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REVIEW

Non-surgical management of BPH: An updated review of current literature and state of the art on natural compounds and medical therapy

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Summary ***Introduction: Benign prostatic hyperplasia (BPH) is a common urological disease that is strongly associated with the aging process and can lead to lower urinary tract symptoms (LUTS). LUTS due to BPH can significantly affect the quality of life of many patients. Among the treatments available for BPH to improve symptoms and functional outcomes, drug therapy and surgical therapy are the options of choice. However, for most patients with symptomatic BPH, medical management remains the cornerstone of treatment. Pharmacologic interventions are often preferred as a first approach, being less invasive compared to surgery. Although the medical treatment of BPH is currently defined by the algorithms of international guidelines, the need for a more personalized approach is increasingly recognized given the wide and heterogeneous range of therapeutic options available.***
Materials and methods: A review of medical therapy for BPH was conducted using relevant articles in PubMed, Scopus, and the Cochrane Central Register of Controlled Trials. In this review, all drug treatments currently available on the international market whose efficacy is scientifically proven are reviewed and described (phytotherapy, alpha-blockers, muscarinic receptor antagonists, 5-alpha-reductase inhibitors, combination therapies, etc.).
Results: A total of 17 randomized clinical trials were selected for review. Further 75 studies were included for analysis and discussion.
Conclusions: As the treatment landscape continues to evolve, tailoring therapy to individual patient needs and preferences is likely to become increasingly important to ensure that treatment strategies are both effective and meet patient expectations.

KEY WORDS: Benign prostatic hyperplasia; Medical therapy; Alpha-blockers; Antimuscarinics; Phytotherapy.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common urological disease that is strongly associated with the aging process (1). Prostate growth is influenced by a combination of intrinsic and extrinsic factors that interact in a complex manner. The pathophysiological pathway includes hormone and androgen exposure as well as growth factors, chronic inflammation and genetics (2). *Lower urinary tract symptoms* (LUTS) due to BPH can have a significant impact on patients' quality of life (3). For most patients with symptomatic benign prostatic hyperplasia, medical management remains the cornerstone of treatment. Pharmacologic measures are often preferred as a first approach as they can relieve symptoms and improve the patient's well-being (4). The landscape of medical treatment for BPH is constantly evolving. The efficacy of over-the-counter medications, plant extracts and natural supplements has not yet been adequately researched and their benefits are still unclear. At the same time, ongoing studies of new pharmacologic agents, such as beta-3 agonists, have the potential to expand the available therapeutic options, providing hope for more targeted and effective strategies in the future. With this review, we aimed to provide an up-to-date overview of the most common medical treatments for LUTS including phytotherapy in the context of BPH.

MATERIALS AND METHODS

In July 2024, a systematic review of medical therapy for BPH was conducted using relevant articles in *PubMed*, *Scopus*, and the *Cochrane Central Register of Controlled Trials*. The review focused on phytotherapy and medical

treatment of BPH. Three authors (GM, FA, GD) independently screened the titles and abstracts of the datasets for eligibility. Reviews, original articles, and case reports were included, while other types of articles were excluded. Evidence was limited to human data and experimental animal studies. Only publications in English were considered. In addition, manuscripts that were not focused on the purpose of the review were not included. The original list of selected articles was supplemented by individual suggestions from the co-authors of the present review. Similarly, articles published before 1990 but considered interesting for the purpose of the review were suggested by the authors and assessed by the screening team.

The reference lists of the selected articles/systematic reviews/meta-analyses were also screened to identify further potentially relevant studies, using the same criteria as for the initial search.

Results

The search strategy has been highlighted using the PRISMA flowchart (5) (Figure 1) and PICO model (6) (***Supplementary matherial***) to summarize the results. The risk of bias of the 17 randomized controlled trials included has been evaluated using the ROB 2 – revised tool (7) (Figure 2).

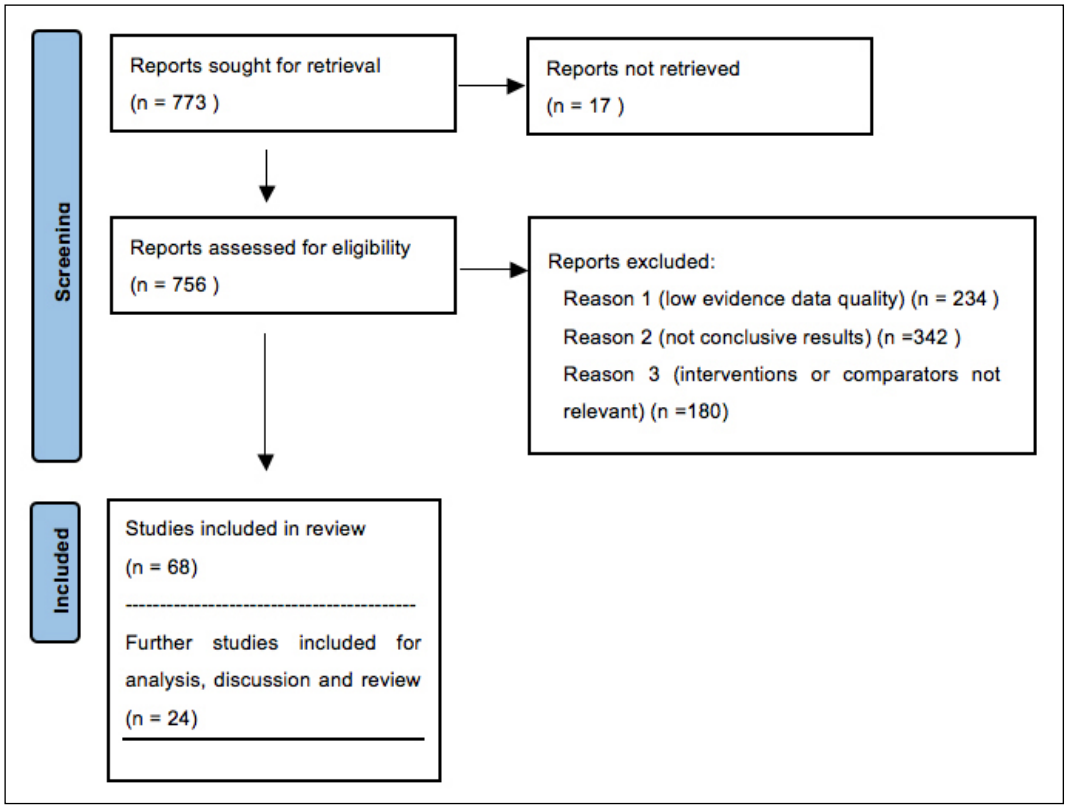

Figure 1.
PRISMA flowchart.

Source: Page MJ, et al. BMJ 2021; 372: n71.

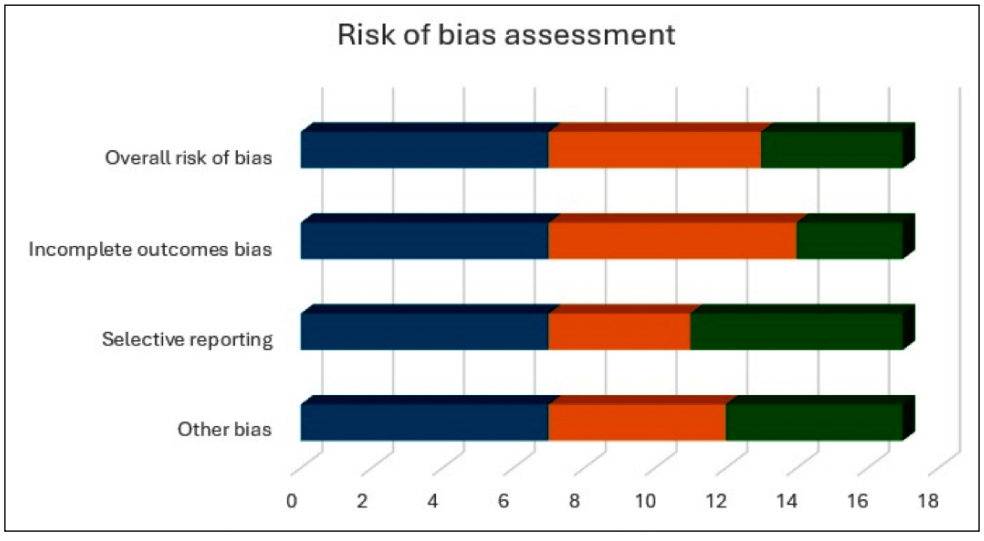

Figure 2.
Risk of bias of the 17 randomized controlled trials evaluated using the ROB 2 – revised tool.

Watchful waiting and dietary lifestyle

Many men with mild LUTS do not find their symptoms bothersome enough to warrant medical treatment or surgery. In addition, many patients are concerned about the potential complications associated with taking medication. In selected cases without clinical complications (renal insufficiency, hematuria, hydronephrosis, urinary tract infections, acute urinary retention…), *Watchful Waiting* (WW) might therefore be an even more attractive choice. In patients with mild LUTS (*International Prostate Symptom Score* - IPSS), the condition can remain stable many times without complications such as acute urinary retention (8). The key issues in the treatment of BPH with WW are the establishment of patient selection criteria and the assessment of risk factors for disease progression. Longitudinal studies such as the *Baltimore Longitudinal Study of Aging* (9) and the *Olmstead County Study* (10) have shown that advanced age, a larger prostate, and decreased urinary flow can predict the need for treatment. The *Veterans Administration Cooperative Study* has shown that in properly selected patients, especially those with low baseline values, watchful waiting can be a viable and safe strategy (11). Before or alongside treatment, lifestyle counseling and self-care information can positively impact men with LUTS due to BPH (12). Key components of this strategy include patient education, reassurance and regular monitoring, combined with specific lifestyle advice aimed at reducing urinary symptoms (12). It is often recommended to reduce fluid intake at times that minimize discomfort, such as before bedtime, and to limit the consumption of caffeine and alcohol, which can exacerbate symptoms such as frequency, urinary urgency and nocturia due to their diuretic effects (13). Techniques such as double voiding, urethral milking and bladder training are also recommended to improve bladder control and reduce dribbling (14). Another important measure is to avoid constipation and situations in which a person has to hold urine. Systematic reviews and meta-analyzes have found that self-management measures that include these lifestyle changes can significantly reduce the severity of symptoms and slow the progression of the disease, thus providing relief (14). This holistic approach not only improves quality of life, but also empowers patients to actively manage their disease.

Phytotherapy

Phytotherapy is a science that uses plant extracts, from leaves to roots to seeds, to achieve benefits in the treatment of diseases (15-17). There are numerous in vitro studies in the literature on the potential benefits of phytotherapy in the treatment of BPH, but little is known about the actual in vivo effects.

Serenoa repens

Serenoa Repens, also known as saw palmetto, is probably the best-known plant available for the treatment of BPH (18). The dried, ripe berry is used for the extraction. Serenoa repens has anti-androgenic activity with inhibition of 5α-reductase and therefore reduces prostate volume; its activity is associated with the action of free fatty acids such as lauric and palmitic acid, which are also responsible for reducing inflammation. For these reasons, saw palmetto can slow down the development of BPH and improve patients' *quality of life* (QoL), IPSS and symptoms (19). There are many different types of extraction from the plant. Hexane extraction has proven to be the most reliable and provides the best results. Currently, Serenoa repens is the only phytotherapy recommended in most of the major international guidelines for the treatment of BPH and its symptoms (20, 21). Most tablets available on the market are 320 mg and are taken once daily. Nevertheless, the dose and efficacy also depend on the extraction method itself.

Cucurbita

The seeds of Cucurbita pepo L. appear to have the property of inhibiting 5α-reductase and testosterone-induced hypertrophy by lowering *dihydrotestosterone* (DHT) levels. Some clinical studies showed an improvement in quality of life and IPSS without altering patients' sexual function during treatment (22, 23).

Urtica

Urtica dioica, the active ingredient of which is the dried root, is frequently used in traditional European medicine for the treatment of BPH. Urtica can reduce the conversion of testosterone into DHT. Several studies have shown a proliferation-inhibiting effect by binding to the membrane receptors of the prostate, thereby inhibiting its proliferative activity in prostate tissue. In vivo studies in rats showed a possible inhibition of 5α-reductase. However, more extensive studies in humans are needed to confirm its benefits (24-26).

Curcuma

Curcuma longa Linn. is often used to treat urinary tract diseases due to its antioxidant and anti-inflammatory properties. In a recent study (27), this plant was able to improve LUTS symptoms, IPSS and Q_{max} score. An improvement was observed both in untreated patients and in patients already treated with alpha-blockers and/or 5α-reductase inhibitors (5-ARI).

Pygeum africanum

Pygeum africanum (*Prunus*) is known among the indigenous population of Africa for its antiproliferative and anti-inflammatory properties. It appears to be able to inhibit prostate growth factors and reduce the production of prostaglandins in the prostate (28). This leads to a reduction in chronic prostatitis and the inflammatory symptoms of BPH. The evidence in the literature regarding the mechanism of actions and the clinical effect is weak.

Pollens

Cernitin, the best-known pollen, is an extract of Secale cereale that has an interesting effect on BPH and can improve both irritative and obstructive symptoms (29). Its effect is achieved by relaxing the smooth muscles of the urethra and apoptosis of the cells of the prostatic transition zone. Some studies based on small samples showed an improvement in IPSS and a decrease in prostate volume after long-term treatment with pollen (30, 31). Peony pollen, the pollen of Paeonia suffruticosa, also appears to be able to attenuate oxidative stress and

inflammation. They could be directly involved in the regulation of the gut microbiota. In addition, some pollen in combination with vitamins (*Deprox 500®*) showed an improvement in the IPSS and the *NIH Chronic Prostatitis Symptom Index* (NIHCPSI), alone or in combination with *Serenoa repens* (32-35). The literature lacks strong evidence on this drug.

Epilobium

Epilobium species are perennial plants whose flowers and leaves are used for the presence of some substances such as phenolic acids, flavonoids, and tannins. The therapeutic effect of Epilobium has been demonstrated *in vitro*, with a reduction in PSA levels and a reduction in the inflammatory response and oxidative stress of prostate cells. In a randomized, placebo-controlled trial, epilobium was shown to improve *post-void residual* (PVR), increase IPSS, and reduce nocturia (36). Other studies have investigated the efficacy of epilobium and showed similar results (37).

Palmitoylethanolamide (PEA)

PEA is an endocannabinoid-like bioactive lipid mediator that belongs to the N-acylethanolamine family. The properties of PEA include a known anti-inflammatory effect and the reduction of testosterone and DHT levels in both the prostate and serum. In addition, PEA can reduce the upregulation of 5α-reductase 2 and androgen receptor induced by BPH (38-40). Most of the available studies were conducted in vitro, while the literature contains only a few in vivo studies.

Other plants

Other plant extracts are used in traditional medicine to treat BPH and its symptoms. Some of these plants are: Hypoxis hemerocallidea, Pinus pinaster, Roystonea regia, Solanum lycopersicum. The substances extracted from these plants appear to have a positive effect on BPH thanks to their antioxidant, anti-inflammatory and anti-carcinogenic properties. However, the current literature is minimal and of limited significance (41-43).

Conventional therapies

Alpha blockers

Among the drugs available for the treatment of LUTS and *bladder outlet obstruction* (BOO) due to BPH, alpha-blockers are the most frequently used. The literature is full of data evaluating the therapeutic benefits of these drugs, which are also recommended in the most widely followed guidelines (12, 44-45). Their mechanism of action is closely related to the presence of many smooth muscle cells in the prostate that are amenable to alpha-adrenergic stimulation (46). This stimulation leads to relaxation of the prostate and bladder neck. The bladder and prostate contain predominantly alpha-1 receptors, which enables the use of selective blockers. The most commonly sold alpha-blockers today are tamsulosin, alfuzosin, doxazosin, silodosin, naftodipil and terazosin (47). The data available in the literature show that alpha-blockers can reduce the IPSS score by 30-40% and improve Q_{max} by 20-25%. One of their most important effects is to reduce the risk of acute urinary retention (48). Unfortunately, these drugs are not free of side effects, such as hypotension and retrograde ejaculation, which are often significant for some patients.

Alpha reductase inhibitors

Another important drug for the treatment of BPH are 5-*alpha-reductase inhibitors* (5-ARI). There are two types of 5α-reductase enzymes, but type 2 is most common in the prostate. This enzyme converts a portion of testosterone into *dihydrotestosterone* (DHT), which plays a role in prostate growth (49). The 5-ARIs act by suppressing the enzyme 5α-reductase. Dutasteride and finasteride are the most commonly used 5-ARIs and are equivalent in terms of results and effect. The PLESS study has shown that finasteride reduces the relative long-term risk of acute urinary retention and the need for surgery compared to placebo. 5-ARIs are able to improve LUTS and Q_{max} (50-52) and their effect may also be important before surgery by reducing prostate bleeding during TURP (53, 54). 5-ARIs are not free from potential side effects such as decreased sexual desire, impotence, gynecomastia, depression and anxiety. One of the properties of 5-ARIs is the lowering of PSA levels. This effect, which has already been observed with other drugs (55) with a different mechanism, is much more pronounced with 5-ARIs. Therefore, the use of 5-ARIs must always be considered in the diagnosis of prostatic neoplasia in order to best select patients with a clinically significant risk of prostatic neoplasia who are candidates for prostate biopsy (56-58).

Muscarinic receptor antagonists

Normal physiological bladder emptying depends on the activation of the contractile muscarinic receptors on the smooth muscle of the bladder tricuspid. This activation is triggered by the neurotransmitter acetylcholine. Five subtypes of G-protein-coupled muscarinic receptors (M1; M2; M3; M4; M5) have been characterized pharmacologically. Most muscarinic receptors in the detrusor muscle are M2 (70%) and M3 (30%) (59). Currently, the most commonly used antimuscarinic drugs are oxybutynin, propiverine, tolterodine and solifenacin (60, 61). The current EAU guidelines recommend the use of muscarinic receptors in men with moderate to severe LUTS who have mainly bladder storage symptoms (12). A considerable number of muscarinic receptors are located in different parts of the body (salivary glands, gastrointestinal tract and central nervous system). Therefore, the side effects of antimuscarinics may affect these areas (62). The most frequently reported adverse effects include blurred vision, constipation and dry mouth (61). Their main effect is to reduce the urge to urinate and the frequency of urination.

In addition, they are able to increase bladder capacity, allowing patients to hold urine for longer periods of time without discomfort. This improvement can significantly increase the quality of life of BPH patients as they need to urinate less frequently. Usually, these drugs are used in combination with alpha-blockers. This combination can be particularly effective in treating both the obstructive and irritative symptoms of BPH.

Beta 3 agonists
Humans have three different subtypes of β-adrenoceptors (β1, β2 and β3). In human bladder tissue, β3-adrenoceptors are predominantly expressed (63). Activation of this receptor is associated with detrusor smooth muscle relaxation during the storage phase of micturition and therefore improves bladder compliance and capacity. Mirabegron is the first β3-adrenoceptor agonist approved in clinical practice and may be an alternative treatment option to antimuscarinics for patients with overactive bladder symptoms (64-66). The efficacy and safety of mirabegron 50 mg compared to placebo and antimuscarinics was evaluated in male patients with overactive bladder in five phase III studies. Mirabegron showed significant improvements in the reduction of micturition frequency compared to placebo. Mirabegron 50 mg has been shown to be relatively safe. Gastrointestinal symptoms and dry mouth are the most commonly reported adverse effects. Mirabegron 100 mg, on the other hand, showed a slightly increased risk of high blood pressure and cardiac arrhythmia (68).

Phosphodiesterase 5 inhibitors
Phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil, vardenafil and avanafil) are the gold standard in the treatment of patients with *erectile dysfunction* (ED). These drugs block the enzyme PDE5 and thus regulate the level of *cyclic guanosine monophosphate* (cGMP) by breaking it down to inactive *5′-guanosine monophosphate* (5′-GMP). This process leads to smooth muscle relaxation in the corpus cavernosum of the penis (69, 70). This relaxation increases the arterial inflow into the penis, which is necessary to achieve and maintain an erection. In addition, tadalafil relaxes the smooth muscles of the bladder and prostate and can thus improve LUTS (71). Therefore, the daily intake of 5 mg tadalafil has been approved for the treatment of BPH. Compared to a placebo, 5 mg tadalafil once daily as monotherapy or in combination with alpha-blockers can significantly improve quality of life and IPSS (72, 73). Phosphodiesterase type 5 inhibitors are generally well tolerated, especially at low doses. The most common side effects are headache, redness of the skin, and nasal congestion (69, 70).

Combination therapy
Although alpha blockers are the treatment of choice in most cases, in many cases their effect alone is not sufficient to relieve the symptoms of BPH. It is therefore possible to combine this therapy with 5-ARIs, PDE5 inhibitors, Mirabegon, antimuscarinics and, of course, phytotherapy, which generally leads to good results. Studies such as COMBAT and CONDUCT have shown that dutasteride plus tamsulosin can improve Q_{max} and IPSS and reduce the risk of acute urinary retention (74, 75). Therefore, combination therapy with 5-ARI and alpha-blockers could be an option for patients with large prostate volume and severe LUTS. Similar studies looking at the combination of alpha-blockers and PDE5 inhibitors (tadalafil), alpha-blockers and mirabegone or alpha-blockers and antimuscarinics have shown that combination therapy is able to reduce LUTS without a significant increase in side effects (76, 77).

Discussion
Medical treatment for BPH has evolved significantly over the years, offering a variety of treatment options aimed at alleviating symptoms and improving overall patient outcomes (78-80). In selected uncomplicated cases, WW and lifestyle changes can play a positive role in the management of BPH symptoms (14). Systematic reviews and meta-analyzes have shown that such self-management measures can significantly alleviate symptoms and control the progression of the disease (14). Nevertheless, the elements of self-care management have not been assessed individually and the lifestyle advice is derived from a formal consensus method, so further research is needed in this area (12). Among the approved drugs for the medical management of BPH, alpha-blockers have been considered a cornerstone of BPH treatment for many years. They provide rapid relief of symptoms, often within a few weeks, and are generally well tolerated (81). However, some patients may experience side effects such as dizziness, orthostatic hypotension, and ejaculatory dysfunction (82). Despite these potential problems, alpha-blockers remain a widely used drug due to their efficacy and rapid onset of action (12). 5-ARI, by lowering dihydrotestosterone levels, can shrink the prostate and improve LUTS over time (12). However, relief may be slower to come compared to alpha-blockers, and potential side effects include sexual dysfunction (83). Moreover, their impact on PSA needs to be considered in relation to prostate cancer screening (12). Despite these concerns, they are a valuable option for the treatment of BPH, especially in patients with prostate enlargement > 40 mL. Treatments with phosphodiesterase-5 inhibitors such as tadalafil, have also shown promise in the management of BPH. These drugs can provide additional relief from symptoms such as urinary urgency and frequency, improve erectile function and help to maintain ejaculatory function (84). They offer a different mechanism of action to conventional BPH therapies and can be particularly useful for patients suffering from both BPH and erectile dysfunction. However, they can cause side effects such as headaches and gastrointestinal discomfort, and interactions with other medications must be carefully monitored. Research on newer agents such as beta-3 agonists, such as mirabegron, is ongoing. These medications target bladder function rather than prostate size and may help relieve storage symptoms such as urinary urgency and frequency. Although the long-term efficacy and safety of these drugs are still under investigation, the available literature suggests that beta-3 agonists may be an effective addition to the BPH treatment options (12). A further possibility that has emerged in recent years is that of suspension therapy for fragile patients or for patients with a combination of different therapies in order to reduce the risk of side effects. However, still few studies are currently available on the topic (85, 86).
One of the most evolving and extensive fields related to the medical treatment of BPH is phytotherapy. Several plant-derived substances are commercially available, including both herbal medicines and dietary supplements (87). Phytotherapy has undeniable advantages, including high tolerability and low side effects (16). They are also easily available online or over the counter. Sometimes patients

find it difficult to adhere to the treatments because the side effects, including retrograde ejaculation, can significantly affect the patient's psychological well-being, leading them to prefer phytotherapy. On the other hand, the evidence on phytotherapy is not conclusive, the mechanism of action is not always fully understood and many of these substances have not undergone the rigorous testing that drugs normally receive. Considering their mostly moderate efficacy, which is inferior to that of approved drugs, there is a lack of strong recommendations in *European* (EAU) or *American Urological Association* (AUA) guidelines (12). However, in a historical period in which there is the threat of further pandemics (88) which can cause an increase in the waiting list of patients suffering from BPH, a correct knowledge of the medical therapy of BPH is of fundamental importance, allowing to manage the patient also through telemedicine and while waiting for surgery (89-91).

Conclusions

In conclusion, the medical management of BPH is currently defined by the algorithms of the EAU and AUA guidelines (12, 92). However, given the broad and heterogeneous range of therapeutic options available, the need for a more personalized approach is increasingly recognized. As the treatment landscape continues to evolve, tailoring therapy to individual patient needs and preferences is likely to become increasingly important to ensure that treatment strategies are both effective and meet patient expectations.

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