Safety and Tolerability of Treatment for BPH

Francesco Montorsi a,*, Ignacio Moncada b

a Cattedra di Urologia, University Vita e Salute-San Raffaele, Milan, Italy
b Department of Urology and Andrology, Hospital Gregorio Marañón, Madrid, Spain

Abstract

Treatment options for benign prostatic hyperplasia (BPH) include watchful waiting, pharmacological therapy, and surgery. For individual patients, treatment choice depends on disease severity, comorbidity, patient preferences, and the comparative efficacy and adverse effects (AEs) of the available therapies. Disease-related symptoms and treatment-related factors influence health-related quality of life (HRQOL), and treatment discontinuation occurs due to lack of efficacy or the occurrence of AEs. This review explores the safety and tolerability of current treatment options. Pharmacological therapies include α1-adrenergic antagonists and 5α-reductase inhibitors (5ARIs). The α1-adrenergic antagonists have comparable efficacy but tolerability profiles that differ according to vasodilatory AEs and ejaculatory abnormalities. Alfuzosin and tamsulosin are better tolerated than terazosin and doxazosin; tamsulosin causes fewer vasodilatory AEs than alfuzosin but causes more ejaculatory abnormalities. AEs associated with 5ARIs are mainly sexual (eg, erectile dysfunction, reduced libido, and gynaecomastia) and tend to be confined to the first year of therapy. Surgery has the potential for short- and long-term complications. Open surgery has been largely replaced by less invasive approaches, particularly transurethral resection of the prostate (TURP). Short-term complications of TURP include death, bleeding, clot retention, transurethral resection syndrome, urinary tract infection, and inability to void; long-term complications include failure to void, retrograde ejaculation, erectile dysfunction, incontinence, and retreatment. More recent approaches (eg, transurethral needle ablation, thermotherapy, and laser therapy) have promising efficacy and safety. Patient expectations of therapy and AEs should be considered to ensure that treatment is tailored to individual patient needs and that HRQOL is maximised.

© 2006 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Cattedra di Urologia, University Vita e Salute-San Raffaele, Via Stamira D’Ancona 20, Milan 20129, Italy. Tel. +39 02 2643 7286; Fax: +39 02 2643 7298. E-mail address: Montorsi.francesco@hsr.it (F. Montorsi).
1. Introduction

From the patient’s perspective, the focus of attention of benign prostatic hyperplasia (BPH) management today centres on patient choice and health-related quality of life (HRQOL) [1]. The HRQOL of patients treated for BPH depends both on disease-related and treatment-related factors. The degree to which the same level of disease-related symptoms and treatment-related side-effects of therapy bother individual patients differs, and this is reflected in appropriately measured HRQOL [1].

From the clinician’s perspective, the aims of treatment for BPH are to: (1) reduce symptoms, (2) improve HRQOL, and (3) prevent progression of the disease and so avoid potentially serious complications such as acute urinary retention (AUR) and the need for surgery. Treatment options include watchful waiting, pharmacologic therapy with $\alpha_1$-adrenergic antagonists or $5\alpha$-reductase inhibitors (5ARIs), or surgery. Appropriate treatment choice depends on disease severity, concurrent medical conditions, patient preferences (eg, for or against surgery), comparative efficacy, and adverse events (AEs) [2]. In elderly patients, potential drug interactions also need to be considered. Discontinuation of treatment can be due to lack of efficacy or the occurrence of AEs. Within this context, the safety and tolerability of the treatment options are reviewed.

2. Safety and tolerability of pharmacologic therapy

2.1. $\alpha_1$-Blockers

The $\alpha_1$-blockers reduce smooth muscle tone in the prostate and result in rapid improvements in urinary symptoms and flow. Currently available $\alpha_1$-blockers include the nonselective $\alpha_1$-blockers, terazosin, doxazosin, and alfuzosin, and the highly selective $\alpha_{1A}$-blocker, tamsulosin. These agents have comparable efficacy; the main difference among these agents relates to their tolerability profiles.

An extensive review of data from trials of $\alpha_1$-blockers, including data from 6333 patients in placebo-controlled trials and 507 patients in direct comparative studies, revealed that alfuzosin (sustained-release formulation) and tamsulosin (0.4 mg modified-release formulation) are better tolerated than terazosin and doxazosin [3]. The discontinuation rate observed with alfuzosin and tamsulosin was similar to that observed with placebo; 4–10% of patients receiving placebo, alfuzosin, or tamsulosin withdrew from these studies. Among patients receiving terazosin or doxazosin, however, an additional 4–10% of patients discontinued therapy. Withdrawal from these studies was mainly due to expected side-effects, including dizziness, postural hypotension, tiredness, stuffy nose, syncope, and ejaculatory dysfunction.

2.1.1. Vasodilatory AEs

It is because the effects of the nonselective $\alpha_1$-blockers (terazosin, doxazosin, and alfuzosin) are not limited to the lower urinary tract but also affect other tissues such as the vasculature, that these agents can cause vasodilatory AEs such as

Fig. 1 – Percentage of patients with (A) dizziness, (B) postural hypotension, (C) who discontinued therapy due to adverse events (AEs) in placebo-controlled studies. ALF = alfuzosin; IR = immediate release; SR = sustained release; TER = terazosin; DOX = doxazosin; TAM = tamsulosin. Reproduced with permission from Djavan B et al. Urology 2004;64:1081–8.
dizziness and postural hypotension. These AEs are a concern because they have the potential to lead to serious complications such as falls and fractures [4]. Due to its selectivity as an $\alpha_{1A}$-blocker, tamsulosin tends to interfere less with blood pressure regulation and causes fewer vasodilatory AEs [4,5].

In the updated meta-analysis of data from trials of the $\alpha_{1}$-blockers conducted by Djavan et al, data from placebo-controlled trials indicated that vasodilatory AEs occurred at rates comparable to or only slightly higher than placebo with alfuzosin and tamsulosin, but occurred at a higher rate than placebo with terazosin and doxazosin (Fig. 1A and B) [6]. Discontinuation due to AEs was lower with alfuzosin XL and tamsulosin compared with terazosin and doxazosin (Fig. 1C) [6].

Data from direct-comparison studies indicated that, overall, tamsulosin is associated with a slightly lower incidence of vasodilatory AEs than other $\alpha_{1}$-blockers. A comparison of tamsulosin and alfuzosin, for example, revealed that compared with baseline, tamsulosin had no effect on blood pressure, whereas alfuzosin caused a significant reduction in both standing and supine blood pressure ($p < 0.05$) [7]. Dizziness was also more common with alfuzosin and terazosin than with tamsulosin, whereas the incidences of syncope and hypotension were similar for tamsulosin and alfuzosin [6]. Discontinuation due to vasodilatory AEs was comparable for tamsulosin and alfuzosin and higher with terazosin; discontinuation due to dizziness was 0.6% with tamsulosin and 2.0% with terazosin [6]. Data from the use of alfuzosin in the clinical setting rather than in trials demonstrate that treatment discontinuation remains at about 4%, and vasodilatory AEs continue to be the main cause of treatment discontinuation [8].

### Table 1 – The nature of adverse events resulting in discontinuation of therapy in the 722 patients who withdrew and incidence in the overall population [8]

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Adverse event leading to withdrawal, % (n = 722)</th>
<th>Incidence in overall population, % (n = 13,389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilatory</td>
<td>59.0</td>
<td>3.20</td>
</tr>
<tr>
<td>Vertigo/dizziness</td>
<td>25.1</td>
<td>1.35</td>
</tr>
<tr>
<td>Syncope/malaise</td>
<td>10.2</td>
<td>0.55</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>7.9</td>
<td>0.42</td>
</tr>
<tr>
<td>Headache</td>
<td>7.2</td>
<td>0.39</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>8.6</td>
<td>0.46</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>21.0</td>
<td>1.16</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>3.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Skin and muscle disorders</td>
<td>3.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Other cardiovascular disorders</td>
<td>3.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Central nervous system disorders</td>
<td>2.6</td>
<td>0.14</td>
</tr>
<tr>
<td>General status</td>
<td>6.7</td>
<td>0.35</td>
</tr>
</tbody>
</table>


2.1.2. **Interaction with cardiovascular disease or cardiovascular medications**

Among patients taking $\alpha_{1}$-blockers, vasodilatory AEs are more common and severe in patients with cardiovascular disease or receiving cardiovascular medications and in those who are elderly [4,8]. Data from direct-comparison studies show that the slightly higher incidence of vasodilatory AEs observed with alfuzosin and terazosin compared with tamsulosin is particularly pronounced in patients aged 75 yr or older and those with cardiovascular comorbidity or comedication [6,7,9].

In the open-label, non-controlled post-marketing surveillance study of alfuzosin, cardiovascular AEs occurred more often in patients aged 75 yr or older than in younger patients. Vertigo/dizziness leading to study discontinuation, for example, occurred in 0.9% of patients aged <65 yr, 1.5% of patients aged 65–74 yr, and 2.3% of patients aged $\geq$75 yr [8]. The risk of withdrawal of a patient aged 75 yr was 1.5-fold higher than for a patient aged 60 yr, and the risk increased with cardiovascular comorbidity or use of cardiovascular medications [10]. Tamsulosin, on the other hand, causes fewer vasodilatory AEs than alfuzosin (particularly in the elderly) and is well tolerated in patients with cardiovascular comorbidity or comedication [4].

### 2.1.3. Ejaculatory abnormalities

In the meta-analysis of data from $\alpha_{1}$-blockers, ejaculatory abnormalities were reported to occur
in about 1% of patients receiving alfuzosin, doxazosin, or terazosin in placebo-controlled trials, which is roughly comparable with the rate of ejaculatory abnormalities observed with placebo [6]. The incidence of abnormal ejaculation with alfuzosin, for example, was reported to be 0.6% in pooled data from three randomised, placebo-controlled studies involving 955 patients [11]. Tamsulosin causes a higher incidence of ejaculatory abnormalities, with rates of 5–11% reported from European and US studies [6]. However, abnormal ejaculation tends to be better tolerated than vasodilatory AEs [12], and abnormal ejaculation with tamsulosin resulted in discontinuation of treatment in <1% of cases in placebo-controlled studies [13]. Despite the existence of a higher incidence of abnormal ejaculation with tamsulosin, in the study by Höfner et al. this was not considered by patients to be a major problem, and there was no overall negative impact on sexual function compared with placebo or alfuzosin [13].

2.1.4. Interaction with phosphodiesterase type-5 inhibitors
Erectile dysfunction increases with age, so it is probable that many men with BPH will also have erectile dysfunction and may use medications for this condition [4]. The phosphodiesterase type-5 inhibitors (PDE5-Is; eg, sildenafil, tadalafil, and vardenafil) are widely used for management of erectile dysfunction, but, like α1-blockers, these agents can cause vasodilatation. Although data on comedication with these two classes are currently limited, the use of PDE5-Is in patients receiving α1-blockers can lead to symptomatic hypotension. The use of sildenafil in conjunction with an α1-blocker is permitted as long as the initial dose of the PDE5-I is low and the patient is stable on the α1-blocker [14]. The precautions for use of vardenafil with an α1-blocker are similar [14].

2.1.5. Conclusions
The α1-blockers are generally well tolerated. The main AEs are vasodilatory effects and ejaculatory dysfunction. Alfuzosin and tamsulosin are better tolerated than terazosin and doxazosin. Tamsulosin causes fewer vasodilatory AEs than alfuzosin, but causes more ejaculatory abnormalities. The use of PDE5-Is for management of erectile dysfunction in patients receiving α1-blockers should be done with care due to the risk of a synergistic lowering of blood pressure.

2.2. 5α-Reductase inhibitors

The 5α-reductase inhibitors (5ARIs) are finasteride, an inhibitor of 5α reductase type I, and dutasteride, a dual inhibitor of 5α reductase types I and II. The 5ARIs inhibit the steroid 5α reductase isoenzymes, which are responsible for the conversion of testosterone to dihydrotestosterone (DHT), the main androgen stimulating prostate growth. Removal of DHT results in relative androgen withdrawal in the prostate, causing shrinking of the gland and subsequent improvements in urinary symptoms and flow, and a reduction in the risk of acute urinary retention [15,16]. Because DHT potentiates the effect of testosterone on erectile function, the sexual side-effects seen with these agents are not unexpected [17]. Treatment-related AEs reported during trials of these agents are mainly sexual events; other AEs occur at an incidence <1%. The 5ARIs are also known to affect testosterone and prostate-specific antigen (PSA) levels.

2.2.1. Sexual AEs and gynaecomastia
In trials of dutasteride and finasteride, the only AEs that occurred more often with these agents than with placebo were sexual AEs and gynaecomastia [16,18,19]. In the phase 3, long-term, double-blind, placebo-controlled studies of dutasteride, for example, the drug-related AEs observed were mainly impotence, reduced libido, ejaculation disorders, and gynaecomastia (Fig. 2) [16,20]. These studies included 4325 patients with BPH who were randomised to receive placebo (n = 2158) or dutasteride (n = 2167), followed for 2 yr in the double-blind phase and then in a 2-yr, open-label extension. Sexual AEs tended to occur during the first 6 mo of therapy but decreased with study duration. The incidence of drug-related gynaecomastia was low and remained constant throughout the study; gynaecomastia occurred in 1.3% of patients in years 1 and 2, 1.8% in year 3, and 0.7% in year 4. Fewer than 1% of European Urology Supplements 5 (2006) 1004–1012

Fig. 2 – Sexual adverse events and gynaecomastia associated with dutasteride use. *Includes breast enlargement and breast/nipple tenderness [16].
patients withdrew due to drug-related sexual AEs in the open-label phase [16].

Data on the sexual AEs associated with finasteride are available from the Proscar Long-Term Efficacy and Safety Study (PLESS), in which 3040 patients with BPH were randomised to receive placebo (n = 1516) or finasteride (n = 1524) and were followed for 4 yr [18]. On entry to the study, a large proportion of patients already had sexual dysfunction; 46% of patients in both groups had a history of sexual dysfunction. During the first year of the study, significantly more patients in the finasteride group (15%) compared with the placebo group (7%) experienced drug-related sexual AEs (p < 0.001). These sexual AEs included reduced libido, erectile dysfunction, decreased ejaculate volume, and other ejaculation disorders (Fig. 3) [18]; most of these AEs were mild to moderate in intensity. During the remaining 3 yr of the study, there was no difference between the groups in the incidence of new sexual AEs (7% in both groups). Sexual AEs resolved with continued therapy in 12% of patients in the finasteride group and 19% of patients in the placebo group, and only 4% of finasteride and 2% of placebo patients discontinued therapy due to sexual AEs.

In a comparator study of dutasteride and finasteride involving 1630 men with BPH, the incidence of drug-related AEs was slightly lower with dutasteride, with a 17% incidence in dutasteride-treated patients and a 20% incidence in finasteride-treated men, primarily of a sexual nature (not significant) [20]. It is interesting to note that although dutasteride is able to reduce DHT levels to a greater extent than finasteride [21], the incidence of AEs is comparable with the two 5ARIs.

2.2.2. PSA levels
In the studies of dutasteride reported by Debruyne and coworkers, PSA levels fell by a mean of 53% from baseline at 2 yr and 57% from baseline at 4 yr [16]. With placebo, PSA levels increased by 15% from baseline at 2 yr, but when dutasteride therapy was started at this point, PSA levels fell to 48% below baseline at 4 yr. A similar effect is seen with finasteride, where a 50% decrease in PSA level has been reported [17]. Thus, although PSA levels fall with 5ARIs, this parameter still maintains its role as a marker of prostatic cancer, and in individuals taking these agents who are also undergoing PSA screening, PSA levels can be doubled and then compared with age-related norms [22]. Recent data from the Prostate Cancer Prevention Trial (PCPT) suggest that PSA performance is improved in patients receiving finasteride, in terms of overall detection of cancer, and for high-grade cancers [23].

2.2.3. Serum testosterone levels
Serum testosterone levels remained within the physiologic range during therapy with dutasteride [16], increasing by 20% from baseline at 2 yr and maintained at 4 yr. With placebo, serum testosterone levels increased by 2% from baseline at 2 yr and increased to 20% above baseline at 4 yr. Finasteride treatment led to a modest (but statistically significant) increase in serum testosterone levels compared with placebo (p < 0.001) [24].

2.2.4. Interaction with cardiovascular drugs and PDE5-Is
The 5ARIs have few, if any, effects on the cardiovascular system, so do not tend to cause vasodilatory AEs such as dizziness or postural hypotension [25]. The 5ARIs do not interact negatively with cardiovascular drugs and use of PDE5-Is is unrestricted with these agents [14].
2.2.5. Conclusions
The overall conclusion from these studies is that 5ARIs are well tolerated. Sexual AEs are the most common drug-related AEs, although they occur infrequently and do have a significant impact on treatment continuation. With both agents, these AEs occur during the first year of treatment, and there is no evidence of increased AEs compared with placebo after the first year of therapy.

2.3. Combination therapy: $\alpha_1$-blocker plus 5ARI
A combination of an $\alpha_1$-blocker and a 5ARI has been assessed in the Medical Therapy of Prostate Symptoms (MTOPS) study. Finasteride and doxazosin in combination provided superior benefits in terms of symptom relief and improvement in maximum flow rate ($Q_{\text{max}}$) than either agent alone [26]. But it has to be considered whether combining the two types of therapy actually increases the likelihood of AEs. The MTOPS study revealed that patients on combination therapy experienced AEs similar to those for each drug alone and that these were typical for patients receiving these classes of drugs, that is, dizziness, erectile dysfunction, postural hypotension, and asthemia. There was a higher incidence of AEs in the combination arm compared with either monotherapy. Nevertheless, the discontinuation rates were lower with combination therapy (18%) compared with finasteride (24%) and doxazosin (27%) monotherapies. The overall safety of long-term combination medical therapy was shown by the fact that none of the side-effects had a frequency greater than six events per 100 patient-years of follow-up. In the Symptom Management After Reducing Therapy (SMART) trial involving a combination of tamsulosin and dutasteride for a fixed period followed by withdrawal of the $\alpha_1$-blocker, the AEs were as expected for either medication [27].

3. Safety and tolerability of surgical approaches

3.1. Open prostatectomy versus less invasive approaches
When considering the safety and tolerability of treatments for BPH, surgery of any form involves hospitalisation and presents a significant rate of short-term and long-term complications. Open prostatectomy, though an effective approach to BPH treatment, is seldom used today except for patients with specific indications (eg, very large prostate gland or renal insufficiency). Interestingly, a recent study by Vela-Navarrete et al. has reported an increased incidence of open procedures conducted between 1992 and 2002 due to larger sized glands [28]. They speculate that this might be due to the longer use of $\alpha_1$-blockers during this period, which allowed the prostate to grow to a greater extent before the need for surgery.

The open procedure has largely been replaced by less invasive techniques [28] and, of these, transurethral resection of the prostate (TURP) is the most widely used. Although promising in terms of efficacy and safety, none of the more recently developed approaches (eg, transurethral needle ablation [TUNA]; transurethral microwave thermotherapy [TUMT]; water-induced thermotherapy [WIT]; and a variety of laser-based approaches), has yet demonstrated clear superiority to TURP in terms of a superior cost–benefit ratio [29]. Of the minimally invasive therapies, European Association of Urology guidelines suggest that holmium laser enucleation of the prostate (HoLEP) can be used safely in patients receiving anticoagulant medication or who are in urinary retention [30]. Good outcomes have been reported immediately after surgery [31] and were comparable to TURP [32]. Retrograde ejaculation occurs in 75–80% of patients, 

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3885</td>
<td>520</td>
<td>1990</td>
<td>1931</td>
</tr>
<tr>
<td>Complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>24.9</td>
<td>13.3</td>
<td>17.2</td>
<td>9.5</td>
</tr>
<tr>
<td>Bleeding requiring transfusions</td>
<td>6.4</td>
<td>0.4</td>
<td>20.2</td>
<td>6.1</td>
</tr>
<tr>
<td>Clot retention</td>
<td>3.3</td>
<td>1.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Transurethral resection syndrome</td>
<td>2.0</td>
<td>0.8</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Myocardial arrhythmia</td>
<td>1.1</td>
<td>1.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.05</td>
<td>0.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Failure to void</td>
<td>6.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2.3</td>
<td>2.1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Death</td>
<td>0.2</td>
<td>0.0</td>
<td>0.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>
but no postoperative erectile dysfunction has been reported [33].

3.2. TURP

In the case of TURP, short-term (mainly perioperative) complications include death, bleeding, clot retention, transurethral resection (TUR) syndrome (hyponatraemia resulting in mental confusion, nausea, vomiting, and raised blood pressure), urinary tract infection, and inability to void, among which, bleeding is the most common. Some of these complications (eg, bleeding and TUR syndrome) may be serious and life-threatening. In the largest TURP series reported so far (a retrospective evaluation of 3885 patients), perioperative mortality was 0.2% and perioperative morbidity was 24.9% [34]. More recent reports give better results, although morbidity remains significant (Table 2) [34–36].

Long-term complications of TURP include failure to void, retrograde ejaculation, impotence, partial or complete incontinence, and retreatment. Example rates for these complications are about 13% for failure to void [37,38], 58% for retrograde ejaculation [39], about 15% for impotence [40,41], about 2% for partial incontinence, and 1% for complete incontinence [42]. Up to 10% of patients require retreatment for urethral stricture or bladder-neck contracture [42]. The current American Urological Association guidelines on BPH estimate the incidence of erectile dysfunction following TURP to be of the order of 10% [43]. A review of 29 randomised controlled trials revealed an incidence of 6.5% following TURP [44].

3.3. Conclusions

Surgery of any form involves hospitalisation and presents a significant rate of short-term and long-term complications. Among the less invasive techniques, TURP is the most widely used. Short-term complications of TURP include death, bleeding, clot retention, TUR, urinary tract infection, and inability to void. Long-term complications of TURP include failure to void, retrograde ejaculation, impotence, partial or complete incontinence, and retreatment.

4. Conclusions

The medical and surgical treatments for BPH are associated with an acceptable level of morbidity. For individual patients, treatment choice depends on disease severity, comorbidity, patient preferences, and the comparative efficacy and AEs of the available therapies. Disease-related symptoms and treatment-related factors also influence HRQOL. Patient expectations of therapy should be considered, particularly with regard to AEs, so that treatment can be tailored to individual patient needs and HRQOL can be maximised.

References

