Medical Therapy of Benign Prostatic Hyperplasia: A Review

Maskey P*

*Assoc. Prof, Urology Unit, Department of Surgery, Patan Academy of Health Sciences, Patan Hospital,

ABSTRACT:

Medical treatment of benign prostatic hyperplasia (BPH) has conventionally been based on alpha blockers and 5-alpha reductase inhibitors. There has been a paradigm shift in this concept with the introduction of other agents. The treatment of BPH should be based not only on the size of prostate and severity of symptoms, but also on the type of symptoms (predominant storage versus obstructive), probability of progression, and the presence or absence of sexual dysfunction

KEY WORDS: benign prostatic hyperplasia, lower urinary tract symptoms medical therapy

INTRODUCTION

Benign prostatic Hyperplasia (BPH) is a common cause of lower urinary tract symptoms (LUTS) in ageing males. These symptoms can be bothersome, and can affect the quality of life (QOL) of an individual patient. The symptoms can arise during the storage phase or the voiding phase of micturition cycle (giving rise to storage LUTS or voiding LUTS), and even after micturition [1]. An individual patient can have varying degrees of storage or voiding symptoms, or an overlap of both these symptoms [2]. Moreover, LUTS associated with BPH is often accompanied by sexual dysfunction, including erectile dysfunction and ejaculatory problems [3].

The primary aim of treatment of patients with BPHis relief of symptoms and improvement of QOL.After the USFDA approved medical therapy for BPH in 1990s, there has been a paradigm shift from surgical (which was previously the gold standard) to medical therapy [4]. This is because medical therapy is effective in relieving symptoms and preventing disease progression, and also because surgery is not 100% successful and can be associated with significant morbidity. It is also to be noted that many patients with BPH, especially those with mild symptoms can be managed with watchful waiting, and in one study 65% of men managed with watchful waiting were still satisfied at 5 years follow-up [5].

The question that arises next is whom should we offer medical treatment? Medical treatment should be offered to men who have bothersome LUTS affecting their quality of life, and to those individuals who show a lifelong commitment to medical treatment, as BPH is often a chronic condition requiring ongoing medical care [6]. Medical treatment should not be prescribed to individuals with complications of BPH, such as refractory acute urinary retention, chronic high-pressure urinary retention, recurrent urinary tract infections, recurrent gross haematuria, renal dysfunction and stone formation: these patients should be surgically managed. The European Association of Urology (EAU) guideline recommends medical treatment for men with moderate to severe LUTS [7].

Several classes of drugs and their combination are used in the treatment of BPH. These include:

α-receptor antagonists
5α-reductase antagonists (5ARIs)
Antimuscarinics
Phosphodiestarase type 5 inhibitors (PDE5I)
β-3 adrenergic agonist
αreceptor antagonists

Alpha receptor antagonists

The α-receptor antagonists are the mainstay of medical treatment of BPH. Caine et al. were the first to

Correspondence :
Assoc. Prof. Dr. Pukar Maskey
Patan Academy of Health Sciences, Patan Hospital
Email : pukarmaskey@hotmail.com
Mobile : 9851079779

demonstrate in 1975 that prostatic tissue contraction was inhibited by phenoxybenzamine, a non-selective antagonist of α1 and α2 adrenoceptors[8]. Prazosin was the first α-1 selective antagonist shown to have beneficial effect in BPH. However, its use did not become popular because of dosing issues and adverse effects on blood pressure[9].

The α-1 adrenoceptors are of three types: α-1a, α-1b and α-1c [10]. The α-1a is the predominat subtype found in the human prostate, is localized to prostatic stroma and mediates prostatic contraction [10]. The α-1a receptors are also present in bladder neck, seminal vesicles and the vas deferens, hence the ejaculatory side-effects with the use of selective α-1a blockers. The α-1b receptors are present mainly in blood vessels and the α-1d receptors in bladder, nasal passages and the spinal cord, accounting for orthostatic hypotension and nasal stuffiness being more common with less α-1a selective antagonists.

The long-acting α-1 selective antagonists, commonly used in BPH, include terazosin, doxazosin, tamsulosin and alfuzosin SR (sustained release).

Terazosin has a half-life of 12 hours, and is given once daily. It requires dose titration. The improvements in symptom score and peak flow rate (PFR) are dose-dependent[11]. The HYCAT study showed that the benefit of terazocin achieved in tertiary level centers could be achieved in community centers as well[12]. In clinical practice, terazosin is started at 1mg dose to avoid the first-dose effect, and dose is increased (upto 10 mg) according to the clinical response.

Doxazosin is another long acting drug with a half-life of 22 hours. It also requires dose titration. Multiple placebo-controlled RCTs demonstrated a dose-dependent statistically significant improvement in symptom score and PFR over placebo with 2mg, 4mg and 8mg of doxazosin[13,14]. Like terazosin, it is started at 1mg to avoid the first dose effect.

Both doxazosin and terazosin produce statistically significant drop in blood pressure in hypertensive men. A similar effect is not seen in normotensive men, and in men with medically controlled hypertension [15,16]. As hypertension is common in the age group of men who have symptomatic BPH, it would seem tempting to treat both conditions with a common drug. However the ALLHAT study demonstrated that doxazosin used as a first line agent for the treatment of hypertension resulted in increased incidence of congestive cardiac failure [17]. Hence it is suggested that concomitant hypertension and BPH should be treated independently with the best available drugs.

Tamsulosin is one of the most commonly used α-1 antagonist. It has 10 times more selectivity for α-1a versus α-1b, and no selectivity for α-1a versus α-1d [18]. It doesn't require dose titration. A 0.4 mg dose has been shown to be more efficacious with equivalent side effects compared to a 0.2mg dose, and a 0.4 mg dose also shows equivalent efficacy but less side effects than a 0.8mg dose[19, 20]. Unlike terazosin and doxazosin, it doesn't cause a clinically significant drop in blood pressure even in hypertensive men. However studies from Asia suggest that a 0.2mg dose can be effectively used as a starting dose, and the dose could be increased to 0.4 mg if required [21,22,23].

Alfuzosin is another commonly used drug, and is classified as a non-specific α-1 antagonist. Currently, sustained release formulation of 10mg is used on a once-daily basis. The ALFUS study showed that alfuzosin produces a significant improvement over placebo in symptom score and PFR and the incidence of dizziness, asthenia and ejaculatory dysfunction was low[24]. The ALTESS study showed that alfuzosin given for 2 years significantly reduced clinical progression, but this was mainly because of reduction in progression of LUTS rather than reduction in the risk of AUR or BPH-related surgery[25].

Silodosin is the latest α-blocker showing 162 times more selectivity for α-1a versus α-1b, and 50 times more selectivity for α-1a versus α-1d receptors[26]. A large RCT showed that 8mg/day silodosin and 0.4mg tamsulosin were comparable in symptom score reduction over placebo[27]. A post-hoc analysis of this study showed that silodosin was superior to tamsulosin in improvingnocturia[28]. It also shows excellent cardiac safety profile, and doesn't cause a meaningful prolongation of QTc interval [29]. However the incidence of anejaculation was higher in the silodosin group [29]. Silodosin is thus a preferred alpha antagonist in patients with cardiac problems, and in patients with nocturia as the predominant symptom.

The latest addition to the list of α-blockers is **Naftopidil**. It shows 3 times affinity for α-1d versus α-1a[30]. It is used in dosages of 50mg and 75mg. Kojima et al.

demonstrated that the dominant expression of alpha 1 receptor subtype varied among individuals, and that tamsulosin and naftopidil were more effective in those with dominant expression of alpha 1a and alpha 1d receptor subtype, respectively[31]. It is more efficacious in patients with predominantly storage LUTS[32,33]

In general, α-blockers reduce symptom score (IPSS) by 30%-45%, and increase PFR by 15%-30% [34]. However, most of the studies also show a placebo response of 10%-30% IPSS reduction, and 5%-15% PFR reduction [36]. These improvement are dose dependent, i.e, greater the dose, greater the improvement in IPSS and PFR, but at a cost of increased side-effects. The time to near-maximum improvement in flow-rate is 2-6 hours for silodosin and 8 hours for tamsulosin, whereas for other alpha blockers it is 2-4 weeks[36,35,36]. However, near-maximum improvement in voiding symptoms usually requires 1-3 months.

Alpha-blockers can be used as long as it is effective in reducing LUTS. Tolerance or tachyphylaxis to alpha-blockers has not been reported[37].

Alpha blockers are also used prior to trial without catheter for acute urinary retention due to BEP. They, however, do not reduce size of prostate or the level of PSA, nor do they reduce the risk of AUR or need for surgery[7].

Common side effects include dizziness, asthenia and postural hypotension, which are highest with terazosin and doxazosin (15%-30%)[36]. These vasodilatory side effects occur more with alfuzosin than with tamsulosin, particularly in the elderly and in patients with cardiovascular comorbidity or comedication[38]. Hence, it is appropriate to take these medicines after meals, and not in an empty stomach. Nasal congestion has been reported with tamsulosin and silodosin, but not with other agents. The so-called retrograde ejaculation associated with alpha blocker use is actually not retrograde ejaculation but anemission, and has been better described as abnormal ejaculation. As mentioned previously, the incidence of abnormal ejaculation is the highest with silodosin (14-30%) followed by tamsulosin (4-11%)[29,36]. Inspite of this, alpha blockers do cause a slight improvement in overall sexual function[40].

Intraoperative floppy iris syndrome which consists of a triad of progressive miosis, billowing and flaccid iris, and iris prolapse through surgical incision during cataract surgery, is seen mainly in patients with tamsulosin use, but can occur in patients taking other alpha blockers[39]. This fact has to be kept in mind before initiating alpha blockers in a patient with cataract.

5-alpha reductase inhibitors (5ARIs)

The 5ARIs inhibit the conversion of testosterone to dihydrotestosterone, the hormone which is required for prostatic growth. Finasteride inhibits type II 5-alpha reductase and reduces the conversion by 70%. Dutasteride inhibits both type I and type II 5-alpha reductase, and reduces the conversion by 95%[7]. However, direct comparison between these two drugs has shown no difference in clinical efficacy and prostate volume reduction[40].

The PLESS study compared 5mg finasteride versus placebo[41]. The mean baseline prostate volume was 55cc. The mean reduction in symptom score and PFR was 3.3 and 1.9 respectively for finasteride, versus 1.3 and 0.2 for placebo. Finasteride reduced the need for surgery by 55% and the risk of acute urinary retention (AUR) by 57%. Prostate size was reduced by 32%. The best resultswere seen in men with a PSA of >1.4 and prostate volume >41cc[42]. These effects begin within several weeks but become noticeable after 6-9 months[43].

In comparison to finasteride, dutasteride seems to be effective even for prostates >30cc.[43,44]

The 5ARIs lower serum PSA by 50% after 6-12 months[45], hence if the 6-month PSA has not decreased to 50% of pretreatment PSA, a biopsy should be considered. 5ARIs are also used to prevent recurrent gross hematuria secondary to BPH, and to reduce post-prostatectomy bleeding[46,47].

Adverse events associated with the use of 5ARIs include sexual related events to the tune of 10%, including decreased libido, erectile dysfunction and ejaculatory dysfunction[48]. Gynecomastia and breast tenderness are also encountered.

Combination of alpha blockers and 5ARIs

One of the important manipulations in the medical management of BPH is the combined use of alpha blockers and 5ARIs, based on the premise that the combination addresses both the static and the dynamic components of BPH-induced bladder outlet

obstruction (BOO). Initial studies, the Veterans Affairs Cooperative Study, and the European PREDICT Study showed that the combination treatment was no better than alpha blocker monotherapy[49,50]. However, two large multicentric studies showed the combination treatment to be beneficial.

The MTOPS study was designed to study the role of combination treatment on disease progression, rather than on symptom score alone [51]. A total of 3047 men with prostates of all size and PSA <10ng/ml were studied for a period of 4.5 years. Disease progression was defined as any one of the following: 4-point increase in symptom score, an episode of AUR, 50% rise in serum creatinine, two or more episodes of UTI in 1 year, urosepsis due to BOO or socially unacceptable incontinence. Both finasteride and doxazosin produced a siginificant reduction in the risk of progression versus placebo (34% and 39%, respectively), but the risk reduction produced by combination of these two drugs was siginificantly more than either monotherapy or placebo (67%). Likewise, the risks of AUR and risk of surgery were significantly reduced by finasteride monotherapy and comination, but not by doxazosin monotherapy. The combination therapy also caused a significant improvement in symptom score and PFR over monotherapy. The number needed to treat (NNT) to prevent a case of progression was 15 for finasteride, 13.7 for doxazosin and 8.4 for combination. When patients with a PSA >4ng/ml were taken, the NNT was 4.7 for combination, and in those with prostate volume >40 cc, the NNT was 4.9, indicating that comination was a much more economically better option in patients with larger prostates.

The CombAT study compared dutasteride and tamsulosin monotherapy with combination in 4844 men for 4 years [52,53]. Compared to MTOPS study, this study was a company (which manufactured dutasteride) sponsored trial and recruited men who were more likely to progress i.e, men with PSA ≥1.5, prostate volume >30cc and IPSS ≥12. Also, compared to MTOPS, there was no placebo arm in this study. The mean prostate volume was 55cc (versus 36.3 in MTOPS). Combination therapy reduced the risk of AUR or BPH-related surgery by 20% over dutasteride and 66% over tamsulosin monotherapy. Similarly, combination reduced clinical progression by 31% over dutasteride and 44% over tamsulosin monotherapy. The combination caused significant improvement in IPSS over dutasteride from month 3, and over tamsulosin from month 9.

A systematic review of combination therapy showed that it is more effective in larger volume prostates[54]. The American Urological Association (AUA) and EAU guidelines recommend combination therapy in patients with higher risk of progression i.e, patients with prostate >40cc, higher PSA and advanced age[7,55]. The two large trials, MTOPS and CombAT, do not state when one should switch from monotherapy to combination therapy. In general, combination therapy is initiated when patients are severely symptomatic or risk of progression is high.

WITHDRAWAL OF ALPHA BLOCKERS FROM COMBINATION

One of the disadvantages of combination treatment is the increased cost and increased incidence of side-effects. It is obvious that withdrawal of one of the agents would lead to a reduction in the cost and side-effects. Withdrawal of alpha blockers is based on the premise that alpha blockers cause initial reduction in symptoms, and 5ARIs maintain this improvement in symptoms by causing reduction in prostate volume over long term.

The SMART 1 trial showed that when tamsulosin was withdrawn from combination treatment, only 16% of those with IPSS <20 had worsening of symptoms, vs 42% of those with IIPSS ≥20[56].

The PROACT showed that after 9 months of combination therapy, alpha blockers can be safely withdrawn and control of symptoms can be maintained with finasteride alone for at least 9 months [57]. Another study by Baldwin et.al showed that withdrawal of doxazocin after a combination treatment with finasteride for 9-12 months resulted in more than 80% of patients experiencing no significant symptom deterioration [58].

Thus it can be seen that alpha blocker withdrawal after 6-12 months of combination therapy will be tolerated by many patients. Patients with severe symptoms (IPSS ≥20) should be treated with a longer duration of combination therapy.

ANTIMUSCARINICS

The administration of antimuscarinics in patients with BPH was traditionally contraindicated because of the

fear of precipitating acute urinary retention. However, it has now been shown that antimuscarinics can be safely used in most men with BPH. Rationale for the use of antimuscarinics include the fact that M2 and M3 receptors are present in abundance in urinary bladder, and mediate the detrusor overactivity present in 45%-50% of men with BOO due to BPH, and in upto 90% of men with more severe BOO [59]. Moreover, storage LUTS are regarded as more bothersome to the patient than voiding LUTS, and alpha blockers may not sufficiently treat storage LUTS.

Most of the studies on antimuscarinic use in BPH have been of short duration (12 weeks), include men with overactive bladder symptoms (increased frequency and urgency, with or without urgency incontinence), and exclude men with a post-void residual urine (PVR) of >150-200cc.

More often, antimuscarinics are used in combination with alpha blockers in those with persistent overactive bladder (OAB) symptoms despite alpha blocker treatment.

In the TIMES study, combination of tolterodine and tamsulosin caused significant reduction in urgency episodes, frequency, nocturia episodes and IPSS, compared to placebo, and there was no difference in the incidence of AUR.[60]

In the SATURN study, combination of TOCAS (tamsulosin oral controlled absorption system) and solifenacin caused a significant reduction in IPSS storage subscore versus TOCAS alone, though a significant reduction in IPSS was not achieved[61]. PVR increased with increasing dose of solifenacin, but the incidence of AUR was low irrespective of the dose of solifenacin.

In NEPTUNE trial, fixed-dose combinations of solifenacin(6mg or 9mg) and TOCAS produced significant IPSS reduction, and improvement in total urgency frequency score over placebo[62]. The combinations also improved quality of life measures, and were well tolerated with low incidence of AUR (only 1 patient in 6mg group and 3 patients in 9 mg group). The NEPTUNE II study showed that the combination caused further improvement in symptoms at week 16, which was maintained for 52 weeks[63].

Commonly reported adverse effects include dry mouth (10-20%) and constipation (2-5%). The incidence of urinary retention reported in most of the studies is low. However, one should keep in mind that the risk of AUR increases with the duration of follow-up, and the short duration of the above studies may not capture the true effect of antimuscarinics in promoting AUR.

To conclude, antimuscarinics may be used as an adjunt to alpha blockers in those with residual bothersome storage symptoms, and are to be avoided in men with a PVR of >200cc.

PHOSPHODIESTERASE TYPE 5 INHIBITORS (PDE5I)

The PDE5I inhibits phosphodiesterase type 5 thereby elevating the level of cGMP, which mediates smooth muscle relaxation. The observation that erectile dysfunction (ED) is common in the age group of men who have BPH forms the basis for the use of PDE5I in BPH. Rationale for their use include improved oxygenation of lower urinary tract, smooth muscle relaxation, negative regulation of proliferation and transdifferentiation of lower urinary tract stroma, reduction of bladder afferent nerve activity, and down-regulation of prostatic inflammation [64,65]. The most common drug used is tadalafil.

A dose-ranging study showed that compared to placebo, tadalafil 5mg/day produced equivalent reduction in IPSS compared to higher doses but with less side effects (back pain, myalgia) [66].

In an RCT,tadalafil 5mg group had improved QOL and significant improvement in IPSS over placebo, but PFR remained unaltered [67]. Such beneficial effects were maintained for upto 1 year in an open-label extension study [68].

Is the beneficial effect of tadalafil on LUTS a result of direct effect on lower urinary tract, or is it indirect, mediated through erectile dysfunction symptom improvement? The post hoc analysis by Brock GB et al. showed that only 7.5% improvement in IPSS could be explained by improvement in IIEF [69].

How does PDE5Is compare with tamsulosin? In an RCT comparing tadalafil 5mg vs tamsulosin 0.4mg vs placebo, both tadalafil and tamsulosin monotherapy produced significant improvement in IPSS (-2.1 and -1.5), and BPH impact index, over placebo [70]. The PFR also increased significantly for both tamsulosin and tadalafil over placebo (2.2 and 2.5).

A meta-analysis done by Gacci et.al showed that PDE5I monotherapy caused significant improvement in IIEF (+5.5) and IPSS (-2.8) vs placebo, but no improvement was seen in PFR. The combination of PDE5I and alpha blocker, however, caused significant improvement in all three parameters versus alpha blockers alone (IIEF +3.6, IPSS -1.8, PFR +1.5)[71].

Another randomized trial showed that co-administration of tadalafil and finasteride provides early improvement in lower urinary tract symptoms versus placebo[72].

β3-adrenoceptor agonists

The β3 adrenoceptor agonist, Mirabegron, is a new addition in the management of LUTS due to BPH. The β3 adrenoceptor is the most abundant β receptor in the urinary bladder, and its stimulation causes relaxation of detrusor and increase in bladder capacity without significant effect in urodynamic profile [73,74]. Mirabegron can thus be potentially used to address detrusor overactivity secondary to BOO due to BPH, and can be a safer alternative to antimuscarinics in men with BOO.

In a study assessing the safety, no difference was seen in PFR and detrusor pressure at peak flow (Pdet at Qmax) between mirabegron 50mg/day, mirabegron 100mg/day and placebo groups[75]. The mirabegron arms also showed significant decrease in micturition frequency relative to placebo. There was 1 AUR each in the placebo and 100mg group, and other adverse effect profile was similar in all three groups.

In another study comparing mirabegron versus tolterodine, the incidence of dry mouth was 3 times less than tolterodine group, and major adverse cardiovascular events were 0.7% in mirabegron 50mg group, 0% in mirabegron 100mg group, and 0.5% in tolterodine ER 4mg group [76]. These short term studies show that mirabegron is safe to use in men with moderate-severe LUTS, especially if the symptoms are predominantly storage symptoms.

CONCLUSION

Medical treatment of BPH should take into account many factors. A patient with risk factors for BPH progression such as moderate to severe symptoms, large prostate and poor urine flow, is better served with combination of alpha blockers and 5ARI. Conversely,in a patient with smaller prostate, alpha blocker monotherapy may suffice. The type of symptom should also be considered. In patients with predominantly storage symptoms, antimuscarinics would be a useful and safe addition to alpha blockers. Mirabegron would be a suitable replacement for those who do not tolerate the side effects of antimuscarinics, but further studies are still needed. Patient's sexual function is also an important consideration, and patients with concomitant ED are best served with tadalafil. It has to be stressed that proper patient education and life-style changes should always go along with medical therapy.

REFERENCES

1 Irwin DE, Milsom I, Abrams P, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study.Eur Urol. 2006 Dec;50(6):1306-14; discussion 1314-5. Epub 2006 Oct 2.

2 Sexton CC, Coyne KS, Wein AJ et al. The overlap of storage, voiding and postmicturition symptoms and implications for treatment seeking in the USA, UK and Sweden: EpiLUTS. BJUI 2009;103 (Suppl 3):12-23.

3 Bruskewitz RC. Quality of life and sexual function in patients with benign prostatic hyperplasia. Rev Urol. 2003: 5(2): 72-80.

4 Lepor H. Medical treatment of benign prostatic hyperplasia. Rev Urol. 2011; 13(1): 20-33.

5 Flanigan RC, Reda DJ, Wasson JH, et al. 5-year outcome of surgical resection and watchful waiting for men with moderately symptomatic BPH: a department of Veterans Affairs cooperative study. J Urol 1998; 160: 12-16.

6 Hollingsworth JM, Wei JT. Economic impact of surgical intervention in the treatment of benign prostatic hyperplasia. Rev Urol. 2006;8(Suppl 3): S9-S15.

7 Hollingsworth JM, Wei JT. Economic impact of surgical intervention in the treatment of benign prostatic hyperplasia. Rev Urol. 2006;8(Suppl 3): S9-S15.

8 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.

9 Lepor H. The evolution of alpha-blockers for the treatment of benign prostatic hyperplasia. Rev Urol. 2006;8(suppl 4):S3-S9.

10 Schwinn DA, Roehrborn CG. α1-adrenoceptor subtypes and lower urinary tract symptoms. Int J Urol. 2008;15:193-199.

11 Lepor H, Auerbach S, Puras-Baez A, et al. A multicenter fixed-dose study of the safety and efficacy of terazosin in the treatment of the symptoms of benign prostatic hyperplasia. J Urol. 1992;148:1467-1474.

12 Roehrborn CG, Oesterling JE, Auerbach S, et al. The

Hytrin Community Assessment Trial study: a one year study of terazosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia. HYCAT investigator group. Urology. 1996; 47(2):159-68.

13 Fawzy A, Braun K, Lewis GP, et al. Doxazosin in the treatment of benign prostatic hyperplasia in normotensive patients: a multicenter study. J Urol. 1995;154:104-109.

14 Gillenwater JY, Conn RL, Chrysant SG, et al. Doxazosin for the treatment of benign prostatic hyperplasia in patients with mild to moderate essential hypertension: a double-blind, placebo-controlled dose response multicenter study. J Urol. 1995; 154:110-115.

15 Kirby RS. Doxazosin in benign prostatic hyperplasia: effects on blood pressure and urinary flow in normotensive and hypertensive men. Urology. 1995;46:182-186.

16 Kirby RS. Terazosin in benign prostatic hyperplasia: Effect on blood pressur and urinary flow in normotensive and hypertensive men. Br J Urol. 1998;82:373-379.

17 ALLHAT officers and Coordinators for the ALLHAT collaborative Research group. Major cardiovascular events in hypertensive patients randomized to doxazosin versus chlorthalidone. JAMA. 200;283:1967-75.

18 Kenny BA, Miller AM, Williamson IJ, et al. Evaluation of the pharmacological selectivity profile of alpha 1 adrenoceptor antagonists at prostatic alpha 1 adrenoceptors: binding, functional and in vivo studies. Br J Pharmacol. 1996;118:871-78.

19 Abrams P, Speakman M, Stott M, et al. A dose-ranging study of the efficacy and safety of tamsulosin, the first prostate-selective α1A-adrenoceptor antagonist, in patients with benign prostatic obstruction (symptomatic benign prostatic hyperplasia). Br J Urol. 1997;80:587-96.

20 Narayan P, Tewari A. A second phase III multicenter placebo controlled study of 2 dosages of modified release tamsulosin in patients with symptoms of benign prostatic hyperplasia. United States 93-01 Study Group. J Urol. 1998;160(5):1701-1706.

21 Kawabe K, Ueno A, Takimoto Y, et al. Use of alpha 1-blocker, YM617, in the treatment of benign prostatic hypertrophy. YM617 Clinical Study Group. J Urol. 1990;144(4):908-911.

22 Li NC, Chen S, Yang XH, et al. The Beijing Tamsulosin Study Group. Efficacy of low-dose tamsulosin in Chinese patients with symptomatic benign prostatic hyperplasia. Clin Drug Invest. 2003;23(12)781-787.

23 SR Shim, JH Kim, Choi H, et al. General effect of low-dose tamsulosin (0.2mg) as a first-line treatment for lower urinary tract symptoms associated with benign prostatic hyperplasia: a systematic review and meta-analysis. Curr Med Res Opin. 2015;31(2):353-365.

24 Roehrborn CG. Efficacy and safety of once-daily alfuzosin in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a randomized, placebo-controlled trial. Urology. 2001;58(6):953-9.

25 Roehrborn CG, for the ALTESS Study Group. Alfuzosin 10 mg once daily prevents overall clinical progression of benign prostatic hyperplasia but not acute urinary retention: results of a 2-year placebo-controlled study. BJU Int. 2006;97:734-741.

26 Rossi M, Roumeguére T. Silodosin in the treatment of benign prostatic hyperplasia. Drug Des DevelTher. 2010;4:291-297.

27 Chapple CR, Montorsi F, Tammela TL, et al. European Silodosin Study Group. 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;59:342-352.

28 Osman NI, Chapple CR, Cruz F, et al. Silodosin: a new subtype selective alpha-1 antagonist for the treatment of lower urinary tract symptoms in patients with benign prostatic hyperplasia. Expert OpinPharmacother 2012;13:2085-2096.

29 Lepor H, Hill LA. Silodosin for the treatment of benign prostatic hyperplasia: pharmacology and cardiovascular tolerability. Pharmacotherapy. 2010;30(12):1303-1312.

30 Masumori N. Naftopidil for the treatment of urinary symptoms in patients with benign prostatic hyperplasia. Therapeutics and Clinical Risk Management. 2011;7:227-238.

31 Kojima Y, Sasaki S, Kubota Y, et al. Expression of α1-adrenoceptor subtype mRNA as a predictor of the efficacy of subtype selective α1-adrenoceptor antagonists in the management of benign prostatic hyperplasia. J Urol. 2008;179(3):1040-1046.

32 Ikemoto I, Kiyota H, Ohishi Y, et al. Usefulness of tamsulosin hydrochloride and naftopidil in patients with urinary disturbances caused by benign prostatic hyperplasia: a comparative, randomized, two-drug crossover study. Int J Urol. 2003;10(11):587-594.

33 Hara N, Mizusawa T, Obara K, et al. The role of naftopidil in the management of benign prostatic hyperplasia. TherAdv Urol. 2013;5(2):111-119.

34 Djavan B, Chapple C, Milani S, 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;64:1081-1088.

35 Marks LS, Gittelman MC, Hill LA, et al. Rapid efficacy of the highly selective α(1A)-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. J Urol. 2013;189(1 Suppl):S122-128.

36 Akin Y, Gulmez H, Ucar M, et al. The effect of first dose of tamsulosin on flow rate and its predictive ability on the improvement of LUTS in men with BPH in the mid-term. IntUrolNephrol. 2013;45(1):45-51.

37 Chapple CR. A comparison of varying α-blockers and other pharmacotherapy options for lower urinary tract symptoms. Rev Urol 2005; 7(Suppl 4):S22-S30.

38 Milani S, Djavan B. Lower urinary tract symptoms suggestive of benign prostatic hyperplasia: latest update on α1-adrenoceptor antagonists. BJU Int. 2005;95(Suppl 4):29-36.

39 Yaycioglu O, Altan-Yaycioglu R. Intraoperative floppy iris syndrome: facts for the urologist. Urology. 2010;76(2):271-276.

40 Nickel JC, Gilling P, Tammela TL, et al. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). BJU Int. 2011;108:388-394.

41 McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. N Engl J Med. 1998;338(9):557-563.

42 Roehrborn CG, Boyle P, Bergner D, et al. Serum Prostate-specific antigen and prostate volume predict long-term cnanges in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. Urology. 1999;54:662-669.

43 [b] CG Roehrborn, Lukkarinen O, Mark S, et al. Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5alpha-reductase inhibitor dutasteride: results of 4-year studies. BJU Int 2005; 96(4):572-577.

44 Gittelman M, Ramsdell J, Young J, et al. Dutasteride improves objective and subjective disease measures in men with benign prostatic hyperplasia and modest or severe prostate enlargement. J Urol 2006; 176(3): 1045-1050.

45 Guess HA, Heyse JF, Gormley GJ. The effect of finasteride on prostate-specific antigen in men with benign prostatic hyperplasia. Prostate. 1993;22(1):31-37.

46 Foley SJ, Soloman LZ, Wedderburn AW, et al. A prospective study of the natural history of hematuria associated with benign prostatic hyperplasia and the effect of finasteride. J Urol. 2000;163(2):496-498.

47 Kim KS, Jeong WS, Park SY, et al. The effect of two weeks of treatment with dutasteride on bleeding after transurethral resection of the prostate. World J Mens Health. 2015;33(1):14-19.

48 Roehrborn CG, Boyle P, Nickel JC, et al. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology. 2002; 60:434-441.

49 Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazocin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. N Engl J Med. 1996;335(8):533-539.

50 Kirby R, Roehrborn C, Boyle P, et al. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazocin and Combination Therapy (PREDICT) trial. Urology. 2003;61:119-126.

51 McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N EnglJ Med. 2003;349(25):2387-2398.

52 Roehrborn CG, Barkin J, Siami P, et al. Clinical outcomes after combined therapy with dutasteride plus tamsulosin or either monotherapy in men with benign prostatic hyperplasia (BPH) by baseline characteristics: 4-year results from the randomized, double-blind Combination of Avodart and Tamsulosin (CombAT) trial. BJU Int 2011;107(6):946-954.

53 Montorsi F, Roehrborn C, Garcia-Penit J, et al. The effects of dutasteride or tamsulosin alone and in combination on storage and voiding symptoms in men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH): 4-year data from the Combination of Avodart and Tamsulosin (CombAT) study. BJU Int 2011;107(9):1426-1431.

54 Füllhase C, Chapple C, Cornu JN, et al. Systematic review of combination drug therapy for non-neurogenic male lower urinary tract symptoms. EurUrol 2013; 64(2):228-243.

55 McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol 2011;185:1793-1803.

56 Barkin J, Guimarães M, Jacobi G, et al. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor dutasteride. EurUrol 2003;44(4):461-6.

57 Nickel JC, Barkin J, Koch C, et al. Finasteridemonotherapy maintains stable lower urinary tract symptoms in men with benign prostatic hyperplasia following cessation of alpha blockers. Can UrolAssoc J 2008;2(1):16-21.

58 Baldwin KC, Ginsberg PC, Roehrborn CG, et al. Discontinuation of alpha-blockade after initial treatment with finasteride and doxazosin in men with lower urinary tract symptoms and clinical evidence of benign prostatic hyperplasia. Urology 2001;58:203-208.

59 Oelke M, Baard J, Wijkstra, et al. Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. EurUrol 2008; 54:419-426.

60 Kaplan SA, Roehrborn CG, Rovner ES, et al. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder. JAMA 2006; 296:2319-2328.

61 vanKerrebroeck P, Haab F, Angulo JC, et al. Efficacy and safety of solifenacin plus tamsulosin OCAS in men with

voiding and storage lower urinary tract symptoms: results from a phase 2, dose-finding study (SATURN). EurUrol 2013; 64:398-407.

62 vanKerrebroeck P, Chapple C, Drogendijk T, et al. Combination therapy with solifenacin and tamsulosin oral controlled absorption system in a single tablet for lower urinary tract symptoms in men: efficacy and safety results from the randomized controlled NEPTUNE trial. EurUrol 2013; 64(6):1003-1012.

63 Drake MJ, Chapple C, Sokol R, et al. Long-term safety and efficacy of single-tablet combinations of solifenacin and tamsulosin oral controlled absorption system in men with storage and voiding lower urinary tract symptoms: results from the NEPTUNE study and NEPTUNE II open-label extension. EurUrol 2015; 67(2):262-270.

64 Giuliano F, Ückert S, Maggi M, et al. The mechanism of action of phosphodiesterase type 5 inhibitors in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. EurUrol 2013;63(3):506-516.

65 Gacci M, Andersson KE, Chapple C, et al. Latest evidence on the use of phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. EurUrol 2016; [Epub ahead of print]. doi: 10.1016/j.eururo.2015.12.048.

66 Roehrborn CG, McVary KT, Elion-Mboussa A, et al. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic: a dose finding study. J Urol 2008; 180(4):1228-1234.

67 Porst H, Kim ED, Casabé AR, et al. Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized , double-blind, placebo-controlled trial. EurUrol 2011; 60(5):1105-1113.

68 Donatucci CF, Brook GB, Goldfischer ER, et al. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension study. BJUI Int 2011; 107(7):1110-1116.

69 Brock GB, McVary KT, Roehrborn CG, et al. Direct effects of tadalafil on lower urinary tract symptoms versus indirect effects mediated through erectile dysfunction symptom improvement: integrated data analysis from 4 placebo controlled clinical studies. J Urol 2014; 191(2):405-411.

70 Oelke M, Giuliano F, Mirone V et al. Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomized, parallel, placebo-controlled clinical trial. EurUrol 2012; 61(5):917-925.

71 Gacci M, Corona G, Salvi M, et al. A systematic review and meta-analysis on the use of phosphodiestare 5 inhibitors alone or in combination with α-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. EurUrol 2012; 61:994-1003.

72 Casabé A, Roehrborn CG, Da Pozzo LF, et al. Efficacy and safety of the coadministration of tadalafil once daily with finasteride for 6 months in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia. J Urol 2014; 191(3):727:733.

73 Yamaguchi O, Chapple CR. Beta3-adrenoceptors in urinary bladder. NeurourolUrodyn 2007; 26(6):752-756.

74 Tyagi P, Tyagi V. Mirabegron, a β3-adrenoceptor agonist for the potential treatment of urinary frequency, urinary incontinence or urgency associated with overactive bladder. IDrugs 2010; 13(10):713-722.

75 Nitti VW, Rosenberg S, Mitcheson DH, et al. Urodynamics and safety of the β3-adrenoceptor agonistmirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. J Urol 2013; 190(4):1320-1327.

76 Chapple CR, Kaplan SA, Mitcheson D, et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β3-adrenoceptor agonist, in overactive bladder. EurUrol 2013; 63(2):296-305.