free flow of urine
- 5 alpha reductase inhibitors: inhibit the conversion of testosterone → Dihydrotestosterone → reduce prostate size
- Anticholinergic: for overactive bladder with BPH and overactive bladder after surgery





Alpha 2 : presynaptic nerve



Pharmacotherapy: Alpha adrenoceptors

Pharmacotherapy: Alpha blockers

- Non selective blocker: Phenoxybenzamine
- Selective short acting alpha 1 blockers: Prazosin, Alfuzosin, Indoramin
- Selective long acting alpha 1: Terazosin, Doxazosin, Alfuzosin-SR
- Partially alpha 1a: Tamsulosin, Sildosin
- Partially alpha 1d: Naftopidil, Tamsulosin

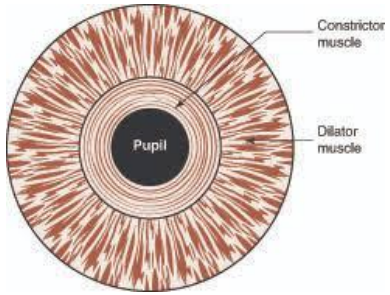
α-ADRENERGIC BLOCKERS

CLASS OF α-ADRENERGIC BLOCKER	DOSE
Nonselective	
Phenoxybenzamine	10 mg bid
Prazosin	2 mg bid
Alfuzosin IR	2.5 mg tid
Long-Acting α1	
Terazosin	5 or 10 mg qd
Doxazosin	4 or 8 mg qd
Alfuzosin SR	10 mg qd
Subtype Selective	
Tamsulosin	0.4 mg qd
Silodosin	8 mg qd

α-ADRENERGIC BLOCKERS

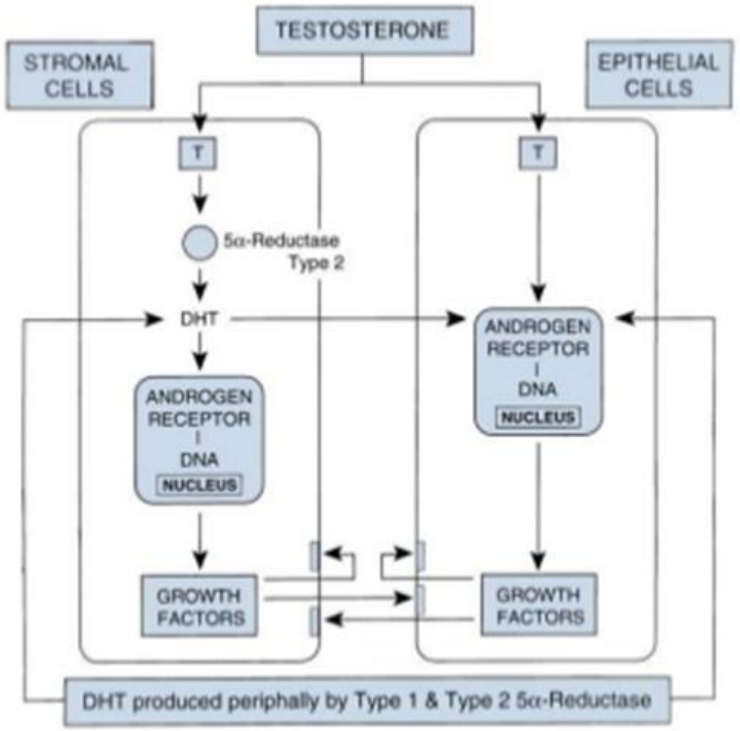
Adverse reactions

- asthenia
- dizziness
- first dose phenomenon
- orthostatic hypotension (requiring dose titration*) with non-subtype-selective blockers*
- ejaculatory dysfunction.
- intraoperative floppy iris syndrome(IFIS) described *with tamsulosin*



IFIS = The relaxes the iris dilator muscle by binding to its post-synaptic nerve endings. Various alpha-blockers are associated with IFIS, but tamsulosin has a stronger association than the others.

Role of Androgen



Pharmacotherapy: 5 alpha reductase inhibitors

5α-reductase inhibitors

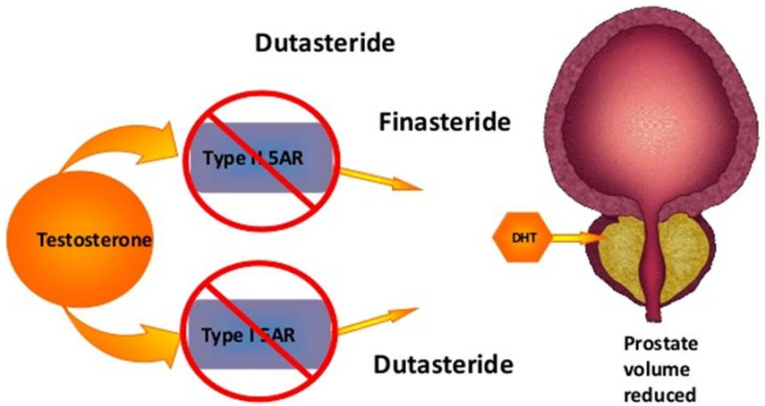
5 alpha Reductase inhibitor

- 5α-reductase is found in 2 types:

  type 1 : found in the prostate, liver and skin

  type 2 : found in the prostate

- finasteride is competetive inhibitor for type 2
- dutasteride is competitive inhibitor for both types
- maximal prostatic volume suppression is achieved after ***6 months***



Bartsch G et al. Eur Urol. 2000;37:367–380.

5α-reductase inhibitors

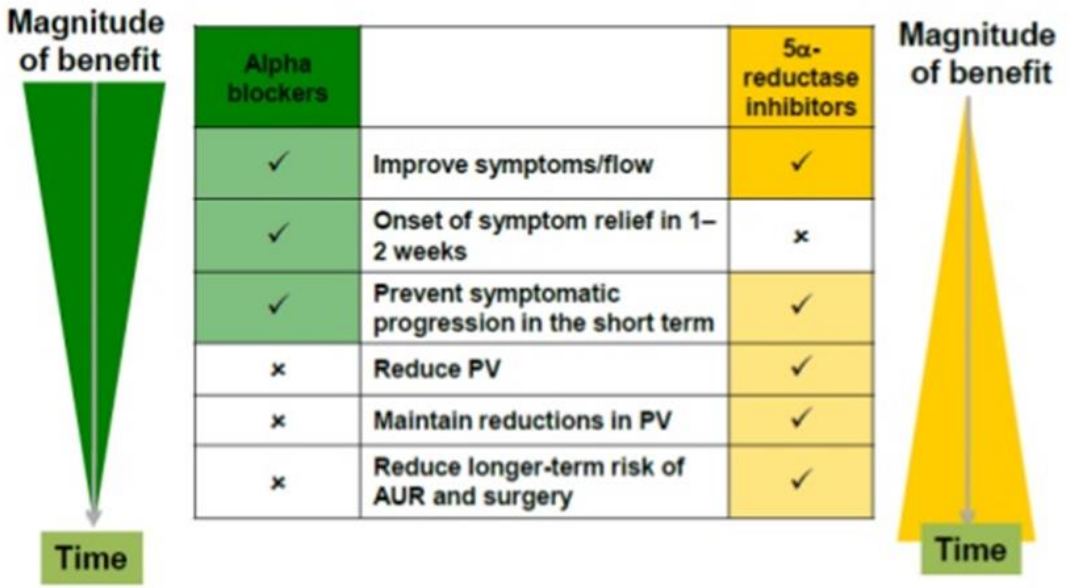
- ***Adverse reactions***
  - Impotence 5-8%
  - Decrease libido 3-7%
  - Decrease in ejaculation 2-4%

Combination Therapy

Combination Therapy with α-Adrenergic Blockers and 5α-Reductase Inhibitors

- combination of dutasteride and tamsulosin was more effective than either drug alone, and reduce the incidence of acute urinary retention.
- Alpha blocker should be withdrawn from combination after the response has been established

Two drug classes with two different patterns of effect



Alpha blockers		5α-reductase inhibitors
✓	Improve symptoms/flow	✓
✓	Onset of symptom relief in 1–2 weeks	×
✓	Prevent symptomatic progression in the short term	✓
×	Reduce PV	✓
×	Maintain reductions in PV	✓
×	Reduce longer-term risk of AUR and surgery	✓

EAU BPH guidelines. Madersbacher S et al. Eur Urol 2004; 46: 547–554
Oelke M et al. EAU guidelines 2012, www.eau.europa.eu accessed April 2012
Roehrborn C *et al.* J Urol 2008;179:616–21

Example of combined therapy
Terazosin + Finasteride
Doxazosin + Finasteride
Tamsulosin + Dutasteride

Benefits and limitations of α-blockers, 5ARIs and their combination

	α-blockers	5ARIs	Combination
Improve symptoms/flow	✓	✓	✓
Onset of symptom relief in 1–2 weeks	✓	✗	✓
Prevent symptomatic progression in the short term	✓	✓	✓
Sustained symptomatic benefit	✗	✓	✓
Reduce prostate volume (PV)	✗	✓	✓
Maintain reductions in PV	✗	✓	✓
Reduce long-term risk of AUR and need for BPH surgery	✗	✓	✓

Medical therapy for BPH/LUTS: current recommendations

	Alpha-blockers	5ARIs	Combination therapy (alpha-blockers and 5ARI)
EAU	For patients with moderate to severe LUTS	For patients with moderate to severe LUTS and an enlarged prostate (>40ml) or elevated PSA (>1.4-1.6µg/l). 5ARIs can prevent disease progression (acute urinary retention and need for surgery)	Should be offered to men with moderate to severe LUTS, enlarged prostates, (>40ml) and reduced Qmax (men likely to develop disease progression). Not recommended for short-term treatment (<1 year)
AUA	For patients with bothersome, moderate to severe LUTS (AUA-SI ≥8)	For patients with LUTS and demonstrable prostate enlargement; may also be used to prevent progression of disease and to reduce the risk of urinary retention and future prostate-related surgery	Appropriate and effective for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, PSA level as a proxy for volume, and / or enlargement on DRE
NICE (UK)	Offer to men with moderate to severe LUTS	Offer to men with LUTS and prostates estimated to be larger than 30 cc or PSA levels >1.4ng/mL, and who are considered at high risk of progression (e.g. older men)	Consider offering to men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30 g or a PSA level greater than 1.4 ng/mL

EAU = European association of urology AUA = American urology association LUTS = Lower urinary tract symptoms

New Trials

- Several new drugs are currently under clinical investigation (phase II-III trials) of which none has been licensed for male LUTS so far. These new drugs target:
  - the prostate, e.g. gonodotrophin-releasing hormone antagonists, oestrogen receptor antagonists,
    - Chlormadinone/allylesternol
    - Zanoterone/Flutamide
  - apoptosis-inducing agents, vaccines, vitamin D agonists, or androgen replacement therapies;
  - the bladder, e.g. β3-adrenoceptor agonists;
  - the nervous system, e.g. neuromuscular blocking agents, tachykinin receptor antagonists.


Discussion
Questions