Future Direction in Pharmacotherapy for Non-neurogenic Male Lower Urinary Tract Symptoms

Roberto Solera, Karl-Erik Andersson, Michael B. Chancellor, Christopher R. Chapple, William C. de Groote, Marcus J. Drake, Christian Gratzke, Richard Lee, Francisco Cruz

Division of Urology, Federal University of São Paulo and Hospital Israelita Albert Einstein, São Paulo, Brazil; Institute of Regenerative Medicine, Wake Forest University School of Medicine and Department of Urology, Wake Forest Baptist Medical Center, Winston Salem, NC, USA; Oakland University William Beaumont School of Medicine, Royal Oak, MI, USA; Department of Urology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; Department of Pharmacology and Chemical Biology, University of Pittsburgh Medical School, Pittsburgh, PA, USA; Bristol Urological Institute and School of Clinical Sciences, University of Bristol, Bristol, UK; Department of Urology, LMU Munich, Campus Grosshadern, Munich, Germany; James Buchanan Brady Foundation, Department of Urology, Weill Cornell Medical College, New York, NY, USA; Department of Urology, Hospital de S. João, University of Porto, Porto, Portugal

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Abstract

Background: The pathophysiology of male lower urinary tract symptoms (LUTS) is highly complex and multifactorial. The shift in perception that LUTS are not sex or organ specific has not been followed by significant innovations regarding the available drug classes.

Objective: To review pathophysiologic mechanisms and clinical and experimental data related to the development of new pharmacologic treatments for male LUTS.

Evidence acquisition: The PubMed database was used to identify articles describing experimental and clinical studies of pathophysiologic mechanisms contributing to male LUTS and, supported by them, new pharmacotherapies with clinical or experimental evidence in the field.

Evidence synthesis: Several pathologic processes (eg, androgen signaling, inflammation, and metabolic factors) and targets (eg, the urothelium, prostate, interstitial cells, detrusor, neurotransmitters, neuromodulators, and receptors) have been implicated in male LUTS. Some newly introduced drugs, such as phosphodiesterase type 5 inhibitors and β3-adrenergic agonists, have just started broad use in clinical practice. Drugs with potential benefit, such as vitamin D3 receptor analogs, gonadotropin-releasing hormone antagonists, cannabinoids, and drugs injected into the prostate, have been evaluated in experimental studies and have progressed to clinical trials. However, safety and efficacy data for these drugs are still scarce. Some compounds with interesting profiles have only been tested in experimental settings (eg, transient receptor potential channel blockers, Rho-kinase inhibitors, purinergic receptor blockers, and endothelin-converting enzyme inhibitors).

Conclusions: New pathophysiologic mechanisms of male LUTS are described that lead to the continuous development of new pharmacotherapies. To date, few drugs have been added to the current armamentarium, and several are in various phases of clinical or experimental investigation.

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1. Introduction

Lower urinary tract symptoms (LUTS) can be subdivided into storage (overactive bladder [OAB]), voiding, and postmicturition subtypes, with OAB symptoms generally the most bothersome [1]. LUTS in men are not disease specific. Benign prostatic hyperplasia (BPH) as a histologic diagnosis and clinical BPH are terms best avoided when describing LUTS in men, due to a bias toward a potential role of the prostate versus other likely contributory mechanisms. A variety of experimental, epidemiologic, and clinical data have shown that LUTS, particularly the storage component (OAB), are multifactorial in origin [2,3].

BPH is extremely prevalent in the aging male population, increasing from 42% in men 50–59 yr of age to 88% in men >80 yr [4]. Approximately 50% of men with histologic BPH develop benign prostatic enlargement (BPE), but only 25–50% of men with histologic BPH have LUTS [2,5,6]. Clearly the inverse is also true: The presence of LUTS in men does not conclusively signify a diagnosis of benign prostatic obstruction (BPO) or bladder outlet obstruction (BOO). In series of male patients presenting with LUTS, only 50% were found to have urodynamically proven BOO [7–9]. LUTS suggestive of BOO may actually be due to an underactive detrusor, regardless of whether BOO is present [10]. Overall, the direct correlation of BPH, BPE, BOO, and LUTS is poor.

The storage symptom complex (OAB) is defined as urgency, with or without urge incontinence, usually with frequency and nocturia [1]. This symptom syndrome was previously considered to be a female disorder [11]. However, using the 2002 International Incontinence Society definitions, the Extended Prostate Cancer Index Composite study evaluated LUTS in 19 165 individuals ≥18 yr of age in five countries and reported a similar prevalence of OAB in men and women—10.8% and 12.8%, respectively [12].

To date, the first-line medical therapy for men with LUTS is α₁-adrenergic receptor antagonists (α-blockers) and 5α-reductase inhibitors (5-ARIs) [5,13]. Despite the high prevalence of OAB symptoms in men, antimuscarinics are not commonly used. Clinical trials have been conducted to assess the efficacy of combination therapy with existing drugs: α-blocker plus 5-ARI, α-blocker plus antimuscarinics, and 5-ARI plus antimuscarinics [14–16]. In addition, new information on different pathophysiologic processes related to LUTS has been reported [3,17]. The present paper considers pathophysiologic mechanisms and possible targets for drug therapy, and it reviews the clinical and experimental data related to the development of these new treatments for male LUTS.

2. Evidence acquisition

A literature search was performed via the PubMed database. Articles describing experimental or clinical data on pathophysiologic mechanisms of male LUTS were selected. Based on the targets and mechanisms included in the first section, articles about new pharmacotherapies for male LUTS were chosen. For this section, newly introduced drugs, drugs in the phase of clinical trials, and drugs in the phase of experimental investigation were included. Only studies published in English were included. Nocturia was not included in the search. A recent review covered this topic comprehensively [18].

3. Evidence synthesis

3.1. Pathophysiologic mechanisms and targets for future therapies (Fig. 1)

3.1.1. Androgen and estrogen receptor signaling in prostatic tissue remodeling

Androgens play a key role in the growth and development of the prostate as well as in the pathogenesis of BPH. Subjects castrated before puberty do not develop BPH [19]. Testosterone is converted to dihydrotestosterone (DHT) by 5α-reductases (5-ARs) predominantly in the stromal tissue. DHT is more potent than testosterone and also has a higher affinity for the androgen receptor (AR), allowing it to accumulate in the prostate even when circulating testosterone levels are low. Intracellular ARs are activated by androgen binding and/or through interactions with growth factor (GF) signaling and protein kinase A pathways [20]. Androgen deprivation, either surgically or chemically with finasteride, a 5-AR type1 inhibitor, or dutasteride, a 5-AR type1 and 2 inhibitor, reduce both circulating and intraprostatic DHT, and prostate volume by 20% [21,22].

Conversely, a few recent studies have pointed out the effect of low androgen levels on urinary functions. Late-onset hypogonadism has been associated not only with erectile dysfunction but also with LUTS. A definitive pathophysiologic explanation is not clear, but the basis for this association relies on the distribution of ARs throughout the LUTS, the impact of androgens on the autonomic nervous system, nitric oxide synthase, phosphodiesterase type 5 (PDE5), RhoA/Rho kinase (ROK) activity, and pelvic blood flow [23]. In a cohort of community-dwelling older men, the ones with higher midlife levels of testosterone to DHT and bioavailable testosterone had a decreased 20-yr risk of LUTS [24]. Male hypogonadism has recently been associated with metabolic syndrome, probably via increased aromatase activity, hypogonadotrophic hypogonadism, and increased activity of the hypothalamic–pituitary–adrenal axis [25].

Estrogen and estrogen-mimicking compounds may also have a role in prostate biology because estrogen receptor (ER)–α is associated with proliferation and ER-β is associated with regulation of proliferation and induction of apoptosis [26]. In the aging man, there is a progressive decrease in the ratio of circulating levels of androgens to estrogens. This is believed to contribute to BPH development through a mitogenic effect on ER–α. Aromatase, which converts androgen precursors to aromatic estrogens, has been identified in the prostatic stroma [21].

3.1.2. Urothelium

The urothelium represents more than a barrier in the bladder. Urothelial cells express nociceptors and mechanoreceptors and when stimulated release several substances
such as adenosine triphosphate (ATP), nitric oxide (NO), acetylcholine (ACh), cytokines, prostanoids, and nerve growth factor (NGF), among others. During the storage phase in patients with detrusor overactivity (DO), possible release of ACh from the urothelium may initiate spontaneous localized contractile activity of the detrusor and trigger "afferent noise" [27].

ATP acts on purinergic receptors: P2X (ligand-gated cation channel) and P2Y (G protein-coupled). Several purinergic receptors are expressed in the urothelium: All seven P2X receptors subunits (1–7) and P2Y subunits 1, 2, and 4. P2X3 receptors were detected on pelvic afferent nerves, dorsal root ganglia, bladder wall, and in a suburothelial plexus of afferent nerves [28–31].

3.1.3. Interstitial cells
Interstitial cells (ICs) occur in the lamina propria and within and adjacent to smooth muscle bundles. ICs in the lamina propria respond to ATP by firing Ca2+ transients, suggesting the existence of a sensory transduction signaling system. In the detrusor, ICs respond to cholinergic agonists, preferentially mediated by M3 receptors [32]. ICs may directly generate detrusor contractile activity during filling and be involved in ACh-mediated voiding contractions [32,33]. In a rat model of partial BOO, there was an increase of ICs in the suburothelial and muscle layers expressing endothelial nitric oxide synthase and neuronal nitric oxide synthase [34]. Imatinib mesylate, a selective inhibitor of c-kit receptor tyrosine kinase, inhibited evoked smooth muscle contraction and spontaneous activity in human OAB but not in normal detrusor. Systemic administration of imatinib mesylate improved bladder capacity, compliance, voided volume, and urinary frequency, and it reduced contraction thresholds and spontaneous activity during guinea pig cystometry [35].

3.1.4. Detrusor and prostatic smooth muscle
Bladder hypertrophy is a consistent response following obstruction in animal models and men [36–38]. Alterations in the smooth muscle structure, in the extracellular matrix, and in the neuronal control and blood flow/ischemia have been associated with the pathophysiology of LUTS [39]. Contractile proteins, such as desmin, actin, and myosin, were shown to be altered in rats with partial urethral obstruction (PUO) and in men with BOO [39]. An increase in collagen deposition was observed in rats with PUO.
Increased levels of basic fibroblast growth factor, epidermal growth factor (EGF), heparin-binding EGF-like growth factor, insulin-like growth factor 1, NGF, and connective tissue growth factor were demonstrated [39,40]. Growth and phenotypic differentiation of sensory afferents and sympathetic efferents in hypertrophied bladders has been attributed to NGF, which may also influence spinal micturition pathways, modulating voiding reflexes, and pain sensation in pathologic conditions [41]. Ischemia may also play a role in bladder hypertrophy. BOO models are associated with a decrease in bladder blood flow [42], and prevention of ischemia decreases bladder hypertrophy and improves detrusor contractility [43].

An abnormally upregulated ROK pathway may alter muscle relaxation in the prostate, urethra, and bladder neck in male LUTS. RhoA/ROK inhibits myosin light chain phosphatase and increases the Ca\(^{2+}\) sensitivity of smooth muscle contraction [44]. RhoA expression was intense in prostatic smooth muscle cells of spontaneously hypertensive rats [44]. In rats with PUO, bladder hypertrophy was accompanied by higher expression of RhoA and ROK, lower myosin phosphatase activity, and enhanced relaxant effects of Y27632, a ROK inhibitor [45]. Pelvic ischemia and/or atherosclerosis have also been associated with upregulation of the ROK pathway [46].

### 3.1.5. Neurotransmitters, neuromodulators, receptors, and neural pathways

#### 3.1.5.1. Norepinephrine and adrenergic receptors

Prostatic stromal cells express \(\alpha_1\) receptors, more specifically \(\alpha_1A\), which provide the prostatic muscle tone. This concept led to the development of \(\alpha\)-blockers for the treatment of LUTS associated with BPO. However, the mechanism of action of these drugs has recently been questioned, given their small effect on urodynamically proven BOO and the poor correlation after treatment between the improvement of LUTS and obstruction. There is discussion about the effect of \(\alpha\)-blockers on extraprostatic \(\alpha\)-ARs, such as those in the bladder and spinal cord, and on other AR subtypes, especially \(\alpha_1D/AR\) [47]. There is experimental evidence that BOO, although not changing the relative expression of \(\alpha_1\)-AR subtypes [48], may enhance the response of \(\alpha_1A\)-AR to adrenergic agonists [49]. Nonopidil, an \(\alpha_1D/\alpha_1A\)-AR selective antagonist (rather \(\alpha_1D\)-AR selective), increased the volume at first desire to void and the volume at maximum desire to void while decreasing DO, which might imply a role—at least in part—in sensory afferent nerve activity [50].

In the bladder, \(\beta\)-ARs predominate over \(\alpha\)-ARs, and the response of the normal detrusor to norepinephrine is relaxation. In human bladder smooth muscle, \(\beta_3\)-ARs are the predominant subtype, both in concentration and in physiologic importance. \(\beta_3\)-AR agonists have relaxant effects in vitro and in animal models of DO [51,52]. \(\beta_3\)-ARs are also expressed in the rat sacral spinal cord. PUO upregulates these adrenoceptors; intrathecal injection of a \(\beta_3\)-AR agonist improved bladder function in obstructed animals with no effect on sham-operated animals, indicating that \(\beta_3\)-AR containing central nervous pathways may be relevant [53].

#### 3.1.5.2. Acetylcholine and muscarinic receptors

The detrusor muscle contains muscarinic receptors (MRs), mainly M2 and M3. M3 receptors are mainly responsible for normal micturition contractions, which depend on Ca\(^{2+}\) mobilization through the activation of the PLC-IP3 pathway, Ca\(^{2+}\) entry through nifedipine-sensitive channels, and activation of the ROK pathway [27,51]. The antimuscarinics are generally assumed to deliver their beneficial effects by blocking MRs on the detrusor muscle. However, increasing evidence now indicates that additional effects involve M3 within the urothelium/suburothelium including bladder afferent nerves [54]. Because antimuscarinics in clinical doses have comparatively modest effects on voiding contractions, their clinical efficacy may reflect influences on the abnormal leak of ACh, from nerve endings or non-neuronal sources during the storage phase that may cause focal myogenic activity or urothelium-sensory fiber stimulation [27].

#### 3.1.5.3. Transient receptor potential channel superfamily

Members of the transient receptor potential (TRP) family channels may respond to stretch and/or chemical irritation, and they participate in urothelial–afferent interactions that underlie sensory perception and overall bladder function. Several members of this receptor family have been implicated in LUTS pathophysiology [55]. In a subgroup of patients with idiopathic DO responding to intravesical resiniferatoxin treatment, bladder TRPV1 messenger RNA (mRNA) expression was higher than in nonresponders and controls [56]. In addition, patients with increased filling sensation exhibited upregulation of TRPV1 mRNA in the trigonal mucosa, which was inversely correlated with the bladder volume at first sensation during filling cystometry [57]. Urothelial TRPV1 and TRPV4 activation increases ATP release, which may contribute to DO and OAB pathophysiology [58].

#### 3.1.5.4. Cannabinoids and cannabinoid receptors

The interest in the modulatory effect of cannabinoid (CB) receptor agonists on voiding function started with the report of improvement of LUTS in patients with multiple sclerosis (MS) using smoked cannabis [59]. CBs act on at least two types of receptors: CB1 and CB2 expressed in several structures of the bladder including urothelium and sensory fibers [60,61]. Sensitization of bladder afferents by inflammation can be partly suppressed by activation of CB receptors, an effect that appears to be mediated by CB1 [62]. Fatty acid amide hydrolase (FAAH), the key enzyme for the degradation of the endogenous cannabinoid agonist anandamide, is expressed in human, mouse, and rat bladder mucosa. FAAH increases anandamide in the bladder tissues and activates CB2 expressed in the urothelium and bladder afferents [63]. In addition to modulating afferent signaling, CB2 receptors also seem to influence cholinergic nerve activity [60].

#### 3.1.5.5. Adenosine triphosphate and purinergic receptors

Although negligible in normal human detrusor neuromuscular excitation, ATP participation in detrusor contraction is prominent in other species and in pathologic conditions in humans, particularly with DO. In vitro bladder preparations...
from patients with OAB and BOO showed a greater contractile response to ATP compared with specimens from normal bladders. In addition, ecto-adenosine triphosphatase activity was lower in overactive bladders, which may lead to greater access to ATP and enhanced contractile activity, contributing to DO [64]. In another study, P2X1 was the main purinoceptor in male human bladder, and its mRNA expression was higher in BOO [65]. In an in vitro study with porcine detrusor strips, detrusor motor drive was enhanced by excitatory muscular P2X1 and by neural P2X3 subunits, facilitating the release of ACh. The experimentally induced downregulation of purine breakdown produced smooth muscle hyperactivity that was reduced by the P2X1,3 blockade [66].

3.1.5.6. Nitric oxide/cyclic guanosine monophosphate activity. NO acts as a nonadrenergic, noncholinergic inhibitory factor responsible for urethral relaxation during voiding and possibly for bladder relaxation during the filling phase [51]. NO has an inhibitory effect on afferent nerve activity [17]. Expression of all the key enzymes of the NO/cyclic guanosine monophosphate (cGMP) signal has been demonstrated in the human prostate. The PDE5 isoenzymes are highly expressed in the bladder, prostate, and their supporting vasculature [67]. In the bladder, NOS-containing nerves are present. Furthermore, the NO/cGMP pathway can modulate smooth muscle cell proliferation, through protein kinase C inhibition [68].

3.1.6. Inflammation
The observation of chronic inflammation coexisting with BPH histologic changes in pathologic specimens led to the suspicion that inflammation plays a role in the development of prostate enlargement and LUTS/BPH [69]. In a retrospective analysis of 1700 BPH patients, chronic inflammation and prostate volume were correlated [70]. Prostatic inflammation was associated with overall clinical progression and increased incidence of acute urinary retention (AUR) [71]. A positive association between high plasma C-reactive protein levels and the odds of reporting moderate to severe LUTS (American Urological Association Symptom Index [AUA-SI] >8) was reported [72].

Local inflammation may be triggered by a viral or bacterial infection, which would lead to the secretion of cytokines, chemokines, and growth factors involved in the inflammatory response with consequent growth of epithelial and stromal prostatic cells. It has been hypothesized that the inflammatory response is perpetuated by the release of prostatic self-antigens following tissue damage, which would sensitize the immune system and start autoimmune responses. Important factors in this process are the prostatic stromal cells, which activate CD4+ lymphocytes and proinflammatory cytokines and chemokines, such as stromal-derived interleukin-8 [73].

Prostanoids (prostaglandins [PGs] and thromboxanes) are synthesized by cyclo-oxygenases (COX-1 and -2) in the bladder after different physiologic stimuli, injuries, and nerve stimulation, and by agents such as ATP and mediators of inflammation. In rats, intravesical instillation of prostaglandin E2 (PGE2) was shown to cause DO [74,75]. BOO in rats was associated with a higher expression of COX-2, suggesting that PGs may be involved in the development of bladder hypertrophy and DO [76,77]. Higher levels of PGE2 and of PGE2 and prostaglandin F2α (PGF2α) were found in the urine of men and women with OAB, respectively [78,79]. PGs have been shown to sensitize bladder afferent nerves via different prostanoid receptors [32].

3.1.7. Metabolic factors
Body weight, body mass index (BMI), and waist circumference have all been positively associated with prostate volume in multiple study populations [80]. In the Baltimore Longitudinal Study of Aging cohort, each 1 kg/m² increase in BMI corresponded to a 0.41-ml increase in prostate volume. Obese (BMI ≥ 35 kg/m²) participants had a 3.5-fold increased risk of prostate enlargement compared with nonobese (BMI <25 kg/m²) participants [81]. Most established aspects of the metabolic syndrome are linked to BPH. The presence of metabolic syndrome is associated with a higher annual BPH growth rate, increased sympathetic activity, and LUTS [25]. Diabetes, increased serum insulin, and elevated fasting plasma glucose have been associated with increased prostate size and increased risks of prostate enlargement, clinical BPH, BPH surgery, and LUTS. The underlying pathophysiologic mechanisms involved in the association of metabolic factors and LUTS/BPH are not completely understood, but systemic inflammation, pelvic ischemia, and increased sympathetic activity may play a role [80–82].

3.2. New advances in pharmacotherapy (according to the identified targets) (Table 1)

3.2.1. Hormonal
The use of antiandrogens or gonadotropin-releasing hormone (GnRH) agonists, widely used for the treatment of prostate cancer, is not warranted for the treatment of male LUTS due to the unacceptable side effects of medical castration. However, GnRH antagonists may lead to an intermediate level of testosterone suppression, achieving therapeutic benefits while avoiding the adverse events (AEs) associated with medical castration [83]. The luteinizing hormone-releasing hormone antagonist cetrorelix, given intramuscularly, caused a 4-point improvement in the International Prostate Symptom Score (IPSS) in excess of the changes observed in the placebo group in a phase 2 randomized controlled trial (RCT) [84]. However, those results were not confirmed in phase 3 clinical trials [85].

Because male hypogonadism is also associated with LUTS, the effect of androgen-replacement therapy (ART) was tested in men with both conditions. In a small RCT, the use of ART led to improvements in IPSS, maximum flow rate (Qmax), and voided volume compared with untreated controls [86].

3.2.2. Antimuscarinics
Antimuscarinics are often neglected in men with only storage symptoms before some kind of prostate-driven
treatment because many urologists believe that male LUTS are always secondary to the prostate. There is also the common perception that these drugs may impair the detrusor contraction and therefore be detrimental in a presumed obstructed patient \[11,87\]. To address this issue, several RCTs evaluated the effect of the combination of antimuscarinics and \(\alpha\)-blockers. The combination was more effective at reducing male LUTS than \(\alpha_1\)-AR antagonists alone in men with OAB and coexisting BPO. Moreover, the combination was safe because the increase in postvoid residual (PVR) and the incidence of AUR were, in general, clinically negligible. It is important to note, however, that most of the studies defined an upper limit of PVR of 200 ml and a lower limit of \(Q_{\text{max}}\) of 5 ml/s in their inclusion criteria \[88–93\].

### 3.2.3. The \(\beta_3\) adrenergic agonists

The \(\beta_3\) selective agonists, which include mirabegron and solabegron, are currently being evaluated or used for the treatment of OAB. Currently, clinical trials with solabegron have only enrolled women, which has not been the case with mirabegron \[94\]. In a phase 3 North American RCT, 1328 patients (25.7% men) were randomized to receive placebo or mirabegron 50 or 100 mg once daily for 12 mo. In the European-Australian phase 3 trial, 1978 patients (27.8% men) were randomized to receive placebo, mirabegron 50 or 100 mg, or tolterodine sustained release (SR) 4 mg once daily for 12 wk. Both doses of mirabegron showed significant improvement in incontinence, frequency, urgency, nocturia, and voided volume per micturition at week 12. Improvements in incontinence and frequency were evident at the first measured time point (4 wk). The global incidence of AEs was similar across the four study groups with the exception of dry mouth that was higher in the tolterodine SR group \[95\]. Unfortunately, a post hoc analysis of the two phase 3 trials with mirabegron to analyze the effect of the compound exclusively in men is not available. Nevertheless, the safety of mirabegron was urodynamically evaluated in 200 men with LUTS and BOO. Patients were randomized to receive mirabegron 50 mg, mirabegron 100 mg, or placebo once daily for 12 wk. Mirabegron at both doses had no effect on urinary flow, detrusor pressure at maximum flow, or bladder contractility. PVR was marginally increased by mirabegron 100 mg but not 50 mg \[96\].

#### 3.2.4. Phosphodiesterase inhibitors

Based on the relaxant effects of drugs on smooth muscle (prostate, urethra, detrusor) and on the association between LUTS and erectile dysfunction, the use of PDE5 inhibitors (PDE5-Is) has been investigated in the treatment of male LUTS \[97\]. The precise mechanism(s) of action of PDE5-I on LUTS, however, remains to be elucidated. As discussed by Andersson et al, PDE5-Is may act on several pathways including upregulating NO/cGMP activity, downregulating Rho-kinase activity, modulating autonomic nervous system overactivity and bladder and prostate afferent nerves, increasing pelvic blood perfusion, and reducing inflammation \[17\].

Several clinical trials on the effect of PDE5-Is on male LUTS have been published. In these studies, different PDE5-Is (sildenafil, vardenafil, tadalafil, and UK-369003) and combinations of an \(\alpha\)-blocker (alfuzosin or tamsulosin) and PDE5-I were compared with placebo or to \(\alpha\)-blocker alone. According to a recent meta-analysis, the use of PDE5-I alone was associated with a significant improvement of IPSS at the end of the studies compared with placebo \[98\]. The association of an \(\alpha\)-blocker and PDE5-I significantly improved IPSS and \(Q_{\text{max}}\) at the end of the studies compared with \(\alpha\)-blockers alone \[97,98\]. Tadalafil is now approved by the US Food and Drug Administration for male LUTS management.

### Table 1 – Future pharmacotherapy for non-neurogenic male lower urinary tract symptoms, their respective targets, and phase of studies

<table>
<thead>
<tr>
<th>Class of drugs</th>
<th>Target</th>
<th>Phase of studies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimuscarinics</td>
<td>M3 muscarinic receptors</td>
<td>Clinical practice</td>
<td>[88–93]</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors</td>
<td>NO/cGMP</td>
<td>Clinical practice</td>
<td>[97,98]</td>
</tr>
<tr>
<td>- ROK</td>
<td>Autonomic nervous system</td>
<td></td>
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<tr>
<td>- Blood perfusion</td>
<td>Inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\beta_3)-agonists</td>
<td>(\beta_3)-adrenergic receptor</td>
<td>Phase 2 (completed)</td>
<td>[94–96]</td>
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<tr>
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<td>Acetylcholine release</td>
<td>Clinical practice</td>
<td>[125,127]</td>
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<tr>
<td>LHRH antagonists</td>
<td>Testosterone</td>
<td>Phase 3 (completed)</td>
<td>[84,85]</td>
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<tr>
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<td>Cannabinoid receptors</td>
<td>Phase 3</td>
<td>[115,116]</td>
</tr>
<tr>
<td>NX-1207</td>
<td>Prostate tissue</td>
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<td>[122]</td>
</tr>
<tr>
<td>PRX-302</td>
<td>Prostate tissue</td>
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<td>[124]</td>
</tr>
<tr>
<td>Vitamin D3 receptor analogs</td>
<td>Vitamin D3 receptors</td>
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<td>[110]</td>
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<tr>
<td>Anti-inflammatory drugs</td>
<td>Inflammation</td>
<td>Phase 1</td>
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<td>Transient receptor potential channels</td>
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<td>[111–113]</td>
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<td>ROK</td>
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<td>Purinergic receptors</td>
<td>Experimental</td>
<td>[120]</td>
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<tr>
<td>Endothelin-converting enzyme inhibitors</td>
<td>Detrusor muscle</td>
<td>Experimental</td>
<td>[121]</td>
</tr>
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</table>

cGMP = cyclic guanosine triphosphate; LHRH = luteinizing hormone-releasing hormone; NO = nitric oxide; ROK = RhoA/Rho kinase.
3.2.5. Anti-inflammatory drugs

In an experimental model of BPH in rats treated with flavocoxid, a dual inhibitor of COX-2 and 5-lipoxygenase (5-LOX), reduced prostate weight and hyperplasia was observed, and indubitable expression of COX-2 and 5-LOX and the production of PGE2 and leukotriene B4 were blunted. The drug also enhanced apoptosis pathways and decreased GF expression [99]. The combination of rofecoxib and finasteride caused a statistically significant improvement in IPSS and Qmax, than finasteride alone at 4 wk but not at 24 wk [100]. The combination of tenoxicam and doxazosin had a positive effect on the IPSS, IPSS-quality of life (QoL), and OAB Symptom Score than doxazosin alone at 6 wk, in particular on storage symptoms [101]. However, no large RCTs followed, so the results should be interpreted with caution.

3.2.6. Vitamin D3 receptor analogs

Human prostatic urethra, prostate, and bladder exhibit vitamin D3 receptors (VDRs) [102]. Elocalcitol, a VDR agonist, may decrease stromal prostate cell proliferation, even in the presence of GFs, and induce apoptosis without interfering with AR signaling [103]. In human and rat bladder smooth muscle, elocalcitol also inhibited RhoA/ROK signaling [104] and limited the COX2/PGE2 pathway [105].

In a rat model of BOO, daily treatment with elocalcitol for 14 d, in a nonhypercalcemic dose, did not prevent bladder hypertrophy, but it reduced the occurrence of spontaneous contractions and the decrease in contractility of the detrusor that occurred with increasing bladder weight, both in vivo and in vitro [106]. Previous treatment with elocalcitol enhanced the effects of tolterodine on bladder compliance of rats with partial BOO [107].

A phase 2 RCT could not demonstrate differences in Qmax and symptoms between elocalcitol and placebo, however, despite the capacity to arrest prostate growth in men ≥50 yr of age with prostatic volume ≥40 ml [108,109]. A recent phase 2b RCT caused a revival of interest in elocalcitol after showing a significant reduction in incontinence episodes and improvement of the Patient’s Perception of Bladder Condition in women with OAB. Unfortunately, male patients were not included [110].

3.2.7. Transient receptor potential channel blockers

Experimental data on the effect of drugs interacting with TRP channels in regard to LUTS have been published; however, no proof-of-concept studies in humans are available. Most of the data on TRP channel blockers originate from inflammation models. In animal models of cystitis or spinal cord transection GRC 6211, an orally active TRPV1 antagonist counteracted bladder hyperactivity and noxious input. At the same doses, the compound had no effect on bladder function in sham animals [111]. Likewise, the TRPV4 antagonist HC-067047 also dose-dependently decreased the voiding frequency and increased the voided volume. However, at the same doses the TRPV4 antagonist also affected sham animals [112]. Systemic coadministration of TRPV1 and TRPV4 antagonists showed an interesting synergistic effect in DO [113]. No studies are available in humans due to the hyperthermic effect of these drugs in pilot studies.

3.2.8. Cannabinoids

Clinical studies with the use of cannabinoids on LUTS are scarce and essentially restricted to MS patients. The efficacy of whole plant extracts of Cannabis sativa was demonstrated in MS patients with LUTS, who experienced significant improvement in urgency, incontinence, frequency, and nocturia [114]. In the multicenter trial of the Cannabinoids in Multiple Sclerosis study, patients who used cannabis extract or ∆9-tetrahydrocannabinol achieved a significant reduction in incontinence episodes over matched placebos [115]. In contrast, Sativex (nabiximols), an endocannabinoid system modulator, failed to reach statistical significance in the primary endpoint, reduction in the daily number of incontinence episodes. The number of daytime voids, total voids per day, and nocturia, however, were significantly reduced in the Sativex group [116].

3.2.9. Rho-kinase inhibitors

Treatment with hydroxyfasudil, a nonselective Rho-kinase inhibitor, ameliorated the bladder dysfunction in male spontaneous hypertensive rats (SHRs). Micturition frequency, single voided volume, and intercontraction interval improved in hydroxyfasudil-treated animals compared with nontreated ones. Bladder blood flow and NGF content in the bladders of the treated animals were similar to those of healthy control animals. The authors theorized that bladder ischemia may be responsible for NGF overexpression in the bladder of SHRs and that hydroxyfasudil ameliorates bladder dysfunction by improving bladder blood flow and ischemia-induced bladder damage [117]. In another experimental study with cyclophosphamide-induced cystitis in rats, hydroxyfasudil significantly increased voided volume and decreased maximum detrusor pressure, whereas the intercontraction interval was not significantly affected. In vitro, the maximum contraction of the concentration-response curves to carbachol was significantly lower in the hydroxyfasudil group [118]. Likewise, another Rho-kinase inhibitor, Y-27632, attenuated the phasic and sustained contraction induced by carbachol in both control and obstructed bladders from rats. The inhibitory effect of Y-27632 was enhanced on the sustained responses to carbachol in the obstructed bladders [119].

3.2.10. Parasympathetic receptor blockers

In an experimental model of neurogenic bladder induced by spinal cord injury (SCI) in female rats, the P2X3/P2X2/3 antagonist AF-353 reduced the field potential in the dorsal horn in response to sudden increase in intravesical pressure. In addition, during cystometry the frequency of nonvoiding contractions was significantly reduced in SCI animals [120].

3.2.11. Endothelin-converting enzyme inhibitors

Endothelin (ET)-1 is a potent vasoconstrictor that has been shown to contract human detrusor and is overexpressed in the detrusor muscle in a rabbit BOO model. Endothelin-converting enzyme (ECE) is responsible for the generation of ET-1. It was hypothesized that the inhibition of ECE could prevent some bladder changes following BOO; thus WO-03028719, an oral ECE inhibitor, was given to
obstructed female rats, leading to a reduction in the incidence of nonvoiding contractions and in the amplitude of normal voiding contractions. The drug has not been tested in humans [121].

3.2.12. Drugs injected into the prostate

3.2.12.1. NX-1207. NX-1207 is an investigational drug for the treatment of LUTS/BPH, currently in phase 3 clinical trials. It is a new therapeutic protein of proprietary composition with selective proapoptotic properties. The drug is injected under transrectal ultrasound guidance into the transition zone of the prostate. The drug produces focal cell loss through apoptosis, leading to prostate tissue shrinkage. In the first US phase 2 clinical trial, three doses of NX-1207 (2.5, 5.0, and 10 mg) were evaluated in a multicenter RCT involving 175 men. The dose of 2.5 mg was selected as the smallest dose showing clinically significant efficacy (mean improvement in AUA-SI: 11.0). The second trial, a multicenter randomized noninferiority study, evaluated two doses (2.5 and 0.125 mg) and an active open-label comparator (finasteride). The mean AUA-SI improvement after 90 d in the intent-to-treat group was 9.71 points for 2.5 mg NX-1207 versus 4.13 points for finasteride (p = 0.001) and 4.29 for 0.125 mg NX-1207 (p = 0.034). The 180-d results also were positive (NX-1207 2.5 mg noninferior to open-label finasteride). None of the clinical studies identified safety issues relating to NX-1207 itself or sexual side effects. The drug is currently under investigation in phase 3 clinical trials in the United States [122].

3.2.12.2. PRX302. PRX302 is a prostate-specific antigen (PSA)-activated protoxin produced via a modified proazeroxin, the inactive precursor of a bacterial cytolytic pore-forming protein. Interestingly, the protoxin requires proteolytic processing by PSA for activation. When injected into the non–PSA-producing dog prostate, PRX302 was inactive, whereas its ability to ablate prostate tissue was observed in the PSA-producing monkey prostate [123].

PRX302 was injected transperineally under transrectal ultrasound guidance into the right and left transition zone in a study of 33 patients with BPH [124]. In phase 1 (n = 15), subjects received increasing concentrations of PRX302 at a fixed volume. In phase 2 (n = 18), the concentration was fixed and the volumes varied. In both phases, a decrease in total IPSS was observed in all cohorts. In phase 1, no relationship between IPSS response and dose was observed. In the phase 1 and 2 studies, respectively, a decrease ≥30% in IPSS was observed in 73% and 67% at day 90, and 64% and 67% in 1 yr. Patients also experienced improvement in QoL and reduction in prostate volume out to day 360. A statistically significant decrease in mean Q_{max} was observed at day 90 in the phase 1 study, which was not sustained out to 1 yr. In the phase 2 study, a 2.8 ml/s improvement was noted out to 1 yr. PRX302 injection decreased prostate mass, with most patients showing a ≥20% reduction in prostate volume after 1 yr. The injection >1 ml had the best overall results. Erectile function was not altered by the treatment. AEs were mild to moderate and transient in nature. The small sample of the studies, however, is a major limitation, particularly because repeated dosing of the toxin may lead to an antibody response [124]. Nonetheless, the preliminary safety and efficacy data make PRX302 a promising minimally invasive targeted treatment for LUTS associated with BPH.

3.2.12.3. Botulinum toxin. Botulinum neurotoxin (BoNT) prevents exocytosis of ACh vesicles at the nerve terminal, thereby inhibiting neurotransmission and muscle contraction. The action of BoNT is not permanent because neuronal death does not occur, and eventually the toxin is inactivated and removed. BoNT subtype A (BoNTA) is the most relevant clinically. OnabotulinumtoxinA (BoNT-ONA), abobotulinumtoxinA, and incobotulinumtoxinA are available BoNTAs [125,126]. Recently, the use of BoNT-ONA in LUTS was comprehensively reviewed. Its efficacy in the treatment of idiopathic DO was demonstrated in several studies including one RCT and a dose-ranging trial. It seems that the dose of 100 U may be the one that appropriately balances the symptoms benefits with the safety profile [125]. Improvement of LUTS associated with BPE has been reported with the use of intraprostatic injection of BoNT-ONA in clinical studies; however, the lack of placebo arms was always a drawback. Recently, intraprostatic injection of BoNT-ONA 100 U, 200 U, and 300 U was tested versus placebo injection in a phase 2 dose-ranging study. IPSS, Q_{max}, and prostate volume significantly improved in all groups, owing to a large placebo effect from the injectable therapy. A post hoc analysis revealed a significant reduction with BoNT-ONA 100 U in prior α-blocker users at week 12, which will be explored in further studies [127].

4. Conclusions

The pathophysiology of male LUTS is highly complex and multifactorial. Changes in the bladder and prostate as well as in related structures, such as the pelvic vasculature and innervation, account for alterations in the normal physiology of the male lower urinary tract. Derangements at the structural, molecular, and cellular levels have been identified, and new pathophysiologic mechanisms are continually described. Different categories of symptoms usually overlap, making it difficult to pinpoint one guilty organ, leading to a broader and more symptom-driven approach to the condition. In this scenario, new drugs have been suggested either as standalone or as add-on treatments to currently established treatments for male LUTS. Some of these drugs are currently being used in clinical practice with short-term results; others are still in clinical or experimental evaluation. Even though some of the new treatments may be promising alternatives, there is still a long way to go until patients can benefit from them.

Author contributions: Francisco Cruz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Soler, Gratzke, Cruz.
Acquisition of data: Soler, Cruz.
Analysis and interpretation of data: Soler, Cruz, Chapple, Andersson.


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