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ORIGINAL ARTICLE

Emerging drugs to target lower urinary tract symptomatology (LUTS)/benign prostatic hyperplasia (BPH): focus on the prostate

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Abstract

Objectives The benign prostatic syndrome, comprising lower urinary tract symptomatology secondary to benign prostatic hyperplasia/enlargement, represents a major health care issue in westernized countries. The pharmacological management involves alpha-adrenoceptor antagonists, intervention into the hormonal control of prostate growth using inhibitors of the enzyme 5-alpha-reductase, and stimulation of the nitric oxide/cyclic GMP pathway by tadalafil, an inhibitor of the phosphodiesterase type 5.

Methods This review summarizes the achievements which have been made in the development of drug candidates assumed to offer opportunities as beneficial treatment options in the management of the benign prostatic syndrome.

Results A review of the literature has revealed that the line of development is focusing on drugs interfering with peripheral neuromuscular/neuronal mechanisms (nitric oxide donor drugs, agonists/antagonists of endogenous peptides, botulinum toxin, NX-1207), the steroidal axis (cetrorelix) or the metabolic turn-over (lonidamine), as well as the combination of drugs already established in the treatment of lower urinary tract symptomatology/benign prostatic hyperplasia (phosphodiesterase 5 inhibitor plus alpha-adrenoceptor antagonist).

Conclusion Many research efforts have provided the basis for the development of new therapeutic modalities for the management of lower urinary tract dysfunctions, some of which might be offered to the patients in the near future.

Keywords Lower urinary tract symptoms (LUTS) · Benign prostatic hyperplasia (BPH) · Pharmacotherapy

Introduction

The so-called benign prostatic syndrome (BPS), comprising lower urinary tract symptomatology (LUTS) alone or secondary to benign prostatic hyperplasia (BPH), is one of the most prevalent pathological conditions in the aging male and represents a major health care concern in most westernized countries. Although benign prostatic enlargement (BPE), characterized by the proliferation of smooth muscle and glandular (epithelial) cells in the transition zone of the prostate, has long been associated with LUTS, it has been recognized that some men with LUTS may not have BPH, and, alternatively, some men with BPH may not have LUTS. However, LUTS may contribute to BPS and, in the case of clinical evidence of outlet obstruction, benign prostatic obstruction (BPO). It is estimated that approximately 40% of men aged older than 50 years are susceptible to moderate to severe BPS/LUTS (as measured by means of the International Prostatic Symptom Score = IPSS; 8–19 = moderate symptoms, 20–35 = severe symptoms), comprising storage (irritative), voiding (obstructive) and post-micturition symptoms. The most frequent symptoms include straining to urinate, slow urinary stream, intermittency, urgency, urinary frequency and nocturia, as well as a debilitating effect on the quality of life (QoL) [1–3]. The prostatic part of the urethra can be considered a part of a functional unit involved in the control of storage and time-to-time efficient

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voiding of urine. Although not fully understood yet, coordinated neuronal input to the smooth muscle of the stromal region of the prostate (via adrenergic varicose nerve fibers and mechanisms mediated by the activation of postjunctional alpha-adrenoceptors) contributes to maintain continence during the filling phase while signals mediated via nitric oxide (NO) and cyclic GMP may play a crucial role for relaxation responses to enable the unimpaired flow of urine during micturition [4]. During the last decades, the treatment of LUTS/BPH has evolved from surgical options to the development of oral therapies acting mainly through maximizing or inhibiting biological mechanisms. To date, the efficacy and safety of alpha-adrenoceptor antagonists, 5-alpha-reductase inhibitors (5-ARI) and the phosphodiesterase 5 (PDE5) inhibitor tadalafil in the treatment of benign diseases of the prostate have been thoroughly evaluated and, as a result of a continuous clinical awareness in this field of urology and ongoing basic and clinical research, several new treatment modalities (for example, nitric oxide donor drugs, agonists/antagonists of endogenous peptides, botulinum toxin, cetrorelix, elocalcitol, NX-1207, lonidamine), as well as the combination of drugs already established in the treatment of LUTS/BPH (for example, a PDE5 inhibitor plus an alpha-adrenoceptor antagonist) are now being discussed and investigated. These agents are assumed to offer a faster on-set of drug action, an improved effect–side-effect ratio and, above all, demonstrating a more advanced and superior efficacy than the previous options, thus, drug development is still focusing on selective, preferentially orally available drugs to influence peripheral intracellular or central hormonal regulatory pathways. The purpose of this review is to describe evolving pharmacological advances in the field of pharmacotherapy for the treatment of LUTS/BPH, some of which are still in the preclinical stage of investigation. A search of primary sources (journals, books) was conducted using the key words benign prostatic hyperplasia (BPH), lower urinary tract symptoms (LUTS), pharmacotherapy/drug treatment, emerging drugs.

Existing treatments

Based on the aforesaid, the current strategies in the pharmacological management of LUTS and BPH involve alpha$_1$-adrenergic antagonists (such as alfuzosin, doxazosin, silodosin, tamsulosin and terazosin) to reduce the resistance of smooth muscle in the bladder neck, prostate and (prostatic) urethra (the dynamic component of obstruction) [5, 6]. The efficacy of alpha-adrenoceptor antagonists is balanced against incidences of side effects that consist of headache, occasionally orthostatic hypotension (associated with dizziness) and also sexual dysfunctions, in particular ejaculatory disorders and a reduction of sexual desire, some of which might be significant. For example, tamsulosin, which has high affinity for the alpha$_{1A}$- and alpha$_{1D}$-adrenoceptor subtypes, is not associated with a clinically relevant lowering of blood pressure, but has high incidences of headache (38%) and ejaculatory side effects (52–70%). Alfuzosin and silodosin also offer an enhanced side effect profile, particularly minimizing hypotension, while silodosin moderately increases sexual adverse events (ejaculation disorders) [7]. There is convincing evidence from short- and long-term clinical trials that combination of an alpha$_1$-adrenoceptor antagonist with an antimuscarinic drug (darifenacin, solifenacin, fesoterodine, tolterodine, oxybutynin, propiverine, trospium chloride) is more effective in reducing OAB symptoms and improving IPSS/QoL in patients not at risk for acute urinary retention than is treatment with an alpha-blocker only [8, 9]. Intervention into the hormonal control of prostate growth by using 5-ARI, such as finasteride (inhibiting 5α-reductase type 2) and dutasteride (inhibiting the activity of both 5α-reductase type 1 and 2), is another approach to ease symptoms [10]. Combination treatment with a 5-ARI and an alpha$_1$-adrenoceptor antagonist is recommended in patients with severe LUTS/an increased risk of disease progression, prostate volume > 40 ml, high postvoid residual urine (PVR), low Q_{max}. Combination therapy results in a greater improvement in LUTS and is considered more effective in preventing patients from disease progression and risk of acute urinary retention (AUR) [11, 12]. Substantial data are also available on the combination of [I] alpha$_1$-adrenoceptor antagonists plus 5-ARI, [Ii] alpha$_1$-adrenoceptor antagonists plus 5-ARI plus anticholinergics or a ß(3) agonist (for example, tamsulosin, dutasteride and imidafenacin), [Iii] 5-ARI plus anticholinergics (for example, dutasteride plus tolterodine), and [iiiI] an alpha-blocker (doxazosin) in combination with a COX-2 inhibitor (tenoxicam). While the first strategy has been proven suitable for the inhibition of disease progression, the second and third seem to represent a promising effective and well-tolerated option to improve persistent overactive bladder/storage symptoms in patients with enlarged prostates (≥ 30 ml) not responding to alpha blockade [13, 14]. The possibility of adapting treatment standard according to individual clinical characteristics of the patients, using two or even more drugs, seems to be a promising path in the management of LUTS/BPH. The safety and efficacy of the PDE5 inhibitor tadalafil in the treatment of LUTS/BPH have been investigated in numerous multi-center, randomized, double-blind, placebo-controlled trials. Due to the pharmacokinetic profile, with a duration to maximal plasma concentration of 1–1.5 h and elimination half-life time ($t_{1/2}$) of more than 10 h, tadalafil is considered suitable for a once-daily dosage regimen. The studies showed that tadalafil can significantly improve total IPSS as well as storage and voiding symptoms [15–17].

Although none of the guidelines of the International Urological Societies explicitly recommends phytodrugs, namely plant extracts processed from Serenoa repens (Saw palmetto), Pygeum africanum (Prunus africana, known by the botanical names African plum or African cherry), Urtica dioica (nettle plant), Cucurbita pepo (pumpkin) and Secale cereale (rye grass), these preparations are well tolerated and have been proposed as an interesting approach to ease LUTS secondary to BPH. However, due to the unknown chemical quality of the preparations utilized for treatment and the fact that most of the clinical studies lack a proven active control (for example, an alpha-adrenoceptor antagonist), are limited by a short duration, a small number of patients enrolled and incomplete documentation of outcomes, positive effects of the said extracts on uroflow, PVR, nocturia and prostate volume were not consistently demonstrated throughout all trials conducted [18, 19].

Potential new and alternative drug treatments

Novel alpha-adrenoceptor antagonists (alpha-blockers): naftopidil, RS-17503 and L-771.688

As mentioned before, alpha$_1$-adrenoceptor antagonists (alpha-blockers) are widely used to relieve BPS-related LUTS. The adverse effects on blood pressure, such as orthostatic hypotension, experienced with the use of this class of drugs have been associated in part to the blockade of alpha$_{1B}$-adrenoceptors in arterial vascular smooth musculature. Consequently, novel α-blocking agents have been developed, characterized by an exceptionally high sub-selectivity for alpha$_{1A}$- versus alpha$_{1B}$-adrenoceptors. This selectivity profile possibly accounts for fewer cardiovascular adverse events and, hence, an improved clinical feature of the drugs. Due to the improved cardiovascular safety profile of the drugs, they are considered a preferable choice of medication for elderly patients requiring increased cardiovascular tolerability [20]. Modulating the activity of the alpha$_{1D}$-receptor subtype has been suggested as an alternative option to ease LUTS secondary to BPH. Naftopidil, known to be a selective alpha$_{1D}$-antagonist, was examined in several-hundred patients in randomized, controlled, multicenter studies for its tolerability, safety and efficacy in the treatment of male LUTS associated with BPH [21]. The drug applied in doses of 25 mg (three times per day) or 75 mg (once daily) for 8 weeks significantly improved total IPSS, IPSS-QoL, BPH impact index (BII), as well as daytime and 24-h voiding frequencies [22–24]. In urodynamic assessments, both the average and maximum flow rates as well as the time to first desire to void were increased, while urethral resistance and urethral closure pressure were reduced. Based upon these measurements, the drug was considered an effective method in the treatment of bladder outlet (urethral) obstruction due to BPH [25]. Naftopidil also showed beneficial outcome in those patients with BPH whose predominant complaints were voiding symptoms, in particular nocturia of ≥ 3 times associated with sleep disturbances [26]. Since pharmacological evidence has implicated that activation of alpha$_{1A}$-adrenoceptors by norepinephrine (NE) in the bladder neck, prostate and urethra is one of the key events in the manifestation of LUTS, the pharmacological properties of additional novel, selective alpha$_{1A}$-adrenoceptor antagonists have been disclosed. L-771.688 (also known as SNAP 6383, developed by Merck Research Laboratories, West Point, PA, USA) has high affinity (K_i less than or = 1 nM) to cloned human, rat and dog alpha$_{1A}$-adrenoceptors and a > 500-fold selectivity over the alpha$_{1B}$- and alpha$_{1D}$-adrenoceptors. Competitive binding studies using [^{3}H]prazosin/[^{125}I]HEAT and [^{3}H]L-771.688 in human and animal tissues known to contain alpha$_{1A}$ and non-alpha$_{1A}$-adrenoceptors further demonstrated the potency and alpha$_{1A}$-subtype selectivity of L-771.688. The compound antagonized the contractions induced by phenylephrine of isolated rat and human prostate, while the contraction of rat aorta induced by norepinephrine (NE) was resistant to L-771.688 [27]. RS-17053, developed by Roche Bioscience (Palo Alto, CA, USA) displays a high affinity for the alpha$_{1A}$-adrenoceptor and a 30–100-fold selectivity over the alpha$_{1B}$- and alpha$_{1D}$-adrenoceptor subtypes. However, in isolated smooth muscle preparations of human LUT tissues, high concentrations of RS-17053 are needed to antagonize responses of the tissue to NE. The estimation of affinity (p_{A2}-value) at alpha$_1$-adrenoceptors mediating the contractions induced by the alpha-adrenoceptor agonist were 7.5 in prostatic periurethral longitudinal smooth muscle (prazosin: 8.6), 6.9 in anterior fibromuscular stroma (prazosin: 8.9), and 7.1 in bladder neck (prazosin: 8.5). These findings may indicate that (1) the contractile responses to NE in the said tissues are mediated by a receptor displaying pharmacological properties different from those of the alpha$_{1A}$-adrenoceptor (for example, the alpha$_{1L}$-adrenoceptor) or (2) multiple forms of the alpha$_{1A}$-adrenoceptor may exist in human LUT that are discriminated by RS-17053 [28, 29]. Further clinical studies are necessary to delineate as to whether the compounds may have significance in the treatment of patients presenting with LUTS suggestive of BPH.

Drugs interfering with the nitric oxide (NO)/cyclic GMP signaling pathway

NO induces smooth muscle relaxing effects by activating the enzyme soluble guanylyl cyclase (sGC), thereby increasing the tissue levels of the second messenger molecule cyclic

guanosine 3′5′-monophosphate (cyclic GMP). This, in turn, interacts with various intracellular components regulating the activities of contractile proteins. In the human prostate, moderate to large amounts of nitric oxide synthase (NOS) have been demonstrated in ganglion cells and in nerve trunks extending from the ganglia, as well as in nerve fibers located around prostatic glandular ducts or running between smooth muscle cells of the prostatic stroma [30, 31]. In human, canine and rat prostate smooth muscle challenged by an alpha-adrenergic agonist, the transmural activation of nerves produces relaxations that were completely abolished by L-NOARG (a compound inhibiting the synthesis of NO). The relaxation responses mediated by NO caused more than a 50% reduction of the tension induced by noradrenaline [32, 33]. As mentioned before, the feasibility of using PDE5 inhibitors to treat LUTS/BPH has been supported and the PDE5 inhibitor tadalafil is administered to patients as an effective once-daily dosage regimen [15–17]. Preliminary results from experimental studies have suggested that, aside from the PDE5, other PDE isoenzymes, such as the PDE10A, which hydrolyzes both cyclic GMP and cyclic AMP, might be relevant in the control of prostate smooth muscle tension. Selective inhibitors of the PDE10, among which are BMS-843496, MP-10 and TC-E 5005, are available and it remains to be elucidated whether or not these compounds do exert urodynamic effects in vivo [34]. The combined administration of PDE5 inhibitors together with an $alpha_1$-adrenoceptor antagonist (alfuzosin or tamsulosin), respectively, for the treatment of LUTS/BPH has also been evaluated. Men with untreated symptoms were randomized to either sildenafil, tadalafil or udenafil or the combination of an alpha-blocker plus PDE5 inhibitor. Study endpoints were changes in IPSS, Q_{max}, Q_{ave} and PVR. Improvement in IPSS was significant in all treatment groups but seen to be most pronounced with the drug combinations. PVR, Q_{max}, frequency and nocturia also significantly improved. The efficacy of tadalafil (20 mg/day) and tamsulosin (0.4 mg/day) versus tamsulosin only (0.4 mg/day) was assessed in randomized, double-blind, cross-over studies (study duration: 45 days to 12 weeks). Improvements in the IPSS and IPSS-QoL scores were greater in those patients who had received the drug combination [35, 36]. In addition, the efficacy of sildenafil citrate (25 mg) plus tamsulosin (0.4 mg) (once daily each, for 6 months) versus tamsulosin plus placebo or sildenafil (25 mg) plus alfuzosin (10 mg) (once daily) was evaluated in men presenting with LUTS/BPH. Improvements in IPSS, Q_{max} and PRV were more pronounced in those patients who were on the combination therapy [37, 38]. Gacci et al. (2012), in a randomized trial with a 12-week follow-up, compared the efficacy of vardenafil (10 mg once daily) plus tamsulosin (0.4 mg once daily) vs. tamsulosin only (0.4 once daily) in 60 patients with LUTS/BPH (and ED). Drug regimens were administered following a 2-week run-in phase with tamsulosin only. The combination of tamsulosin and vardenafil was more effective in treating LUTS (and ED) than was tamsulosin alone. Significant differences were shown between the treatment groups for the following outcome parameters: irritative IPSS subscores (IPSS, IPSS-B = IPSS bothersomeness/tolerance score), OAB-q (overactive bladder questionnaire) and IIEF [39]. Thus, it seems there is convincing evidence that combination therapy is more efficacious than monotherapy with either agent in the treatment of LUTS/BPH.

Since the NO signaling has become an attractive target in drug development in the field of urology, an unique class of drugs known to release NO has been investigated in vitro with regard to their potential to treat dysfunctions of the lower urinary tract. Endogenous organic nitrates ($RONO_2$), nitrites (RONO) and thionitrites, better known as *S*-nitrosothiols (R-S-N=O), are anti-atherogenic and blood pressure lowering compounds acting via the NO/cyclic GMP pathway. *S*-Nitrosothiols offer advantages over inorganic nitrates, are effective at much lower doses (40 times less) and do not share the drawbacks of existing drugs (ISDN = isosorbide dinitrate, PETN = pentaerythrityl tetranitrate). Initial clinical studies have suggested that *S*-nitrosothiols may be beneficial in a variety of cardiovascular disorders, such as atherosclerosis and its sequelae, arterial hypertension and coronary syndromes [40–42]. It has been assessed using the tissue bath technique (mechanical recording of force generation) that GSNO (*S*-nitrosoglutathione) and SNC (*S*-nitrosocysteine) can reduce the generation of contractile force (in response to stimulation by both the alpha-adrenergic agonist norepinephrine or vasoconstrictor peptide ET-1) of tissue strips isolated from the transition zone of the prostate. The relaxing effects of the drugs were paralleled by a 5–17-fold (time- and dose-dependent) increase in tissue levels of cyclic GMP. The production of cyclic AMP was also enhanced significantly; however, this increase was not dose-dependent [43, 44]. In contrast, studies using a cell culture set-up and smooth muscle cells (PSMC) isolated by means of the *Explant Culture Technique* from the transition zone of the human prostate reported no effects of SNACET (*S*-nitroso-*N*-acetylcysteine ethyl ester) on the tonic contraction of the PSMC brought about by the vasoconstrictor peptide ET-1 (1 nM), while the number of contracted cells was significantly reduced by GSNO and SNP (sodium nitroprusside) [45]. Since there is evidence from clinical studies regarding an association between an age-related impairment of blood flow to the prostate (causing chronic glandular ischaemic processes) and the development of BPH, the *S*-nitrosothiol *S*-nitroso-*N*-acetylpenicillamine (SNAP) has been investigated on pig prostatic small arteries precontracted by noradrenaline [46, 47]. SNAP evoked concentration-dependent relaxation; however, this response did not increase further in the presence of ODQ, an inhibitor of the cyclic GMP-generating enzyme

soluble guanylyl cyclase (sGC). It was concluded from the findings that the vasodilatation elicited by NO and NO donor drugs could prove useful to reverse/prevent abnormal local blood flow patterns that might lead to prostatic ischaemia and hypoxia-stimulated prostate growth [48]. Up until today, only a few clinical studies have assessed the immediate effects of NO-based drugs (organic nitrates) on micturition parameters in patients with BPH. It has been shown by uroflowmetry in preliminary, placebo-controlled studies that a sublingual formulation of isosorbide dinitrate (ISDN), given in a dose range from 20 to 200 mg to patients with symptomatic (obstructive) BPH (with BPH-related AUR, one of the most severe long-term complications of BPH), enabled spontaneous voiding, significantly increased average and peak flow rate, mean voided urine volume, decreased the volume of residual urine and improved the IPS score [49, 50]. It was concluded from the findings that organic nitrates, such as ISDN, could offer a new approach in the treatment of obstructive lower urinary tract symptoms and lower the overall risk for AUR in the patients (by decreasing bladder outlet resistance) [51]. Hence, NO-releasing drugs might represent a putative novel option for the pharmacological modification of disease-related alterations of the NO/cyclic GMP pathway in the out-flow region (LUT) [52, 53]. Further studies may prove whether effective pharmacological treatment strategies based on this knowledge are likely to emerge in the future. Because the normal function of the male LUT is, to a certain degree, dependent on the activity of the smooth musculature in the bladder, prostate and urethra, targeting these tissues might help to restore unimpaired storage and voiding of urine.

Cetrorelix (luteinizing hormone-releasing hormone antagonist)

As mentioned above, intervention into the steroidal axis, in particular the biological action of testosterone and its active form dihydrotestosterone (DHT), has been identified as a possible approach to the clinical management of patients with BPH-related LUTS. Aside from inhibitors of the enzyme 5-alpha reductase, known to convert testosterone into DHT, modulation of the activity of the luteinizing hormone-releasing hormone (LHRH) provides another strategy interfering with hormone-dependent events (for example, the proliferation of stromal cells) in the prostate. The expression of LHRH receptors has been shown by immunocytochemical and molecular biology methods in cultured human BPH cells (BPH-1 cell line) as well as in prostate tissue excised from patients with BPH [54, 55]. Cetrorelix (SB-75), an antagonistic analogue of LHRH, does not only produce transient reduction in circulating testosterone levels but also inhibits the proliferation of the BPH-1 cell line in response to growth factors, such as the insulin-like growth factor (IGF) and fibroblast growth factor. Moreover, the drug can reduce the production of interleukins, epidermal growth factor (EGF), transforming growth factor β1 (TGF ß1) and vascular endothelial growth factor (VEGF) A in the prostate, and also down-regulate the expression of the proliferating cell nuclear antigen (PCNA, a specific feature of cells in the proliferation phase) and receptor proteins specifically binding LHRH, EGF and alpha$_1$-adrenergic agonists [56]. Data from in vivo studies suggest that the reduction in serum levels of circulating testosterone does only in part account for the beneficial effects of cetrorelix, the effectiveness could rather be due to the suppression of various inflammatory cytokines and growth factors, presumably through direct blockade of prostatic LHRH receptors. Since this mode of pharmacological action requires a specific drug dose that does not induce castration levels of testosterone, so that sexual dysfunctions, such as decreased libido, and the controversy of PSA (prostate specific antigene) effect/potential sub-selection of high grade prostate carcinoma in patients with or without metastatic disease might not be a relevant issue with the clinical use of SB-75. In a double-blind, randomized, multicenter dose-ranging study (duration: 28 weeks) in 250 patients with BPH (IPSS $\geq$ 13), intramuscular injections of cetrorelix (pamoate) (60 mg and 30 mg) provided rapid and sustained symptomatic improvement. A marked dissociation was observed between an only moderate and transient suppression of serum testosterone and the persisting effects on symptoms of BPH [57]. Additional studies are essential to shed light on the precise mechanism of action of LHRH antagonists in the prostate and the future role of this class of drugs in the clinical management of BPH.

Botulinum toxin (BoTx)

Botulinum toxin (BoTx), produced by strictly anaerobic bacteria of the *Chlostridium botulinum* strain, is one of the most potent toxins synthesized and secreted by organisms inhabiting the natural biospheres of the earth. BoTx mainly blocks the presynaptic release of the neurotransmitter acetylcholine and can, thereby, induce complete paralysis of striated (skeletal) and smooth musculature. BoTx mediates this effect via binding to the so-called SNARE complex (*soluble N-ethylmaleimide-sensitive factor attachment protein receptor*), a protein essentially involved in the process of exocytosis of intracellular acetylcholine-containing vesicles into the synaptic neuromuscular gap [58]. Seven different types of the toxin, designated as serotypes A–G, have yet been classified. BoTx does not only inhibit the release of acetylcholine but also inhibit other transmitter compounds of the efferent autonomic nervous system, such as the calcitonin gene-related peptide (CGRP), glutamate and substance P (SP) [59]. Due to its neurotoxic properties, the use of BoTx in the treatment of LUTS/BPH has

been suggested to inhibit autonomic efferent effects on both prostate growth and contraction and also induce apoptosis of prostate tissue. Thereby, BoTx could potentially target the main factors contributing to LUTS secondary to BPH: the increase in smooth muscle tone (dynamic component) and the excessive growth of stromal tissue (smooth muscle and connective tissue) in the transition zone (static component) [60]. In clinical studies using BoTx type A, the intraprostatic injection (200 units) of the drug via a transrectal or transperineal access appeared to be well tolerated. Two (2) months after treatment, symptom scores of the patients, residual urine and prostate volume were significantly reduced (by 52–64%), while mean peak urinary flow rate had increased [61, 62]. These results were confirmed by a prospective, non-randomized, single-arm cohort study evaluating both the patient-reported and objective outcome parameters after a single intraprostatic injection of BoTx A in men with LUTS due to clinical BPH. After 3 months, patients reported a reduction in the International Prostate Symptom Score (IPSS) and the IPSS health-related quality of life item score. An increase in maximum urinary flow rate and a reduction in the volume of postvoid residual urine were also registered. There was a statistically significant positive correlation between patients' satisfaction and both baseline IPSS and the reduction in IPSS [63]. Striking contrary findings emerged from a multicenter double-blind, randomized, placebo-controlled, long-term (72 weeks) study exploring the efficacy of BoTx A (100 U, 200 U, 300 U) in more than 300 men with LUTS/BPH of the following characteristics: IPSS ≥ 12, total prostate volume (TPV) = 30–100 ml, and Q_{max} = 5 ml/sec to 15 ml/s. Here, significant improvements from baseline in the outcome parameters (IPSS, Q_{max}, TPV, transition zone volume) were observed in all groups, including those patients who had received placebo. Adverse events were similar across all treatment groups. A post hoc sub-analysis revealed a significant reduction in IPSS (BoTx A vs. placebo) in those subjects only who had been using alpha-adrenoceptor antagonists prior to the inclusion into the study protocol [64]. Although intraprostatic BoTx is safe and well tolerated, it remains to be elucidated whether or not it might represent a promising new approach to the treatment of BPH. At the time of writing this, the overall level of evidence of clinical benefits and treatment efficacy is still low and further randomized, appropriately designed studies are mandatory to investigate whether or not this type of injection therapy is indeed effective and clinically meaningful [65].

Elocalcitol (BXL-628, vitamin D3 agonist/analogue)

BXL-628, which was under development by BioXell SpA (Milan, Italy), is a synthetic derivative of the active form of vitamin D, 1,25-dihydroxyvitamin D3, a secosteroid hormone that binds with high affinity to the vitamin D receptor (VDR). Activation of this nuclear receptor exerts a number of diverse biological functions. It has been shown that human bladder neck, prostate and urethra display the expression of the VDR [66]. In in vitro settings using tissue bath experiments, molecular biology and immunohistochemistry, BXL-628 reduced the responsiveness of isolated bladder smooth muscle to the muscarinic agonist carbachol and prevented the activation of Rho kinase (ROCK/ROK), an enzyme known to synergistically promote smooth muscle constriction via Ca^{2+}-sensitizing pathways, in bladder and prostate tissue obtained from patients affected by BPH [67]. In primary cell cultures of the human prostate, elocalcitol partially reverted the upregulation of messenger RNA encoding for COX-2 and IL-8 induced by exposure of the cells to pro-inflammatory cytokines, such as IL-17, interferon-gamma and tumor necrosis factor-alpha [68]. This indicates that the drug may possess the ability to limit local chronic inflammatory responses, which have been considered a key determinant in the pathophysiology of BPH. Elocalcitol also inhibited the androgen-dependent and androgen-independent proliferation of cultured benign prostatic stromal cells more potently than did the 5 alpha-reductase inhibitor finasteride [69]. However, in a phase 2, double-blind, randomized placebo-controlled clinical trial conducted to evaluate the effect of BXL 628 on prostate volume in a cohort of 119 patients with BPH (prostate volume ≥ 40 ml), the percentage change in prostate volume seen after 12 weeks of treatment with either elocalcitol (0.15 mg daily) or placebo was only − 2.90 (BXL-628) vs. + 4.32 (placebo). Not surprisingly, no significant changes in baseline Q_{max} values were registered following treatment (BXL-628: − 0.30, placebo: + 1.50). Although it was claimed by the investigators that the changes seen in urinary symptoms frequency, urgency and nocturia were comparable to those exerted by the $alpha_1$-adrenoceptor antagonist tamsulosin, the AUA Symptom Index Score (baseline vs. final visit) did not significantly decrease in those patients who were on elocalcitol (BXL-628: − 1.77, placebo: − 3.45) [70]. Meanwhile, putatively based on the disappointing data, the clinical development of elocalcitol has been terminated. Despite its novel mechanism of action and improved tolerability over existing classes of drugs, it seems unlikely that the compound would have potentially contributed to the armamentarium in the therapeutic market of LUTS/BPH.

Agonists/antagonists of vasopressin and tachykinin receptors

There is evidence that, aside from the classical transmitter compounds of the sympathetic and parasympathetic systems, non-adrenergic, non-cholinergic (NANC) factors are also involved in the control of temporary events in the human upper and lower urinary tract. It is already well established

that the release of peptides is another important mechanism by which the normal function of the human LUT, including the storage and voiding of urine, is maintained. The neurohypophyseal peptide arginine-vasopressin (AVP) has been assumed as one of the factors contributing to such a control. AVP is synthesized in the hypothalamic area of the brain and is stored in the pituitary gland. Upon an internal neuronal stimulus, the peptide is released into the systemic circulation. AVP is mainly involved in the inhibition of diuresis by increasing the resistance via vasoconstriction of the vascular bed of the kidneys; however, the peptide has also been demonstrated to be widely distributed in sympathetic nerve fibers innervating peripheral tissues of mammals, including the urogenital tract [71]. Nocturia is a common and bothersome symptom that is very prevalent in men with LUTS/BPH. Nocturia is defined as a nocturnal voiding frequency of two or more episodes, severely impacting the quality of life of the patients. The most common causes for nocturia are nocturnal polyuria/24 h polyuria and overactive bladder secondary to BPH. To date, nocturia represents the greatest unmet medical need in the management of LUTS/BPH [72, 73]. VA 106483, a small molecule drug candidate with antidiuretic properties, is currently under development by Vanita Therapeutics Ltd. (Southhampton, England, UK). VA 106483 has been characterized as a vasopressin agonist and is supposed to act directly in the collecting ducts of the kidney by binding to and activating vasopressin receptors of the V2 subtype. It has been proposed to investigate VA 106483 for the treatment of nocturia in a phase 2 clinical trial enrolling 30 patients with BPH. It remains to be established whether VA 106483 does indeed demonstrate a dose-dependent pharmacological effect and has, therefore, the potential to be an efficacious and well-tolerated new drug for the treatment of BPH-related nocturia [74–76]. Direct local effects of vasopressin on the prostate and urinary bladder have also been described. It has been shown that physiological doses of AVP (1 nM or 10 nM) can induce contraction of isolated rabbit urinary bladder smooth muscle and also prostate tissue obtained from various species, including humans. In the tissue bath experiments using prostate preparations, the potencies and efficacies registered were similar to those of noradrenaline and methacholine [77, 78]. AVP also elicited concentration-dependent tonic contractions of the prostatic urethra and bladder neck of rat and rabbit, while the V2 receptor agonist deamino-Cys1,Val4,D-Arg8]-vasopressin (dDAVP) showed no effect on basal tension. The contractions brought about by AVP were potently antagonized by SR 49059, an antagonist of the vasopressin receptor subtype V1A. In contrast, the V1B antagonist SSR 149415 failed to antagonize the contractions mediated by AVP of the urethral tissue [79]. It was concluded from these findings that AVP has a physiological role in the contraction of prostate/urethral smooth musculature. Consequently, antagonism of the activity of the V1A receptor may have a therapeutic significance in patients with LUTS/BPH. To the best of our knowledge, to date, no V1A receptor antagonist is under preclinical or clinical investigation by any pharmaceutical company for potential use in the treatment of LUTS/BPH or other benign diseases of the human urinary tract. Tachykinins, including substance P (SP), neurokinin A and B, hemokinin 1 and endokinins, form a family of endogenous neuropeptides acting through G-protein coupled receptors denoted as NK1, NK2 and NK3. These peptides and receptors have been discussed in the view of possible therapeutic implications in the treatment of urological disorders. For example, it was demonstrated that isolated specimens of the human prostate and prostatic urethra were potently contracted by the NK2 agonist GR 64349 (a synthetic derivative of SP), these responses were antagonized in the presence of the NK2 receptor antagonist L 659.837, while the selective NK3 antagonist appeared to be ineffective even at high concentrations (30 μM) [80]. Although these data imply the possibility that selective modulation of NK(2) receptor function might be a new approach to the treatment of LUTS associated with BPH, up until today, no phase 2 clinical studies investigating selective NK antagonists have been completed, most were terminated for various reasons [81]. Currently, the challenge remains to define in detail the potential of NK receptors to become effective pharmacological targets in the treatment of non-malignant urological diseases and to introduce a selective NK antagonist into clinical use.

Selective cannabinoid (CB) receptor agonists

Experimental studies have proven that the endocannabinoid system (ECS), comprising of the cannabinoid receptors (CB), their ligands, such as anandamide = *N*-arachidonoylethanolamide/AEA, 2-arachidonoylglycerol = 2-AG (endogenous cannabinoids) and tetrahydrocannabinol = THC, and enzymes controlling the turnover of endocannabinoids (fatty acid amide hydrolase = FAAH, known to degrade/hydrolyze anandamide into arachidonic acid and ethanolamine, monoacylglycerol lipase = MAGL, hydrolyzes 2-AG to arachidonic acid and glycerol) is involved in controlling the function of the lower urinary tract in humans. Components of the ECS (CB1, CB2, FAAH) have been shown by Western blot technique and immunohistochemistry to be located in lower urinary tract tissues [82–84]. With regard to the prostate, in non-diseased tissue, immunoreactivity specific for CB1 and CB2 was found located in nerves that were also positive for NOS or CGRP; whereas, in nodular hyperplasia, nerves containing CB1 and 2 were scarce or even absent. In tissue bath studies, the CB1/CB2 agonist CP 55940 decreased nerve-mediated contractions of the prostate preparations. Although the effects turned out to be less pronounced than those exerted by allyl isothiocyanate, cinnamaldehyde or

sodium hydrogen sulfide, it was concluded that the findings might suggest a role for CB receptors in mechano-afferent signaling and epithelial homeostasis in the human prostate [85]. Up until today, no selective CB receptor agonists, such as CP 55940, JWH-122, LEI101, RCS-4, THJ-2201 and XLR-11, have been investigated in clinical settings with regard to their efficacy to treat LUTS/BPH. Increased understanding of the expression and pharmacology of cannabinoid receptors in the LUT will accelerate research on the clinical use of cannabinoid receptor agonists in the management of dysfunctions of the male LUT, thereby avoiding unfavourable psychotropic effects of these agents.

NX-1207 (fexapotide triflutate, neuropeptide, precise mechanism of action yet unspecified)

NX-1207 (fexapotide triflutate, FT), which is currently being developed for clinical use to target LUTS associated with BPH by Nymox Pharmaceutical Corp. (Hasbrouck Heights, NJ, USA) and Serex Inc. (Montreal, Quebec, Canada), is a peptidergic compound supposed to act via exerting pro-apoptotic properties and neurochemical effects. The precise mechanism of action of the drug has not yet been fully specified by the sponsoring companies. Following transrectal injection (2.5 mg FT) into the prostate in an office-based procedure, NX-1207 promotes pro-apoptotic events, which may eventually induce focal cell loss, thereby leading to a reduction in prostate volume with subsequent both short- and long-term improvement in storage and voiding symptoms [86–88]. In a number of phase 2 clinical trials, the compound has been shown to improve symptoms substantially better than the currently approved medications for BPH treatment administered orally. Changes in IPSS from baseline were higher and the incidence of AUR or surgical intervention for BPH was reduced in patients treated with FT when compared to the placebo group or a cohort who was on conventional oral medications for BPH. No significant safety issues were reported by the patients or investigators [89]. Larger Phase 3 protocols will show whether NX-1207 is a candidate for an efficacious, safe and well-tolerated *First-in-Class Drug* to be used for the minimally invasive, hospital or office-based treatment of patients with BPH of all severity degrees.

Lonidamine (TH-070, hexokinase inhibitor)

Both normal and hyperplastic prostate tissues concentrate citrate within the glandular epithelial cells in the peripheral zone; however, there is evidence that hyperplastic prostate tissue is characterized by the unique dependency on energy production via glycolysis instead of the aerobe (oxygen dependent) citric acid cycle (Krebs cycle). Glycolysis is much less efficient in producing energy from glucose than is the Krebs cycle. Thus, when (diseased) cells shift energy production to glycolysis, they must increase the levels of the proteins needed to transport and metabolize glucose. So-called metabolic targeting takes advantage of these differences to selectively target certain cells. TH-070 (lonidamine, under development by Threshold Pharmaceuticals, Redwood City, CA, USA), a derivative of indazole-3-carboxylic acid, is an orally active small molecule that inhibits glycolysis by the inactivation of hexokinase, an enzyme (dependent on Zn^{2+}) that catalyzes the first step in glycolysis. The inhibition disrupts energy metabolism and causes apoptosis of cells. Recent studies have also demonstrated that lonidamine influences pyruvate uptake into the mitochondria by potently inhibiting the mitochondrial pyruvate carrier (MPC) [90]. By capitalizing on the unique energy requirements of many solid malignancies, lonidamine has already been used as an adjunct to either radiation or chemotherapy in the treatment of several cancer entities, such as lung, breast and liver cancer [91]. Results of a phase 2 trial of lonidamine in BPH (150 mg once daily for 28 days) were encouraging, demonstrating a significant decrease in prostate volume (as assessed by transrectal ultrasound), an increase in Q_{max}, a decrease in postvoid residual urine volume (PVR), as well as improvements in the IPSS and a fast reduction in serum levels of PSA [92, 93]. In cancer therapy, patients have been treated with 40 times the daily dose of lonidamine used in the BPH trials, with negligible toxicity. The data suggest that TH-070 is safe and effective and may represent a unique and novel approach to the treatment of BPH by metabolic targeting.

Conclusion

Due to the continuous increase in the population of aging males in westernized countries, the BPS, comprising LUTS alone or secondary to BPH, represents a major health care issue necessitating a substantial need for effective therapies. The pharmacological management of symptoms related to BPH has successfully focused on intervention into intracellular signaling pathways mediating the function of the human prostate and urethra (for example, alpha-adrenoceptor antagonism, enhancement of the NO pathway or targeting the hormonal control of prostate growth have been proven to be effective approaches for the treatment of LUTS/BPH). The process of evolving new pharmacological strategies to target LUTS secondary to BPH continues to focus mainly on orally active drugs. The observation that certain proteins, peptides and receptors are expressed in the human LUT supports the hypothesis that they are involved in the control of several signaling pathways contributing to the normal function of the prostate. The disruption or enhancement of such pathways might result in non-vascular or

vascular smooth muscle relaxation, increased blood flow in the LUT or enhance the activity of afferent nerves or apoptotic mechanisms in the transition zone of the prostate. The data available at present suggest that new compounds are on the horizon which are assumed to be efficacious in terms of promoting/restoring normal tissue function and exerting limited adverse events. While some drugs have already been approved and are prescribed to the patients (PDE5 inhibitors), others have entered into the phase of clinical investigation (naftopidil, isosorbide dinitrate, botulinum toxin, NX 1207, lonidamine) or are still in the preclinical stage of their development (Cetrorelix, peptide receptor agonists/antagonists, *S*-nitrosothiols, cannabinoid receptor agonists) (see Table 1). Upcoming new drugs are expected to be at least equal or even superior to the existing treatments with regard to the on-set of their pharmacological action, the response rate, control of symptoms and delay in the progress of the disease. Even if these drugs do not prove to be superior to the efficacy of the existing monotherapy strategies, they might be indicated as an add-on option in patients with on-going persistent symptoms while receiving, for example, an alpha-blocker or PDE5 inhibitor. Combining different agents to affect multiple peripheral targets in the prostate and, thereby, maximizing intracellular signaling might contribute to an improvement of treatment efficacy. An upcoming ideal drug treatment for LUTS/BPH should somehow involve active agents that can modulate signal transduction pathways in the prostate (such as the NO/cyclicGMP cascade, the LHRH or cannabinoid system or the peptidergic signaling) with a certain degree of tissue selectivity and is

Table 1 Drug candidates (all of them in the clinical/preclinical investigative state of development) assumed to have effects on prostate tissue (smooth muscle, nerves, glandular nodes) and may, thus, exert beneficial outcomes in the treatment of voiding and storage symptoms associated with the benign prostatic syndrome (BPS)

Drug candidates	Mode of pharmacological action	Phase of investigation
Alpha$_1$ adrenoceptor antagonists		
naftopidil	Alpha$_{1D}$ receptor antagonist	Clinical (phase 3) *n* = 32 [25] *n* = 153 [24] *n* = 80 [23] *n* = 177 [26]
L-771.688 (SNAP 6383)	Alpha$_{1A}$ receptor antagonist	Preclinical
RS-17503	Alpha$_{1A}$ receptor antagonist	Preclinical
Nitric oxide (NO) donating compounds		
GSNO (*S*-nitroso-glutathione)	S-Nitrosothiol (NO donor drug)	Preclinical
SNC (*S*-nitrosocysteine)	S-Nitrosothiol (NO donor drug)	Precilincal
Isosorbide dinitrate (ISDN)	Nitrate (NO donor drug)	Clinical (phase 2) *n* = 80 [49] *n* = 60 [50]
Agonists/antagonists of peptide receptors		
VA 106483	Vasopressin receptor agonist	Preclinical
L 659.837	Tachykinin (NK2) receptor antagonist	Preclinical
Others		
Cetrorelix	LHRH antagonist	clinical *n* = 250 [57]
Botulinum toxin (BoTx)	Blocks presynaptic release of neurotransmitters	clinical (phase 3) *n* = 41 [62] *n* = 468 [61] *n* = 75 [63]
elocalcitol (BXL-628)	Vitamin D3 agonist/analogue	Clinical (phase 2) *n* = 119 [70] (development terminated)
CP 55940, JWH-122, LEI101, RCS-4, THJ-2201, XLR-11	Selective cannabinoid (CB) receptor agonists	Preclinical
NX-1207 (fexapotide triflutate = FT) [89]	Neuropeptide (mediates tissue apoptosis via neurotoxic effects?)	Clinical (phase 2/3) *n* = 995 [90]
Lonidamine (TH-070)	Hexokinase inhibitor (metabolic targeting)	Clinical (phase 2) *n* = 30 [93]

See text for proposed combinations of existing pharmacological treatments. *n* = total number of patients included in clinical trials

administered preferentially via the oral route. As clinical experience with the compounds addressed in this review is assumed to grow continuously, this field will remain for the next years an exciting and innovative subject in urological pharmacology.

Author contributions SÜ: data collection, manuscript writing. GTK: data collection, manuscript writing. DT: data collection/analysis, manuscript editing. AS: data collection, manuscript writing. AB: data collection/analysis. MAK: manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest and have received no payment for the preparation of the manuscript.

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