LONG TERM SAFETY AND EFFICACY OF ALPHA BLOCKERS FOR BPH: THE UROLOGISTS VIEWPOINT

KALYAN KUMAR SARKAR

Benign prostatic hyperplasia (BPH)

- BPH affects **70%** of US men aged 60-69 years, and **80%** of those aged ≥70 years.

- The Boston Area Community Health (BACH) survey demonstrated that LUTS increased from **8%** in men aged 30-39 years to **35%** in men aged 60-69.

- European and Korean UrEpik study reported that the prevalence of male LUTS increased **10%** per decade from 40-79 years of age.

- Roos 1989, New England Journal of Medicine
  - Mortality and Morbidity after transurethral and open prostatectomy

TU OR NOT TU:

THAT IS THE QUESTION !!

"Urologists are a quiet and unassuming group, proud of their contribution to medicine and endoscopic surgery : into their still pond has rolled in a boulder!"

EDITORIAL, LANCET 1989

A TRIUMPH FOR TRANSLATIONAL MEDICINE

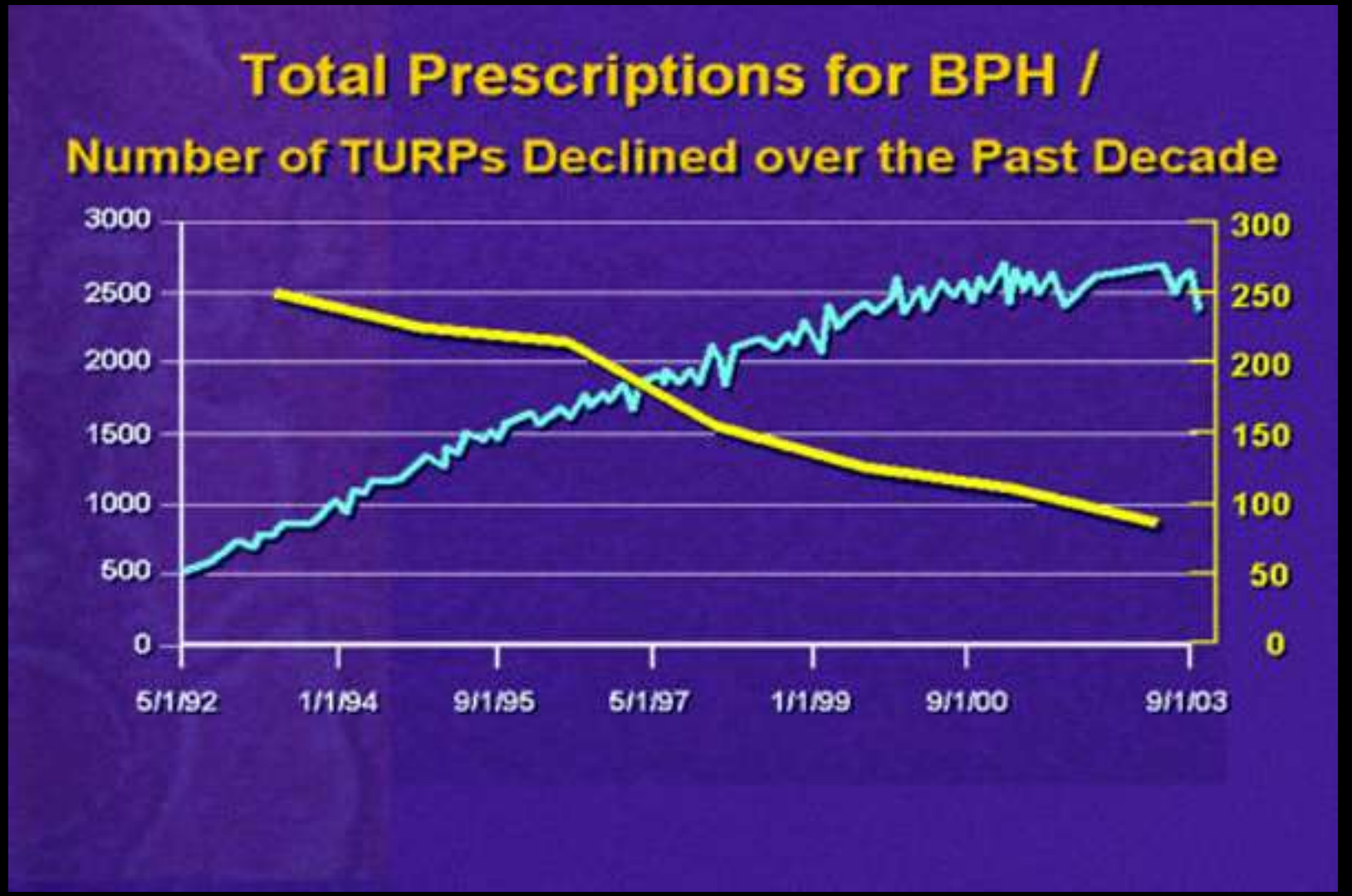
- . Caine M, Raz S, Zeigler M. Adrenergic and cholinergic receptors in the human prostate, prostatic capsule and bladder neck. Br J Urol. 1975;27:193–202.
- **Abstract**
- The adrenergic and cholinergic receptors of the human prostatic capsule, prostatic "adenoma", and bladder neck, were investigated by the in-vitro isometric technique. The prostatic capsule was found to be very rich in both alpha-adrenergic receptors and cholinergic receptors. The prostatic adenoma was moderately rich in alpha-adrenergic receptors, but cholinergic receptors were absent. Beta-adrenergic receptors were absent in the prostatic adenoma, and there was an equivocal response in less than half the specimens of the prostatic capsule. An attempt was made to distinguish between the trigonal component at the posterior bladder neck, and the true bladder neck muscle both posteriorly and antero-laterally. The results indicat that the "posterior bladder neck" seen at operation is predominantly trigonal muscle, and is poor in cholinergic receptors. The adrenergic response is variable in the true bladder neck muscle, but is present and strong in the trigonal muscle. This response is characteristically gradual in its development. In view of the findings in this investigation, it is suggested that certain instances of acute retention of urine in prostatic patients are due to over-stimulation of the alpha-adrenergic receptors, particularly those in the prostatic capsule. Similarly, the accepted clinical contraindication to the use of cholinergic drugs for retention in the prostatic patient is supported by the distribution of the cholinergic receptors in the tissues examined.

- Caine M, Pfau A, Perlbert S. The use of alpha adrenergic blockers in benign prostatic obstruction. Br J Urol. 1976;48:255–263

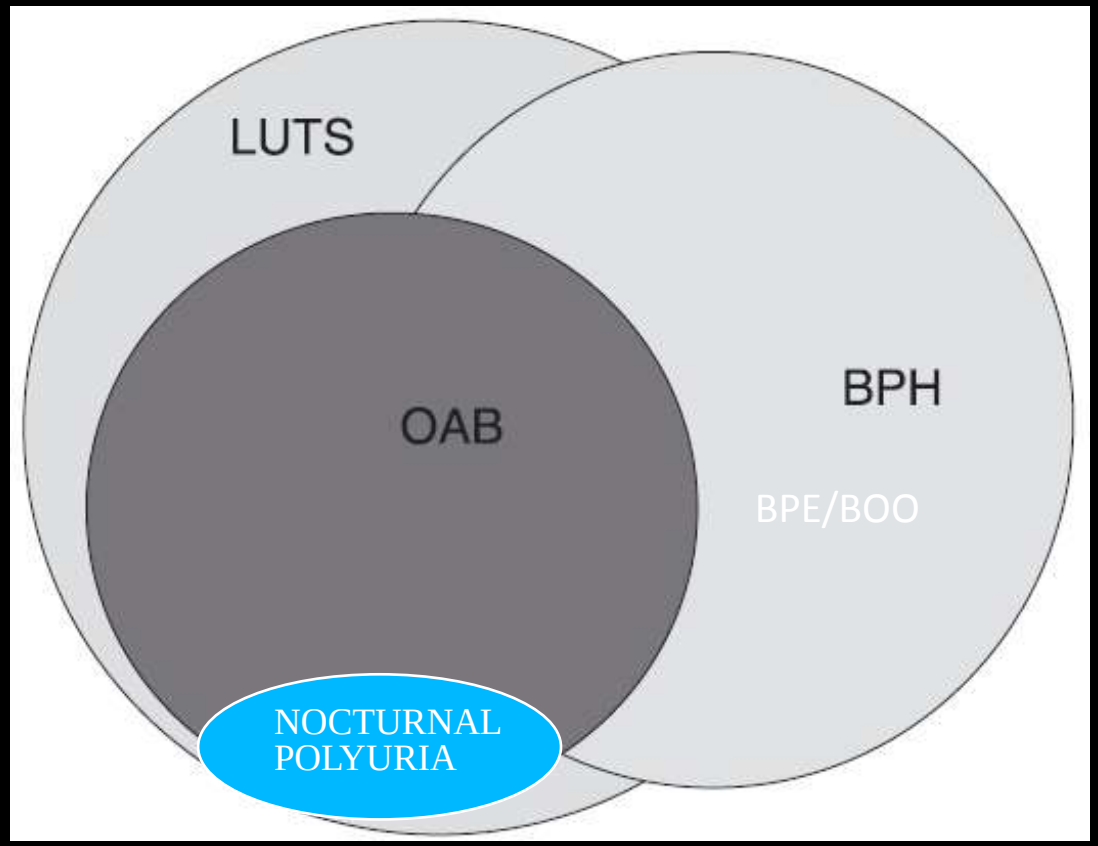
- As a result of previous in-vitro studies on the alpha-adrenergic receptor activity of the human prostate and prostatic capsule a trial was made of alpha-adrenergic blockers for the relief of obstructive prostatic symptoms. Considerable benefit was obtained in several groups of patients, as demonstrated either by the relief or prevention of complete retention, or by diminution in residual urine or improvement in urinary flow-rate recordings. A number of illustrative cases are described, and the indications for the use of this treatment are suggested. It is emphasised that this treatment provides symptomatic relief only, and in no sense purports to be a treatment of the enlarged prostate itself.

- Br J Urol. 1978 Dec;50(7):551-4.
- **A placebo-controlled double-blind study of the effect of phenoxybenzamine in benign prostatic obstruction.**
- Caine M, Perlberg S, Meretyk S.
- **Abstract**
- A double-blind placebo-controlled study of phenoxybenzamine for the symptomatic treatment of benign prostatic obstruction is reported. Statistically significant evidence of an improvement in both the peak and mean flow-rates was found. Both diurnal and nocturnal frequency were significantly diminished. Residual urine was unaffected, and the possible reasons for this are discussed. Urethral pressure recordings confirmed the reduction in the closure pressure in the prostatic segment of the urethra. It was concluded that there was good evidence that the treatment is effective.

Medical management of BPH



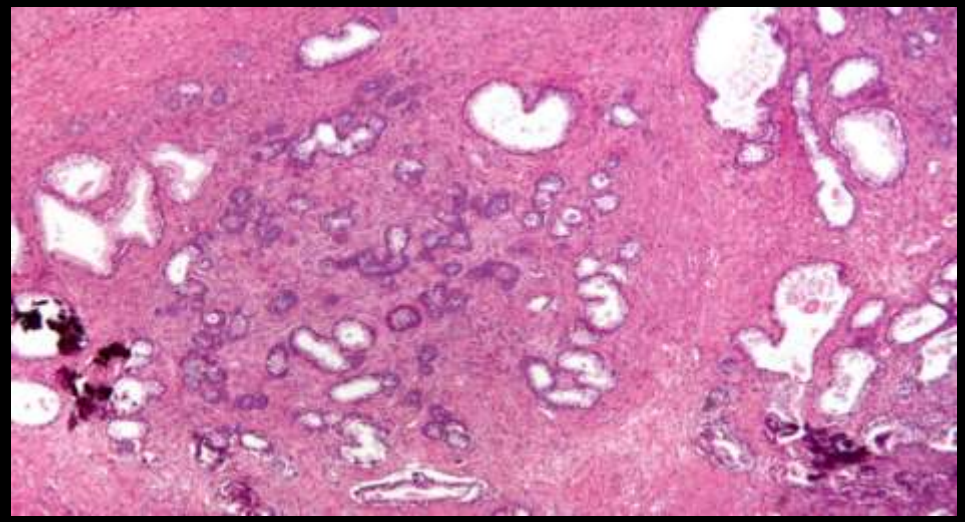
PROSTATISM : BPH/LUTS



McNeal describes two phases of BPH progression.

The first phase consists of an increase in BPH nodules in the periurethral zone

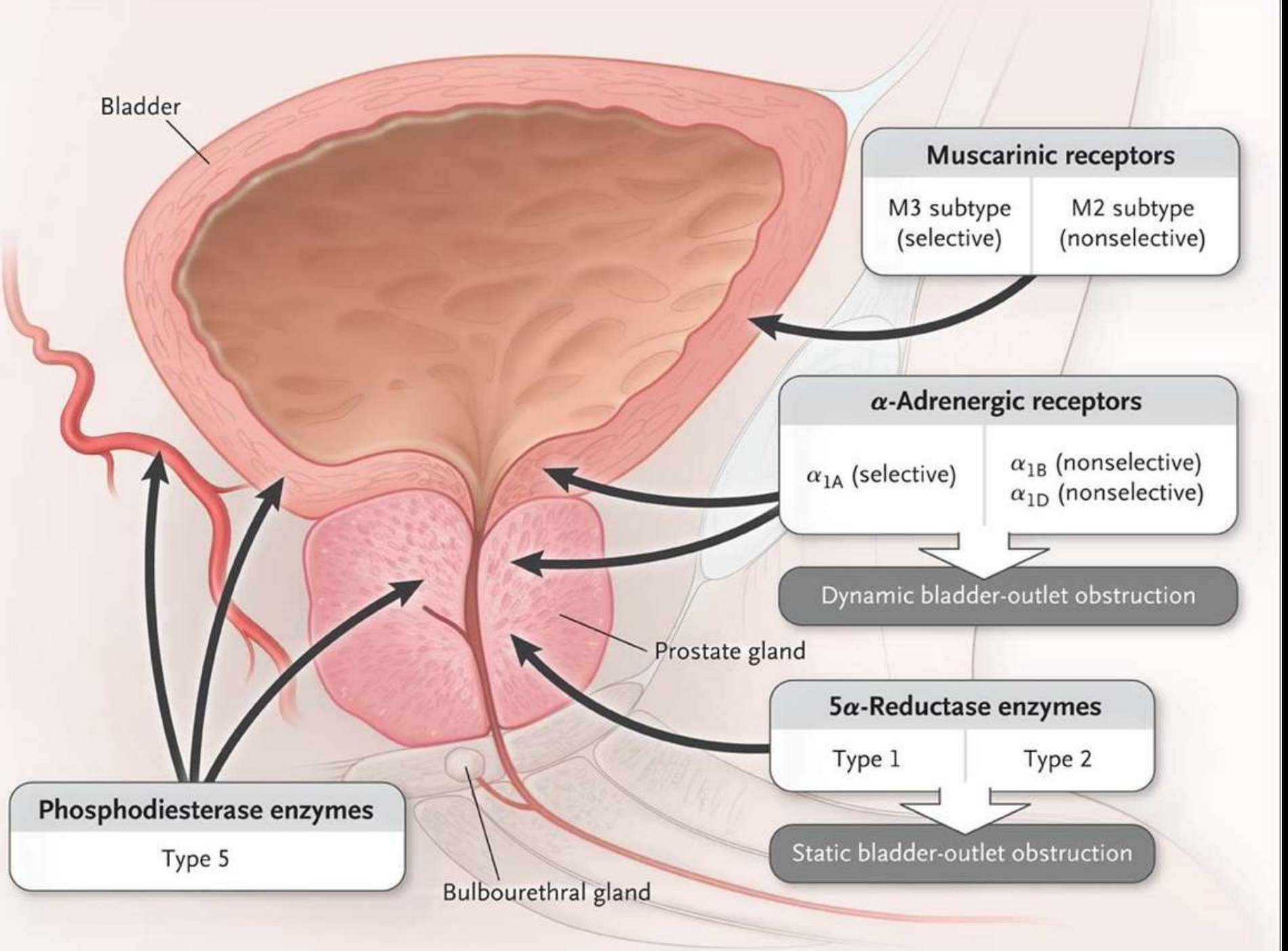
Second a significant increase in size of glandular nodules.

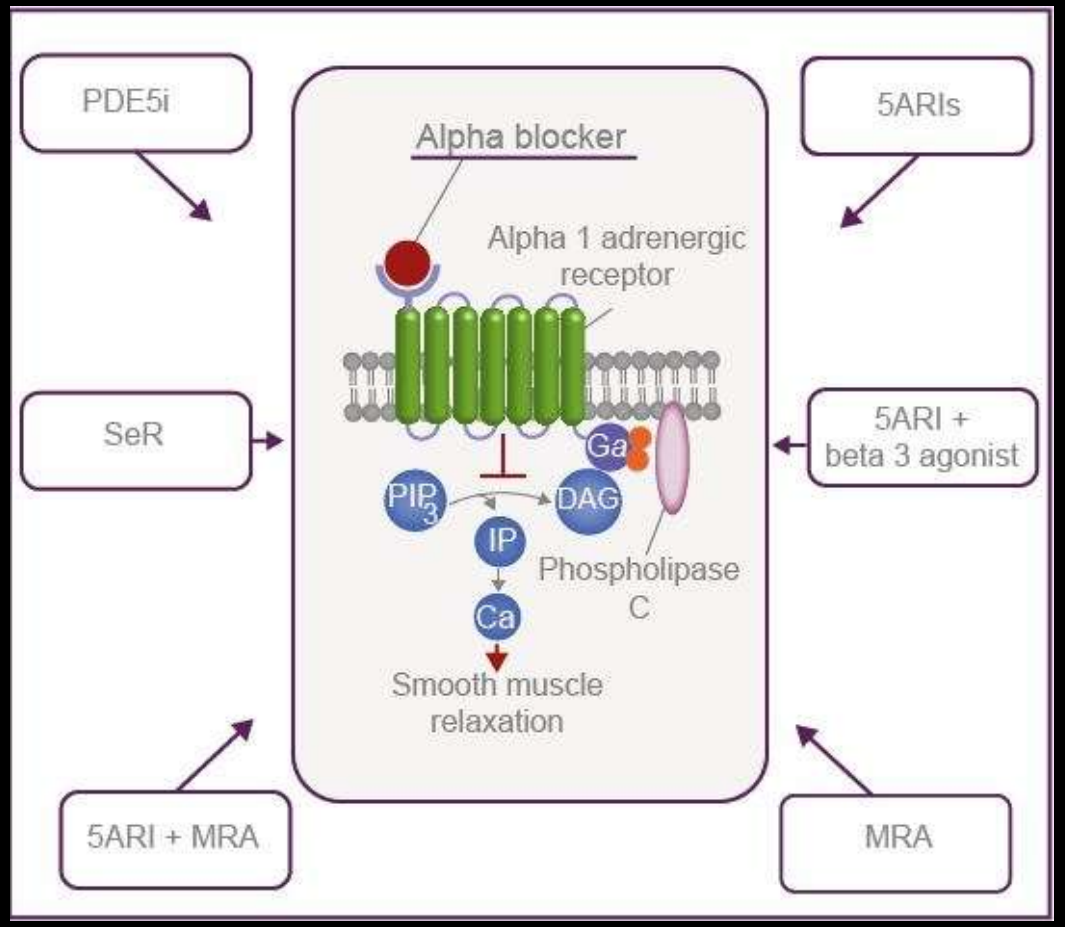


Risk factors for BPH and male LUTS

Non-modifiable	Modifiable
Age	Hormones Testosterone Dihydrotestosterone Estrogen
Genetics	Metabolic syndrome
Geography	Obesity Diabetes Diet
	Physical Inactivity
	Inflammation

Patel and Parsons et al. Indian Journal of Urology, Apr-Jun 2014, Vol 30, Issue 2

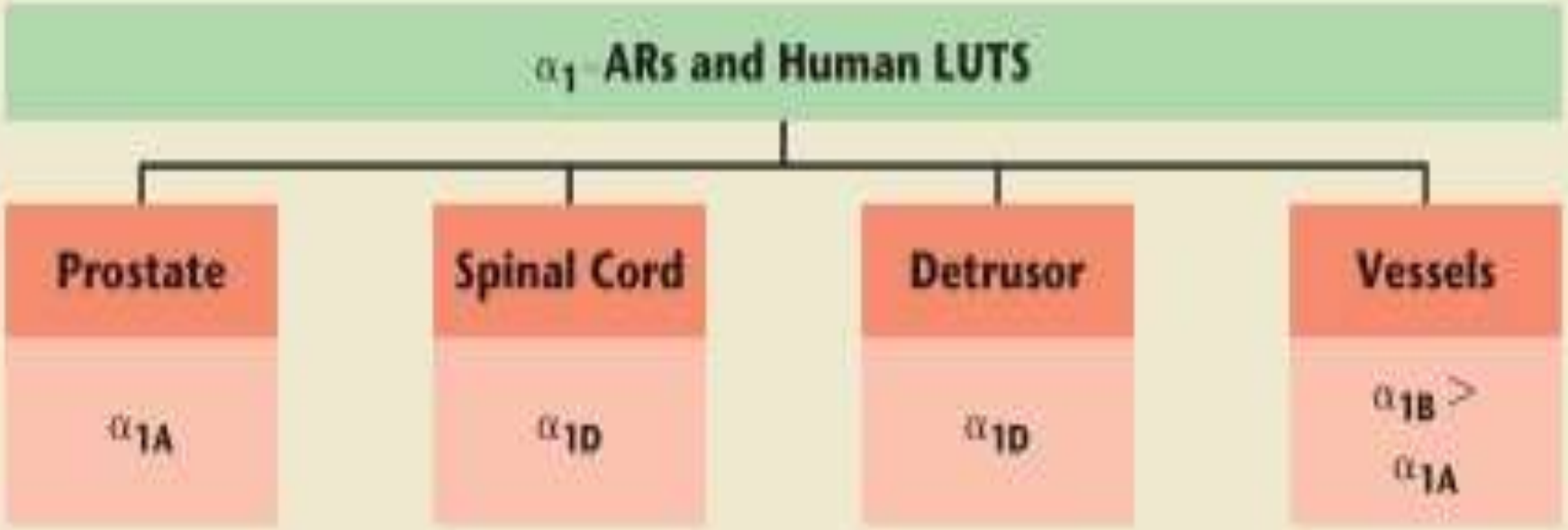

Bladder
Muscarinic receptors
M3 subtype (selective)
M2 subtype (nonselective)
α-Adrenergic receptors
α1A (selective)
α1B (nonselective)
α1D (nonselective)
Dynamic bladder-outlet obstruction
Prostate gland
5α-Reductase enzymes
Type 1
Type 2
Static bladder-outlet obstruction
Phosphodiesterase enzymes
Type 5
Bulbourethral gland


PDE5i
5ARIs
Alpha blocker
Alpha 1 adrenergic receptor
SeR
5ARI + beta 3 agonist
Ga
PIP3
DAG
IP
Phospholipase C
Ca
Smooth muscle relaxation
5ARI + MRA
MRA

α1-Adrenoceptor antagonists (α1-blockers)

Mechanism of action:

- Inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and BOO
  - Michel, M.C., et al. Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. Br J Pharmacol, 2006. 147 Suppl 2: S88..
- However, α1-blockers have little effect on urodynamically determined bladder outlet resistance
  - Kortmann, B.B., et al. Urodynamic effects of alpha-adrenoceptor blockers: a review of clinical trials. Urology, 2003. 62: 1., and treatment-associated improvement of LUTS correlates poorly with obstruction
  - Barendrecht, M.M., et al. Do alpha1-adrenoceptor antagonists improve lower urinary tract symptoms by reducing bladder outlet resistance? Neurourol Urodyn, 2008. 27: 226.
- Thus, other mechanisms of action may also be relevant



- ↓BOO
  - α_{1A} ARs in bladder neck and prostate
- ↓LUTS
  - α_{1A} in bladder neck and prostate smooth muscle
  - α_{1D} in bladder
  - α_{1D} in sensory afferents and central nervous system
- ↓Vascular interaction
  - α_{1B} in blood vessels

α-Adrenergic-Receptor Blockers

- The wide distribution of $\alpha 1_B$ and $\alpha 1_D$receptors in vascular and central nervous system tissues explains their common side effects (e.g., hypotension, fatigue, and dizziness)
- Tamsulosin and silodosin block α_{1A}-adrenergic receptors better than α_{1B}-adrenergic receptors and are considered to be selective for the α_1-receptor subtype, although their side-effect profiles are generally similar to those of the nonselective

Drug	Dose / day	Selectivity
Non Selective		
Prazosin	2-20 mg	$\alpha_{1A} = \alpha_{1B} = \alpha_{1D}$
Doxazosin	1-8 mg	$\alpha_{1A} = \alpha_{1B} = \alpha_{1D}$
Terazosin	1-20 mg	$\alpha_{1B} = \alpha_{1D} > \alpha_{1A}$
Alfuzosin	10 mg	$\alpha_{1A} = \alpha_{1B} = \alpha_{1D}$
Selective		
Tamsulosin	0.4-0.8 mg	$\alpha_{1A} = \alpha_{1D} > \alpha_{1B}$
Silodosin	8 mg	$\alpha_{1A} > \alpha_{1D} \gg \alpha_{1B}$

α1-AR subtype selectivity	
Drug	**α1A / α1B ratio**
Silodosin	162 (Highest selectivity)
Tamsulosin hydrochloride	9.55
Naftopidil	0.372

Clinical Interventions in Aging 2011:6

Table 1. Selected Summary of α-Blocker Efficacy

Agent	Reference	N	Change in Qmax (ml/s)	Change in Boyarsky symptom score	Change in AUA symptom score
Prazosin 2mg bid	Kirby, et al.[18]	55	+4.8*	N/A	N/A
Prazosin 2mg daily	Chapple, et al.[19]	75	+1.6	N/A	N/A
Terazosin up to 10mg daily	Lepor, et al.[20]	285	+1.9*	-2.3*	N/A
Doxazosin 4mg daily	Chapple, et al.[21]	135	+1.5*	N/A	N/A
Doxazosin up to 8mg daily	Fawzy, et al.[23]	100	+2.2*	N/A	-3.2*
Doxazosin up to 12mg daily	Gillenwater, et al.[24]	248	+3.5*	-2.1*	N/A
Tamsulosin 0.4mg daily	Lepor, et al.[25]	756	+1.23*	-1.6*	-2.8*
Tamsulosin 0.4mg daily	Narayan, et al.[26]	735	+0.59*	-1.08*	-3.84*
Tamsulosin 0.4mg daily	Chapple, et al[30]	384	3.53*	N/A	-6.7*
Alfuzosin 10mg daily	Roehrborn, et al.[27]	955	+1.2*	N/A	-2.2*
Silodosin 8mg daily	Marks, et al.[28]	661	+2.8*	N/A	-4.2*
Silodosin 8mg daily	Chapple, et al[30]	381	+3.77*	N/A	-7.0*

* denotes $p<0.05$

Table 6. Pharmacokinetics and Adverse Effects of Medical Treatments for BPH

Agent	T1/2 (hours)	Food Effect	Adverse effects
Doxazosin	22	12% reduction in AUC	Cardiovascular including dizziness, congestive heart failure, peripheral edema, palpitations, chest pain, and tachycardia (25%), floppy iris syndrome
Terazosin	14	None	Dizziness, lightheadedness, palpitations and weakness (30%), floppy iris syndrome
Tamsulosin	5-7	30% decrease in AUC	Decline in blood pressure that can result in dizziness (5-15%), retrograde ejaculation (6%), and rhinitis (12%), floppy iris syndrome. IFIS most associated with tamsulosin use.
Alfuzosin	10	50% increase in AUC when taken with food	
Silodosin	13.3	Should be taken with food	
Finasteride	6	None	Decreased libido (6.4%), erectile dysfunction (8.1%), ejaculatory disorder (0.8%), gynecomastia (0.5%), breast tenderness (0.4%), rash (0.5%)
Dutasteride	5 weeks	10-15% decrease in Cmax	
Oxybutynin	2-3	25% increase in AUC	Dry mouth (71.4%), dizziness (16.6%), constipation (15.1%), somnolence (14%), nausea (11.6%), urinary hesitancy (9.5%), urinary retention (6%)
Tolterodine	3	53% increase in bioavailability	Dry mouth (39.5%), dysuria (1-10%), blurred vision (5%), urinary retention (1.7%)
Darifenacin	13-19	None	Dry mouth (35%), constipation (21%), dyspepsia (9%), UTI (5%), abdominal pain (4%)
Solifenacin	45-68	3% increase in AUC	Dry mouth (28%), constipation (13%), UTI (5%), blurry vision (5%)
Trospium	20	80% decrease in AUC	Dry mouth (20%), constipation (10%), headache (4%)
Sildenafil	4	29% decrease in Cmax	Headache (16%), flushing (10%), dyspepsia (7%), nasal congestion (4%), UTI (3%)
Tadalafil	17.5	None	Headache (15%), dyspepsia (10%), back pain (6%), myalgia (3%), nasal congestion (3%), flushing (3%)
Vardenafil	4-5	18-50% reduction in Cmax	Headache (15%), flushing (11%), rhinitis (9%), dyspepsia (4%), sinusitis (3%)

Data taken from www.drugs.com

Download table as image.

Efficacy:

- Indirect comparisons and limited direct comparisons between α1-blockers demonstrate that all α1-blockers have a similar efficacy in appropriate doses
  - Djavan, B., et al. State of the art on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Urology, 2004. 64: 1081.
- Clinical effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days
  - Barendrecht, M.M., et al. Do alpha1-adrenoceptor antagonists improve lower urinary tract symptoms by reducing bladder outlet resistance? Neurourol Urodyn, 2008. 27: 226.].

Efficacy:

- Controlled studies show that α1-blockers typically reduce IPSS by approximately 30-40% and increase Qmax by approximately 20-25%.
- Considerable improvements also occurred in the corresponding placebo arms . In open-label studies, an IPSS improvement of up to 50% and Qmax increase of up to 40% were documented.
    - Djavan, B., et al. Longitudinal study of men with mild symptoms of bladder outlet obstruction treated with watchful waiting for four years. Urology, 2004. 64: 1144
    - Michel, M.C., et al. Comparison of tamsulosin efficacy in subgroups of patients with lower urinary tract symptoms. Prostate Cancer Prostatic Dis, 1998. 1: 332.]. In open-label studies, an IPSS improvement of up to 50% and Qmax increase of up to 40% were documented
- A recent SR and meta-analysis suggested that Qmax variation underestimates the real effect of α1-blockers on BPO, as small improvements in Qmax correspond to relevant improvements in BOO index in PFS
    - Fusco, F., et al. alpha1-Blockers Improve Benign Prostatic Obstruction in Men with Lower Urinary Tract Symptoms: A Systematic Review and Meta-analysis of Urodynamic Studies. Eur Urol, 2016. 69: 1091.

Efficacy:

- α1-blockers can reduce both storage and voiding LUTS. Prostate size does not affect α1-blocker efficacy in studies with follow-up periods of less than one year, but α1-blockers do seem to be more efficacious in patients with smaller prostates (< 40 mL) in longer-term studies

- McConnell, J.D., et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med, 2003. 349: 2387.
- Boyle, P., et al. Meta-analysis of randomized trials of terazosin in the treatment of benign prostatic hyperplasia. Urology, 2001. 58: 717.
- Roehrborn, C.G. Three months' treatment with the alpha1-blocker alfuzosin does not affect total or transition zone volume of the prostate. Prostate Cancer Prostatic Dis, 2006. 9: 121.
- Roehrborn, C.G., et al. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. J Urol, 2008. 179: 616.
- Roehrborn, C.G., et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur Urol, 2010. 57: 123.].

Efficacy:

- The efficacy of α1-blockers is similar across age groups

  - Michel, M.C., et al. Comparison of tamsulosin efficacy in subgroups of patients with lower urinary tract symptoms. Prostate Cancer Prostatic Dis, 1998. 1: 332

- In addition, α1-blockers neither reduce prostate size nor prevent AUR in long-term studies

  - Roehrborn, C.G. Three months' treatment with the alpha1-blocker alfuzosin does not affect total or transition zone volume of the prostate. Prostate Cancer Prostatic Dis, 2006. 9: 121.
  - Roehrborn, C.G., et al. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. J Urol, 2008. 179: 616.
  - Roehrborn, C.G., et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur Urol, 2010. 57: 123.].

- The efficacy of α1-blockers is similar across age groups . Nevertheless, IPSS reduction and Qmax improvement during α1-blocker treatment appears to be maintained over at least four years.

Tolerability and safety

- Tissue distribution, subtype selectivity, and pharmacokinetic profiles of certain formulations may contribute to the tolerability profile of specific drugs.
- The most frequent adverse events of α1-blockers are asthenia, dizziness and (orthostatic) hypotension.
- Vasodilating effects are most pronounced with doxazosin and terazosin, and are less common for alfuzosin and tamsulosin
    - Nickel, J.C., et al. A meta-analysis of the vascular-related safety profile and efficacy of alpha-adrenergic blockers for symptoms related to benign prostatic hyperplasia. Int J Clin Pract, 2008. 62: 1547.].
- Patients with cardiovascular comorbidity and/or vaso-active co-medication may be susceptible to α1-blocker-induced vasodilatation
    - Barendrecht, M.M., et al. Treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: the cardiovascular system. BJU Int, 2005. 95 Suppl 4: 1].

Tolerability and safety

- In contrast, the frequency of hypotension with the α1A-selective blocker silodosin is comparable with placebo
    - Chapple, C.R., et al. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Eur Urol, 2011. 59: 342.].
- In a large retrospective cohort analysis of men aged > 66 years treated with α1-blockers the risks of falling (odds ratio [OR] 1.14) and of sustaining a fracture (OR 1.16) was increased, most likely as a result of induced hypotension
    - Welk, B., et al. The risk of fall and fracture with the initiation of a prostate-selective alpha antagonist: a population based cohort study. BMJ, 2015. 351: h5398.].

Adverse ocular event

- An termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery
  - Chang, D.F., et al. Intraoperative floppy iris syndrome associated with tamsulosin. J Cataract Refract Surg, 2005. 31: 664.].
- A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all α1-blockers. However, the OR for IFIS was much higher for tamsulosin.
  - Chatziralli, I.P., et al. Risk factors for intraoperative floppy iris syndrome: a meta-analysis. Ophthalmology, 2011. 118: 730.].
- It appears prudent not to initiate α1-blocker treatment prior to scheduled cataract surgery, and the ophthalmologist should be informed about α1-blocker use

LIBIDO ED EjD

- A SR concluded that α1-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but can cause abnormal ejaculation
    - van Dijk, M.M., et al. Effects of alpha(1)-adrenoceptor antagonists on male sexual function. Drugs, 2006. 66: 287.].

LIBID0 ED EjD

- Originally, abnormal ejaculation was thought to be retrograde, but more recent data demonstrate that it is due to a decrease or absence of seminal fluid during ejaculation, with young age being an apparent risk factor.

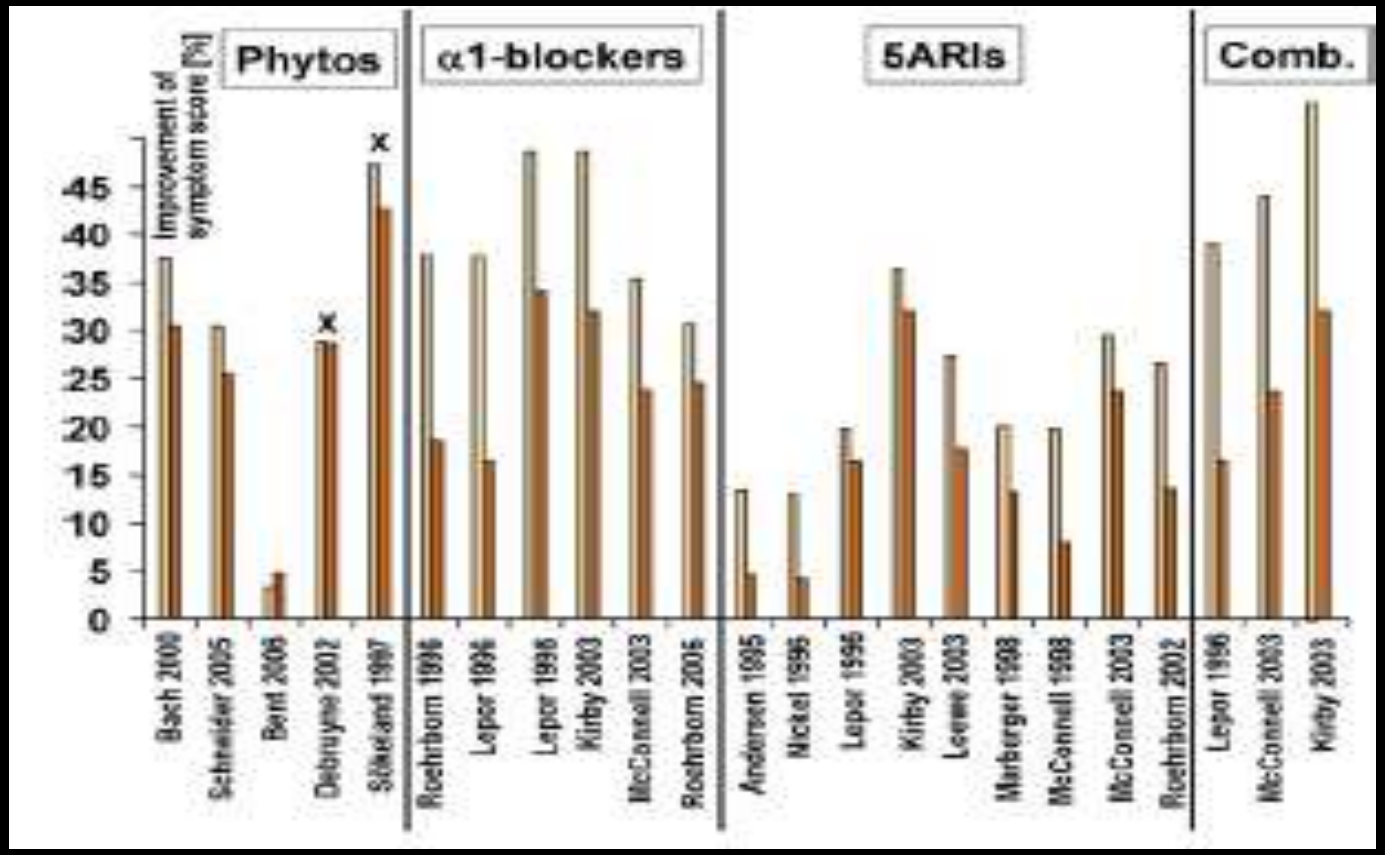
- In a recent meta-analysis ejaculatory dysfunction (EjD) was significantly more common with α1-blockers than with placebo (OR 5.88). In particular, EjD was significantly more commonly related with tamsulosin or silodosin (OR: 8.57 and 32.5) than placebo, while both doxazosin and terazosin (OR 0.80 and 1.78) were associated with a low risk of EjD. In the meta-regression, the occurrence of EjD was independently associated with the improvement of urinary symptoms and flow rate, suggesting that the more effective the α1-blocker is the greater the incidence of EjD.

- Gacci, M., et al. Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis. J Sex Med, 2014. 11: 1554.].

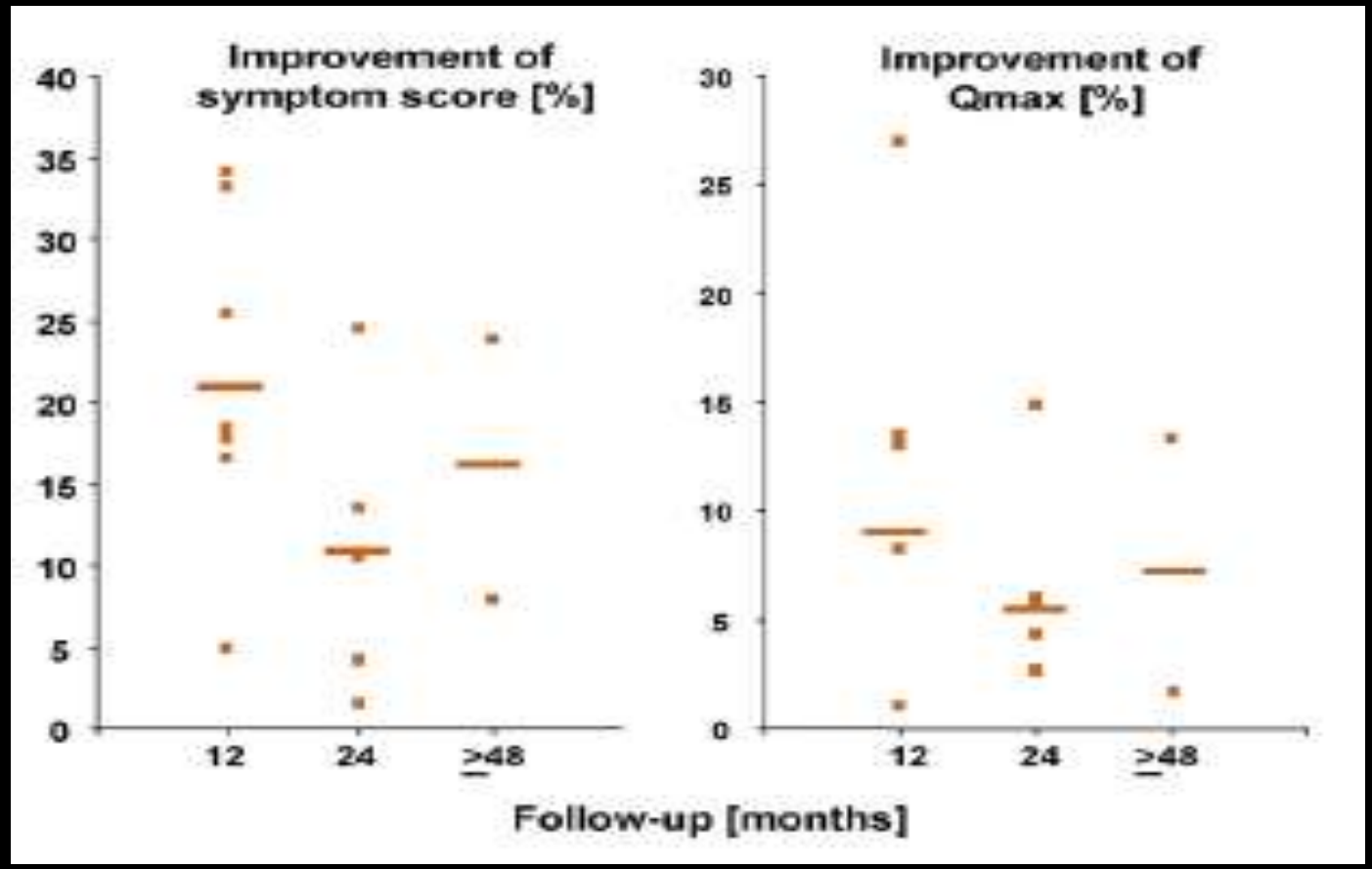
Practical considerations:

- α1-blockers are often considered the first-line drug treatment for male LUTS because of their rapid onset of action, good efficacy, and low rate and severity of adverse events.
- do not prevent occurrence of urinary retention or need for surgery.
- Ophthalmologists should be informed about α1-blocker use prior to cataract surgery.
- Elderly patients treated with non-selective α1-blockers should be informed about the risk of orthostatic hypotension.
- Sexually active patients treated with selective α1-blockers should be counselled about the risk of EjD.

PLACEBO EFFECT



PLACEBO EFFECT



How Many Men Stop Medical Therapy for BPH?

- Kaplan et al : 30% of patients stopped their medications at 2 years.
- Hong et al : 77.1% of men remained on medical therapy at 54 months.
- Predictive factors were more severe symptoms and a larger prostate volume at baseline.
- In an open-label long-term study of the safety and efficacy of terazosin in 494 men with BPH, 56.9% were still taking terazosin at 42 months.
- In 450 men prescribed doxazosin and followed long-term, the continuation rate was 58.4% at 48 months.

- Kaplan SA, Goluboff ET, Olsson CA, et al. Effect of demographic factors, urinary peak flow rates, and Boyarsky symptom scores on patient treatment choice in benign prostatic hyperplasia. Urology.1995;45:398–405. [PubMed]
- Hong SJ, Ko WJ, Kim SI, Chung BH. Identification of baseline clinical factors which predict medical treatment failure of benign prostatic hyperplasia: an observational cohort study. Eur Urol. 2003;44:94–100.[PubMed]
- Lepor H. Long term efficacy and safety of terazosin in patients with benign prostatic hyperplasia. The Terazosin Research Group. Urology. 1995;45:406–413. [PubMed]
- Lepor H, Kaplan SA, Klimberg I, et al. Doxazosin for benign prostatic hyperplasia: long term efficacy and safety in hypertensive and normotensive patients. J Urol. 1997;157:525–530. [PubMed]

Eur Urol. 2015 Sep;68(3):418-25.

Drug adherence and clinical outcomes for patients under pharmacological therapy for lower urinary tract symptoms related to benign prostatic hyperplasia: population-based cohort study.

Cindolo L1, Pirozzi L2, Fanizza C2, Romero M2, Tubaro A3, Autorino R4, De Nunzio C3, Schips L5.

- Abstract
- BACKGROUND:
- Little is known about drug adherence in men treated for lower urinary tract symptoms (LUTS). Benign prostatic hyperplasia (BPH) is one of the causes of LUTS.

- RESULTS AND LIMITATIONS:
- The 1-yr adherence was 29% in patients exposed to at least 6-mo therapy. Patients on CT had a higher discontinuation rate in the first 2 yr compared to those on monotherapy ($p<0.0001$). Overall hospitalization rates for BPH and BPH surgery were 9.04 and 12.6 per 1000 patient-years, respectively. A lower risk of hospitalization was observed for 5ARI compared to AB therapy (hazard ratio [HR] 0.46 and 0.23; $p<0.0001$). CT was associated with a reduced risk of hospitalization for BPH surgery (HR 0.94; $p<0.0001$) compared to AB. Discontinuation of drug treatment was an independent risk factor for hospitalization for BPH and BPH surgery (HR 1.65 and 2.80; $p<0.0001$) regardless of therapeutic group. Limitations include the paucity of clinical measures and the absence of patient-reported outcomes.

- CONCLUSIONS:
- Adherence to pharmacological therapy for BPH is low and could affect clinical outcomes. Long-term 5ARI and CT use was associated with an independent reduced risk of hospitalization for BPH surgery. Our findings suggest the need for new strategies to increase patient adherence to prescribed treatment and more appropriate prescribing by physicians.

Longer-term harms from observational studies

- We identified two observational studies reporting longerterm AEs related to silodosin treatment [55,56]. In a 40-wk open label extension (cumulative treatment duration of 52 wk) of a previous RCT, 435 patients completed the extension in which a total of 431 experienced 924 AEs [55]. Twenty-nine patients (4.4%) experienced serious AEs including two deaths; none of the serious AEs were considered drug related, although no criteria were reported. The second study reviewed FDA data for AEs associated with ABs and found the evidence of silodosin insuffient to compare with other ABs [56]. We identified one study examining long-term AEs associated with solifenacin/AB combination therapy, reporting an open extension from a previous RCT for a subset of patients with inclusion criteria that included a postvoid residual 150 ml [57]. Forty-seven percent of participants who continued solifenacin/AB combination treatment reported treatment-emergent AEs, most commonly dry mouth, constipation, and dyspepsia. In addition, 86 serious AEs occurred in 64 patients and included three deaths, six cases of AUR (0.7%), and three cases of intervertebral disc protrusion. We found two longer-term observational studies on tadalafil [58,59]. In a 42-wk open label extension of a previous trial, 59% of 394 participants reported at least one AE and 9% withdrew due to an AE. Serious AEs were reported in 3% (11 participants) [58]. In another open extension study in a subset of 229 of 886 original participants, nearly 5% experienced serious AEs [59].

Eur Urol. 2017 Apr;71(4):570-581. doi: 10.1016/j.eururo.2016.09.032. Epub 2016 Oct 4.
Comparative Effectiveness of Newer Medications for Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: A Systematic Review and Meta-analysis.
Dahm P1, Brasure M2, MacDonald R3, Olson CM2, Nelson VA2, Fink HA4, Rwabasonga B2, Risk MC5, Wilt TJ6

- .

- EVIDENCE SYNTHESIS:
- We synthesized evidence from 43 randomized controlled trials as well as five observational studies. Based on improvement of mean International Prostate Symptom Score and quality of life scores, the effectiveness of the newer ABs was not different from the older ABs (moderate strength of evidence [SOE]), but had more AEs (low SOE). Antimuscarinics/AB combination therapy had similar outcomes as AB monotherapy (all moderate SOE), but often had more AEs. Phosphodiesterase type-5 inhibitors alone or in combination with ABs had similar or inferior outcomes than ABs alone. Evidence was insufficient for the beta-3 adrenoceptor agonist. For all newer agents, the evidence was generally insufficient to assess long-term efficacy, prevention of symptom progression, or AEs.

- CONCLUSIONS:
- None of the drugs or drug combinations newly used to treat LUTS attributed to BPH showed outcomes superior to traditional AB treatment. Given the lack of superior outcomes, the studies' short time-horizon, and less assurance of their safety, their current value in treating LUTS attributable to BPH appears low.

CONCLUSION

- A sharp contrast may exist between the longest controlled trial (4.5 yr) and the situation in real life with treatment periods up to one or two decades of life.

- Real-life and registry data will be the only source of this important information in the future.