The Long-Term Outcome of Medical Therapy for BPH

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Abstract

Objectives: The lack of cure with medical therapy implies life-long treatment emphasising the need for a thorough understanding of the long-term outcome. We review the natural history, markers for progression, placebo effect, efficacy, pharmacoeconomic aspects, and preventive measures.

Methods: Literature review with particular reference to long-term controlled studies using plant extracts, α1-blockers, 5α-reductase inhibitors (5-ARIs), and combination therapy.

Results: There is a long-lasting (≥12 mo) placebo response of symptoms (20% decrease) and maximum flow rate (10% rise). The five long-term controlled trials of plant extracts are inconclusive and therefore their role in contemporary medical management is still controversial. The α1-blockers provide fast amelioration of symptoms yet have no relevant impact on the risk of acute urinary retention or surgery. Combination therapy should be reserved for moderately or severely symptomatic patients with a high risk of progression; in the majority of patients the α1-blocker can be safely stopped after 6–12 mo. The preventive use of 5-ARIs in men with no or mild symptoms at risk of progression is scientifically sound yet not generally accepted mainly for economic reasons.

Conclusions: A sharp contrast exists between the duration of 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.

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1. Introduction

Medical management has become the standard of care for men with bothersome lower urinary tract symptoms (LUTS) suggestive of benign prostatic enlargement (BPE)/benign prostatic obstruction (BPO) in the absence of a strong indication for surgery [1–3].

The World Health Organization-Benign Prostatic Hyperplasia (WHO-BPH) Consensus Conference has defined standards regarding the evaluation of medical therapies for LUTS due to BPE/BPO: prospective, randomised against placebo/standard therapy and with a minimum study period of 12 mo [4].

The lack of cure with drugs implies life-long treatment unless severe complications, lack of efficacy, or side-effects necessitate termination. Given the current life expectancy, this means that a man in his sixties will have to take these drugs over one to two decades of life. Therefore, a detailed knowledge on the long-term outcome is of paramount interest. The high prevalence of this disorder and demographic changes further underline the socioeconomic relevance of this disease [5–8].

This review highlights a number of important aspects regarding the long-term medical management of LUTS, such as the natural history, markers for progression, placebo effect, long-term efficacy, pharmacoeconomic aspects, and preventive measures.

2. Methods

A MedLine-based research covering 1990–2006 was performed (abstracts were not considered). Regarding efficacy and tolerability we concentrated on controlled trials with a minimum follow-up of 12 mo, and small-sized studies were excluded (Table 1).

### Table 1 – Overview of randomised controlled trials with a minimum follow-up of 12 mo

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Active</th>
<th>Comparator</th>
<th>Duration, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plant extracts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bach, 2000 [36]</td>
<td>476</td>
<td>Pumpkin extract</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Schneider, 2005 [35]</td>
<td>246</td>
<td>Stinging nettle roots</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Bent, 2006 [34]</td>
<td>225</td>
<td>Saw Palmetto</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Debruyne, 2002 [38]</td>
<td>704</td>
<td>Saw Palmetto</td>
<td>Tamsulosin</td>
<td>12</td>
</tr>
<tr>
<td>Sökeland, 1997 [37]</td>
<td>543</td>
<td>Sabal/Stinging nettle roots</td>
<td>Finasteride</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2194</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>α1-Blocker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roehrborn, 1996 [47]</td>
<td>2084</td>
<td>Terazosin</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Lepor, 1996 [48]</td>
<td>710</td>
<td>Terazosin</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Lepor, 1998 [49]</td>
<td>418</td>
<td>Tamsulosin</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Kirby, 2003 [50]</td>
<td>503</td>
<td>Doxazosin</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>McConnell, 2003 [27]</td>
<td>1493</td>
<td>Doxazosin</td>
<td>Placebo</td>
<td>54</td>
</tr>
<tr>
<td>Roehrborn, 2006 [28]</td>
<td>1522</td>
<td>Alfuzosin</td>
<td>Placebo</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6730</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>5-ARIs</strong></td>
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<tr>
<td>Andersen, 1995 [56]</td>
<td>707</td>
<td>Finasteride</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Nickel, 1996 [57]</td>
<td>613</td>
<td>Finasteride</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Lepor, 1996 [48]</td>
<td>615</td>
<td>Finasteride</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Kirby, 2003 [50]</td>
<td>492</td>
<td>Finasteride</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Lowe, 2003 [58]</td>
<td>487</td>
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<tr>
<td>Marberger, 1998 [59]</td>
<td>2902</td>
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<td>Placebo</td>
<td>24</td>
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<tr>
<td>McConnell, 1998 [60]</td>
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<td>Placebo</td>
<td>48</td>
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<tr>
<td>McConnell, 2003 [27]</td>
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<td>Finasteride</td>
<td>Placebo</td>
<td>54</td>
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<tr>
<td>Roehrborn, 2002 [61]</td>
<td>4325</td>
<td>Dutasteride</td>
<td>Placebo</td>
<td>24</td>
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<tr>
<td><strong>Total</strong></td>
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<td></td>
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<td><strong>Combination therapy</strong></td>
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</tr>
<tr>
<td>Lepor, 1996 [48]</td>
<td>614</td>
<td>Terazosin/Finasteride</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>McConnell, 2003 [27]</td>
<td>1523</td>
<td>Doxazosin/Finasteride</td>
<td>Placebo</td>
<td>54</td>
</tr>
<tr>
<td>Kirby, 2003 [50]</td>
<td>518</td>
<td>Doxazosin/Finasteride</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2655</strong></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

All published series on plant extracts, α1-blockers, and combination therapy were added; for finasteride a few older studies were not considered (see Methods). 5-ARIs = 5α-reductase inhibitors.
3. Natural history and the concept of progression

A thorough understanding of the natural history is of paramount importance in interpreting long-term medical trials. The natural history is best studied from longitudinal, ideally population-based studies, such as the Olmsted County Study, Health Professional Follow-up Study or Krimpen Study, the largest European longitudinal study on this issue [9–14]. Useful information can also be derived from registries and the placebo arms of controlled trials [15]. All approaches have their advantages and limitations, such as the Hawthorne effect or the natural regression to the mean [16]. Furthermore, BPH-related outcomes tend to be underestimated in the placebo arm of clinical trials compared with community-dwelling men [17].

All aspects of BPE/LUTS/BPO progress with age [10, 18–20]. The median annual prostate growth in the Olmsted County Study was 1.9%. In parallel, LUTS deteriorate with age as moderate-to-severe LUTS are present in about 25% of men in their sixties, 30% of men in their seventies, and up to 40% in those older than 70 yr [21]. Although LUTS tend to worsen over time, 20–30% of patients experience a prolonged remission [22]. Little is known regarding the natural history of BPO because there is only one long-term urodynamic-based longitudinal study suggesting that untreated BPO does not significantly deteriorate in the long term [23]. The maximum flow rate (Qmax) declines around 2%/yr depending on the baseline flow rate, age, prostate volume, and symptom severity [24]. Serious complications such as acute urinary retention (AUR) or the need for surgery are rather rare events, in the range of 0.2–1%/yr [10, 25, 26].

The impact of medical therapy on BPH progression was first studied in detail in the Medical Trial of Prostatic Symptoms (MTOPS) [27]. In this study, progression was defined as symptomatic worsening (American Urological Association [AUA] score ≥4), occurrence of AUR/prostate surgery, incontinence, renal failure, or recurrent urinary tract infection [27]. Over 4.5 yr only 17% within a typical LUTS population developed a progression event in the placebo arm, with symptomatic worsening by far most frequent event (78%), followed by AUR (12%), and urinary incontinence (9%) [27].

Fig. 1 – Placebo response in long-term medical trials. The data of all trials listed in Table 1 were analysed; some trials contained no detailed information regarding maximum flow rate (Qmax). Each dot indicates the placebo arm of one study, the horizontal bars the respective mean values.

4. Risk factors for progression

Age, severe LUTS, low Qmax, high postvoid residual (PVR), enlarged prostate, and high serum prostate-specific antigen (PSA) are risk factors for AUR and BPH-related surgery [16–20]. Slawin et al presented the first nomogram to predict AUR by modelling 4294 men treated in phase 3 dutasteride trials [29]. This nomogram included the AUA score, bother index, prior α1-blocker therapy, prostate volume, PSA and Qmax. Such nomograms may enable an individualised, risk-adapted, and economical medical management in the future [29].

5. Long-term outcome of medical therapy

5.1. Placebo effect

There is considerable evidence of a long-lasting placebo effect [30, 31]. This placebo effect is demonstrable for subjective and objective parameters (Fig. 1). The mean improvement of symptom score after 12 mo was 21.4% (range: 4.8–34%), after 24 mo 10.9% (range: 1.5–24.5%), and after 4.5 yr 15.9% (range: 7.9–23.8%; Fig. 1). Qmax improved for a mean of 12.4% after 12 mo (0–27%), 5.3% after 24 mo...
The placebo response shows remarkable differences in the various trials (Figs. 1–3). These differences are most likely caused by different inclusion/exclusion criteria, study designs, dosing, etc. In fact, the highest placebo response (eg, Fig. 2, Lepor 1998 [49]) exceeds the active drug of many other trials. These data, despite being impressive, do not describe the real placebo effect because this is partly dissipated in the placebo-run in phase. Nickel et al have reported such an analysis based on a 25-mo placebo-controlled trial [32]. Total symptom score improved by 2.3 points (16%) and the Qmax by 1.0 ml/s (+10%) at 25 mo [32]. These changes were indeed slightly higher than the respective placebo responses reported traditionally (excluding the run-in phase). The mechanisms leading to this prolonged placebo response remain poorly understood, yet condition-specific factors and self-management, patient-specific factors, and trial-specific factors are likely to be involved [30,33].

5.2. Efficacy

5.2.1. Plant extracts

In countries with a long tradition in phytotherapy (Austria, Germany, France) plant extracts still reach market shares up to 30% [6,7]. Only five randomised, controlled studies with a follow-up of 12 mo are available; longer controlled studies have not been reported [34–38] (Table 1). Due to different extraction techniques each extract needs to be analysed separately [39,40]. Bent et al randomised 225 patients 1:1 between saw palmetto and placebo [34]. This highly published and probably best designed phytotherapy trial was negative, leading to the conclusion that this extract was identical to placebo (Figs. 2 and 3) [34]. Schneider and Rübben randomised 226 patients 1:1 into a placebo or a stinging nettle roots arm [35]. After 12 mo, the symptom score decreased by 4.7 points (−25%) with placebo and by 5.7 points (−30.5%) with the stinging nettle root extract (Fig. 2). Changes of Qmax and PVR volume were identical in both arms, yet not described in detail [30]. Finally, Bach et al randomised 476 men 1:1 to placebo or a pumpkin extract [36]. After 12 mo, the International Prostate Symptom Score (IPSS) decreased by 5.5 (−30.6%) in the placebo arm and by 6.7 (−25.4%) in the plant extract arm (Fig. 2). Data of Qmax and prostate volume were not available [36]. Two extracts have been tested against standard therapy: saw palmetto against tamsulosin and a combination product (saw palmetto/stinging nettle root) against finasteride [37,38] (Table 1 and Figs. 2 and 3). Both trials revealed similar outcomes regarding symptoms, Qmax, and PVR between the plant extract and standard therapy; unfortunately, these two trials contained no placebo arms (Figs. 2 and 3). Based on these limited data, it is not surprising that the statement of various BPH guidelines for plant extracts range from negative to only tentatively positive [2,41,42]. The large numbers of meta-analyses cannot supplement prospective studies according to WHO standards, which should ideally contain a placebo arm [43–45].
5.2.3. The 5α-reductase inhibitors

Dutasteride and, particularly, finasteride are the most intensively studied drugs for BPH (Table 1 and Figs. 2 and 3) [27,48,50,56–61]. To date no comparative trial between the two 5α-reductase inhibitors (5-ARIs) has been published in the peer-reviewed literature and a comparison based on the existing data is flawed due to different inclusion/exclusion criteria. The 5-ARIs are the only drugs for BPH that reduce prostate volume by 20–25% [27,48,50,56–61]. LUTS improve in about 20–30%, and this improvement is maintained for 4.5 yr in controlled settings [27,48,50,56–61]. The three long-term combination trials suggest a superiority of α1-blockers in improving LUTS [27,48,50]: Prospective European Doxazosin and Combination Therapy (PREDICT, 12 mo): symptom score reduction −49% (doxazosin) versus −36% (finasteride); VA Cooperative Study (12 mo): −38% (terazosin) versus −20% (finasteride); and MTOPS (4.5 yr): −35% (doxazosin) versus 29% (finasteride) (Fig. 2) [27,48,50]. Uroflow improves less impressively by 10–20%; again α1-blockers are slightly superior in this respect (Fig. 3) [27,48,50].

5.2.4. Combination therapy

The rationale for combining α1-blockers and 5-ARIs is their differential mode of action in managing LUTS secondary to BPE/BPO (Table 1) [27,48,50]. The VA Cooperative Study and the PREDICT trial failed to demonstrate a benefit for combination therapy over α1-blocker monotherapy (Figs. 2 and 3). The 12-mo duration of these two trials, however, was too short to demonstrate a benefit of combination therapy on the natural history [62]. Hence, MTOPS is the only combination trial with a sufficient duration to provide sufficient answers in this respect [27,62]. Combination therapy reduced the risk of progression by 68% compared to placebo, 39% versus finasteride and 42% versus doxazosin. In terms of individual secondary end points within the study, combination therapy resulted in benefits over both α-blocker (doxazosin) and 5-ARI (finasteride) for median improvement in AUA score −7.0 (± 44%) versus −6.0 (± 35%) and −5.0 (± 29%) points and Qmax +3.7 (+35%) versus +2.5 (+24%) versus +2.2 (± 21%) ml/s [27,62]. In general, there was a strong correlation (correlation coefficient: 0.86, p < 0.0001) between the symptomatic and objective improvement in the long-term trials analysed herein (Figs. 2 and 3). These data demonstrate that patients with a more significant improvement in uroflow exhibit also a more profound symptom improvement. Interestingly, a similar trend that did not reach statistical significance (p = 0.8) was also observed for the placebo arm.

Further data from the MTOPS study suggest that combination therapy has the greatest benefit in reducing symptoms and the risk of AUR in men with higher baseline prostate volume or PSA [63]. These findings are confirmed by real-life data [64]. For several reasons the duration of combination therapy is relevant: (1) economic aspects (although generics reduce costs), (2) side-effects, (3) the fact that combination therapy provides no relevant advantage over 5-ARI monotherapy regarding the impact on the natural history, and (4) the 5-ARI exerts the full clinical efficacy after 6 mo. The Symptom Management After Reducing Therapy (SMART-1) demonstrates that withdrawal of the α1-blocker is possible in men with moderate LUTS after 6 mo; those with severe LUTS may require a longer combined treatment time (9–12 months) [65].

5.3. Side-effects and drop-out rates

5.3.1. Plant extracts

Plant extracts exhibit a good tolerability that has been emphasised as one of the pros of this approach that renders plant extracts particularly attractive for sexually active men who want to avoid the sexual
side-effects of α₁-blockers and 5-ARIs [34–38,66]. Claus Roehrborn was among the first to highlight the importance of reporting discontinuation rates when comparing clinical trials [31]. Fig. 4 (in analogy to Roehrborn’s original graph [31]) presents discontinuation rates of all randomised controlled trials analysed herein (Table 1). Discontinuation rates of the four plant extract trials that provide information on this aspect were low at 0% [37], 8.9% [34], 14.4% [38], and 14.6% [36].

5.3.2. The α₁-blockers
Safety and tolerability of α₁-blockers, 5-ARIs, and combination therapy have been recently described in great detail in European Urology and we largely refer to this article [67]. The main adverse events (AEs) are vasodilatory effects and ejaculatory dysfunction. Cardiovascular AEs occur more frequently in patients aged 70 yr or older than in younger patients. Alfuzosin and tamsulosin are generally better tolerated than terazosin and doxazosin. Tamsulosin causes fewer vasodilatory AEs than alfuzosin, but more ejaculatory abnormalities in the range of 5% to 10% [46]. Preliminary data suggest that alfuzosin may even improve various aspects of sexual function [68,69]. The phosphodiesterase type 5 inhibitors (PDE5-Is) in patients receiving α₁-blockers should be prescribed with care due to the potential risk of a synergistic lowering of blood pressure, although recent short-term controlled trials suggest that a clinically significant hypotension is unlikely to be induced [70,71]. A new small-pupil syndrome, called intraoperative floppy iris syndrome (IFIS), was recently described in patients undergoing cataract surgery and taking α₁-blockers [72,73]. Urologists must be aware of this rare complication and should inform patients and ophthalmologists accordingly [73]. Drop-out rates in the majority of α₁-blocker trials were higher than those with 5-ARIs (Fig. 4) [31]. When interpreting these data one has to be aware that the majority of these trials were performed with “older” α-blockers (doxazosin/terazosin) known to have a higher rate of AEs [46]. The only long-term trial with a “modern” α₁-blocker (eg, alfuzosin) suggests a lower drop-out rate (30% after 2 yr) [28].

5.3.3. The 5-ARIs
The only AEs that occurred more often with the 5-ARIs than with placebo were sexual AEs (<10%) and gynaecomastia (2%) [67]. Sexual AEs tend to occur during the first 6–12 mo and there is no evidence of increased AEs compared with placebo thereafter. Both 5-ARIs reduce serum PSA by approximately 50% yet maintain its role as a serum tumour marker for prostate cancer by doubling the value [74]. Recent data from the Prostate Cancer Prevention Trial (PCPT) suggest that PSA performance is even improved in patients receiving finasteride [74]. Serum testosterone levels increase by approximately 20% due to reduction of serum dihydrotestosterone (DHT) [75]. 5-ARIs do not interact with cardiovascular drugs and use of PDE5-Is is unrestricted [67]. Discontinuation rates in the 5-ARIs trials were lower than in the α₁-blocker trials; 10–20% of patients discontinued after 2 yr (Fig. 4) [31].

5.3.4. Combination therapy
MTOPS 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 asthenia [27]. There was a higher incidence of AEs in the combination arm compared with either monotherapy. Nevertheless, discontinuation rates were lower with combination therapy (18%) compared to finasteride (24%) and doxazosin (27%) monotherapy [27].

5.4. Impact on the natural history
Given the fact that the concept of medical therapy is a lifelong strategy, the impact of any medical approach on the natural history of the disease (AUR/surgery) is of importance. Although open-label and post-marketing studies can provide some evidence
in this respect, randomised, controlled trials (RCTs) remain the gold standard to reliably assess this issue. The low incidence of AUR and of surgical intervention emphasise the need for long-term placebo trials. The substantial costs of such trials explain the paucity of long-term data.

5.4.1. Plant extracts
Three 12-mo trials provide information regarding the impact on AUR [34,37,38]. In two studies, the rate of AUR was identical between the plant extract and the respective comparator; in the third study the plant extract was even superior to finasteride regarding the risk of AUR (0.8% vs. 2.9%) [34,37,38]. The fact that plant extracts (such as α1-blockers) have no impact on prostate volume and PSA renders a positive impact on the natural history (AUR/need for surgery) unlikely.

5.4.2. The α1-blockers
Two long-term (2 yr and 4.5 yr), placebo-controlled trials allow a reliable assessment of the impact of α1-blockers on the natural history [27,28]. The MTOPS study showed that doxazosin given for 4.5 yr has no effect on prostate volume, challenging the in vivo clinical relevance of the in vitro apoptotic potential [27,76]. Doxazosin only delayed the time to AUR by about 2 yr, but did not significantly reduce the cumulative incidence when compared to placebo (2.7% vs. 2.0%) after 4.5 yr [27]. The cumulative incidence of invasive therapy was also not significantly affected by doxazosin [27]. This study has been criticised for the use of a rather “old” α-blocker and it has been doubted whether these data can be extrapolated to modern α1-blockers. Such a trial has been recently published [28]. Roehrborn et al randomised 1522 men 1:1 into a placebo and an alfuzosin arm; patients were followed for 24 mo [28]. Alfuzosin did not reduce the risk of AUR (alfuzosin 2.1% vs. placebo 1.8%, p = 0.82) [28]. There was a trend towards a lower risk for surgery in the alfuzosin arm (5.1% vs. 6.5%) that did not reach statistical significance [28]. In summary, the two long-term placebo-controlled trials as well as indirect evidence from registry data suggest that doxazosin and alfuzosin have no relevant impact on the natural history [27,28]. Souverein et al studied a population-based cohort of 5671 patients using the PHARMO Record Linkage System [77]. Patients taking α1-blockers had a significantly increased risk of BPH-related prostatic surgery compared to those receiving 5-ARIs [77]. This difference was sustained after stratification of time period and the inclusion of patients who had surgery within 1 mo of treatment initiation [77].

Despite these data, the concept of a trial without a catheter (TWOC) with α-blockade is likely to become widely accepted [78–80]. Little is known regarding the impact on AUR [34,37,38]. In two studies, the rate of AUR was identical between the plant extract and the respective comparator; in the third study the plant extract was even superior to finasteride regarding the risk of AUR (0.8% vs. 2.9%) [34,37,38]. The fact that plant extracts (such as α1-blockers) have no impact on prostate volume and PSA renders a positive impact on the natural history (AUR/need for surgery) unlikely.

5.4.3. 5-ARIs
The 5-ARIs have a well-documented positive impact on the natural history [27,59–61]. Dutasteride reduces the risk for AUR compared to placebo by 48% and the risk for surgery by 55% [61]. Long-term trials with finasteride yielded comparable reductions. In MTOPS (4.5 yr) the risk reduction for AUR was 68% and for the risk of surgery 64%; in the Proscar Long-term Efficacy and Safety Study (PLESS) (4 yr), the respective numbers were 57% and 55% and in the Proscar Worldwide Efficacy and Safety Study (PROWESS) (2 yr) 57% and 40% [27,59,60]. The 2-yr open extension of the 4-yr PLESS trial has documented a sustained decrease in the incidence of AUR and BPH-related surgery [81]. PLESS and MTOPS results underline the link between increased baseline serum PSA levels and prostate volume and the increased risk for AUR/BPH-related surgery. Patients with prostate volume >30 ml and a serum PSA of >1.6 ng/ml (such as those with a baseline Q max <10.6 ml/s, PVR > 39 ml, and older than 62 yr) had an increased risk for AUR/surgery. These data support a risk-stratified patient management (see below); patients at an increased risk for progression are the ideal cohort for long-term 5-ARIs.

5.4.4. Combination therapy
As indicated above, the VA Cooperative Study and PREDICT trials were too short (12 mo) for a reliable assessment in this respect. Hence, only the MTOPS study can provide relevant information [62]. Although combination therapy was most effective in reducing the risk of overall progression, this approach was not superior to 5-ARI monotherapy and may provide relevant information [27,48,50]. Within 4.5 yr, the cumulative incidence of AUR was 0.8% for finasteride and 0.5% for combination therapy compared to 2.4% for placebo [27]. Similarly, the incidence of BPH-related surgery was 5.0% for placebo versus 1.8% for finasteride and 1.5%
with combination therapy [27]. Subsequent analyses of the MTOPS study identified prostate volume as a decisive factor; combination therapy had the greatest benefit in reducing symptoms, bother, and the risk of AUR in men with higher baseline prostate volume and PSA [62].

6. Pharmacoeconomic aspects

The Trans European into the Use of Management Policies for BPH in Primary Healthcare (TRIUMPH) study determined medical consumption and costs during a 1-yr follow-up in a cross-sectional European study [82]. Treatment costs for 5057 patients (66 yr) averaged at €858/patient ranging from €292 in the United Kingdom to €1337 in Poland [82]. Medication was the most important (75%) cost driver followed by surgery (15%) and diagnostic steps (8%). Choice of medication, complications, and undergoing surgery were associated with higher costs [82]. Remarkable are the substantial differences in prescribing patterns throughout Europe [83]. The range of prescribing plant extracts in six European countries ranged from 3.5% (Italy) to 37% (Germany), of α-blockers from 60.4% (Germany) to 98.5% (United Kingdom), and of 5-ARIs from 1.5% (United Kingdom) to 7.2% (Poland) [83]. These data suggest that most likely other than medical factors trigger the choice of medical management [83]. Verhamme et al reported on discontinuation rates in a real-life setting (GP-database in the Netherlands) [84]. Discontinuation rates were 33% for α-blockers, 27% for 5-ARIs, and 29% for combination therapy [84]. In real life, the median total duration of use of pharmacologies was short, only 3 mo. Hence, clinical trials artificially improve persistence and adherence [84]. McDonald et al performed a pharmacoeconomic analysis of the MTOPS data and projected the costs over a 15-yr period [85]. As expected, combination therapy was more expensive than monotherapy with doxazosin but also more effective. The calculated costs of combination therapy per quality of life-year gained was $34,085 for all patients; this amount declined to $27,283 for men at a higher risk of progression (PSA > 3.2 ng/ml), a value that was considered cost effective [85]. Disantostefano et al calculated BPH-related costs over 20 yr in detail [8]. Treatment costs within the first year were estimated at $195 (US dollars) for watchful waiting, $628 for α1-blockers, $900 for 5-ARIs, $1333 for combination therapy, $4073 for transurethral microwave thermotherapy (TUMT) and $7201 for TURP [8]. The annual costs for subsequent years of the six treatments were $108, $541, $870, $1247, $54, and $54, respectively [8]. After 20 yr the most costly therapy was combination therapy followed by 5-ARIs, TURP, TUMT, α1-blockers, and watchful waiting. The α1-blockers are the least expensive treatment (apart from watchful waiting) and are effective in relieving symptoms yet have no effect on the natural history [8]. In the future real-life pharmacoepidemiologic data by linking dispensing and prescribing data will provide important insights in influencing drug use in the general practice, for example, who is using what and for how long [86].

7. Prevention

Intraprostatic DHT is the principal intracellular androgen in the prostate and plays a key role in the development of BPE. Therefore, early intervention with 5-ARIs is a logical preventive approach. Such data were recently reported for the PCPT [87]. After 7 yr, all LUTS/BPE/BPO parameters were favourable in the finasteride arm: urgency, 12.9% vs. 15.9%; AUR, 4.2% vs. 6.3%; TURP, 1.0% vs. 1.9%; prostatitis, 4.4% vs. 6.1%; and urinary tract infection, 1.0 vs. 1.3% [87].

8. Targeting the patient

8.1. When to intervene?

The optimal time point to initiate medical therapy is a matter of debate. Although all guidelines recommend a conservative approach for men with minimal symptoms, several observations argue in favour of early intervention [2,41,42]. First, the PCPT data suggest even the preventive use with finasteride [87]. Second, long-term data of the watchful waiting versus TURP VA trial showed that patients initially randomised to TURP had a better long-term outcome [88]. And finally, the 4-yr dutasteride trial demonstrated that longer therapy results in a better long-term outcome [89]. The mechanisms leading to these observations remain poorly defined, yet increasing BPO, detrusor hypocontractility, and detrusor overactivity are most likely involved [90]. Medical therapy should not be continued uncritically. Vela-Navarrete et al have shown that within a decade (1992–2002) patients undergoing BPH surgery were older (72 vs. 69 yr) and had larger prostates, and there was a higher rate of open surgery (28.6% vs. 18.8%) [91]. The authors speculated that these observations were due to the progressive nature of the disease, which is not affected by α1-blockers [91].
8.2. How to intervene?

Current knowledge on the natural history, on risk factors for progression, and on the long-term outcome of medical therapy provides the scientific basis for a risk-adapted management [2,16,19,20,41,42]. Plant extracts are currently not clearly recommended by any BPH guidelines [2,41,42]. The α1-blockers are the therapy of choice for patients with moderate to severe bothersome LUTS and a low risk of progression (ie, a prostate volume <30–40 ml). Combination therapy should be reserved for moderately or severely symptomatic patients with a high risk of progression; the α1-blocker can be safely stopped after 6–12 mo [65]. The preventive use of 5-ARIs in men with no or mild LUTS combined with a higher risk of progression, despite scientific soundness, is currently not a generally accepted.

9. Conclusions

Although the knowledge on the long-term outcome of medical therapy has increased substantially, it is still limited [92]. There is a sharp contrast between the duration of the longest controlled trial (4.5 yr) and the situation in real life with treatment periods up to one to two decades of life. Within the past decade no new classes of drugs in the management of LUTS due to BPH have been introduced into clinical practice [93,94]. The pathogenesis of BPH is still largely unresolved, but multiple partially overlapping and complementary systems (nerve, endocrine, and immune) and local para/luminocrine pleiotropic factors are likely to be involved [95]. It is hoped that upcoming generations of BPH drugs will interfere with these molecular mechanisms, thus enhancing the efficacy of the conservative approach.

Conflicts of interest

The authors have nothing to disclose.

References


