Investigational therapies targeted to the treatment of benign prostatic hyperplasia

Stavros Gravas & Jean JMCH de la Rosette†
†University of Amsterdam, AMC University Hospital, Academic Medical Center, Department of Urology, Amsterdam, The Netherlands

Introduction: The desired goals of treatment of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) include sustained, clinically significant improvement in symptoms and quality of life and/or slowing or preventing the progression of the condition. There is a continuing interest in research for new therapies for BPH due to the high prevalence of the condition and the unmet expectations of patients and physicians from the efficacy of available therapies.

Areas covered: The aim of this paper is to provide the latest data on new medical treatments for LUTS/BPH, defined as pharmacological treatments not yet commonly available and/or currently under investigation. Articles were identified by means of a computerised Google and PubMed search and a search of the trial registries.

Expert opinion: Many potential targets for future drugs have been evaluated but it is obvious that there is a wide variation in the degree of mature of each therapy. Time and high-quality studies will decide which of these potential drugs will fade away without fulfilling the initial promises. At the moment, phosphodiesterase type 5 inhibitors are claiming their position in the armamentarium of BPH treatment.

Keywords: 5-α reductase inhibitors, α-blockers, benign prostatic hyperplasia, botulinum toxin-A, carotenoids, elocalcitol, hormonal therapy, LHRH antagonists, lower urinary tract symptoms, NX1207, phosphodiesterase inhibitors, PRX302

1. Introduction

Lower urinary tract symptoms (LUTS) include the subcategories of storage (daytime urinary frequency, nocturia, urgency, urinary incontinence), voiding (slow stream, splitting or spraying, intermittency, hesitancy, straining, terminal dribble) and post-micturition symptoms (sensation of incomplete emptying, post-micturition dribble) [1]. Nowadays, it is well recognised that male LUTS can result from several pathophysiological conditions including the prostatic enlargement but also bladder dysfunction.

The present review will focus only on symptoms caused from prostate and it will provide the latest data on new medical treatments for LUTS due to benign prostatic hyperplasia (BPH), defined as pharmacological treatments not yet commonly available and/or currently under investigation.

2. Current medical therapy

The prevalence of BPH and LUTS rises markedly with increased age. BPH affects 70% of US men 60 – 69 years of age and 80% of those 70 years or older [2]. In the Olmsted County Study (a population-based study) the prevalence of...
Article highlights.

- There is a continuing interest in research for new therapies for the management of male LUTS due to the high prevalence of the condition and the unmet expectations of patients and physicians regarding the efficacy of available therapies.
- The current main players in the field of medical treatment of LUTS/BPH are α-blockers and 5ARIs either as monotherapy or as combination.
- LUTS/BPH and ED are prevalent and frequently associated in ageing men, and available clinical data suggest that PDE5-Is which are first-line therapy for ED may be used for treating LUTS. Tadalafil has been recently licensed for the management of LUTS/BPH.
- LHRH antagonists including CET, degarelix, tevarelix, elagolix and ozarelix have been evaluated for treatment of LUTS/BPH in Phase II and III clinical trials. They are currently considered as investigational therapies.
- The clinical efficacy and safety of BONT/A for LUTS/BPH have been studied but there is a wide variation in techniques, doses administered and duration of treatment effect. Therefore, BONT/A is considered as an investigational therapy.
- Other therapies such as NX-1207 and PRX302 have shown promising outcomes in Phase I and II studies, and results from Phase III trials are awaited with interest.

This box summarises key points contained in the article.

moderate-to-severe LUTS was 26, 33, 41 and 46% in men in the fifth, sixth, seventh and eighth and older decades of life, respectively [3]. Medical treatment should be offered to men with bothersome LUTS when conservative management options (e.g., behavioural treatment) have been unsuccessful or are not appropriate [4,5]. The current medical treatment of LUTS/BPH includes two general classes of drugs namely the α-blockers and the 5α-reductase inhibitors (5-ARIs), either as monotherapy or as combination in specific clinical situations.

2.1 α-Blockers

The male prostate and urethra contain α1-adrenergic receptors with the α1A subtype being the most prevalent and mediating contractile response of prostate. α-blockers theoretically act by antagonising the effect of endogenously released noradrenaline on prostate smooth-muscle cells resulting in prostate tone reduction and consequently in the improvement of the dynamic aspects of voiding.

Several α-blockers are available on the market including alfuzosin, doxazosin, tamsulosin and terazosin. α-blockers have been extensively studied, and meta-analyses on their efficacy are available and provide high level of evidence [6-8]. However, head-to-head trials between the different α-blockers are scarce but on a conceptual basis it seems that all α-blockers are equally effective at adequate doses [9]. In general, α-blockers have a rapid onset of action achieving an International Prostate Symptom Score (IPSS) reduction of about 35 – 40% and urine maximum flow rate (Qmax) increase of about 20 – 25%, but considerable improvements have also been seen in the corresponding placebo arms [9,10]. The newest entry in the class is silodosin. The efficacy and safety of silodosin in the treatment of LUTS/BPH have been evaluated in three high-quality Phase III randomised placebo-controlled trials [11-13], while in addition it has been proved to be at least as effective as tamsulosin [13].

α-blockers may have different side-effect profiles but it remains to be determined whether an α1-selectivity is the only and main factor determining good tolerability. The most frequent side-effects, experienced in approximately 5 – 9% of patients, include asthenia, dizziness, (orthostatic) hypotension, rhinitis, abnormal ejaculation (with an ejaculation being more common for silodosin), and the recently described intraoperative floppy iris syndrome, an adverse ocular event that complicates cataract surgery.

2.2 5-ARIs

The enzyme 5α-reductase (type 1 and type 2 isoenzymes) converts testosterone to dihydrotestosterone (DHT), playing a crucial role in the initial development and normal growth of the prostate [14]. Finasteride (inhibits only the type 2 enzyme) and dutasteride (inhibits both the type 1 and type 2 enzymes) are the two 5-ARIs available on the market. They cause apoptosis of prostatic epithelial cells, resulting in prostate size reduction by an average of 15 – 25% over time [15,16].

5-ARIs have a slow onset of action, and the available data suggest that clinical efficacy depends on initial prostate volume; therefore, they are suitable for long-term treatment in men with enlarged prostates. In general, 5-ARIs improve IPSS by approximately 15 – 30%, decrease prostate volume by approximately 18 – 28% and increase Qmax by approximately 1.5 – 2.0 ml/s in patients with LUTS due to prostate enlargement after 2 – 4 years of treatment [4].

The Enlarged Prostate International Comparator Study was a head-to-head randomised, comparative study between finasteride and dutasteride. It was found that after 1 year of treatment, prostate volume reduction from baseline was similar in both groups (26.3 and 26.7% for dutasteride and finasteride, respectively), while improvements in IPSS (5.8 vs. 5.5) and Qmax (2.0 vs. 1.7 ml/s) were greater for dutasteride than finasteride, but not statistically significant [17].

5-ARIs are well tolerated and have only minimal side-effects. The most common adverse events are sexual dysfunction including reduced libido, erectile dysfunction (ED) and, less frequently, ejaculation disorders and gynaecomastia [15-18].

2.3 Combination therapy

The next reasonable step in the medical treatment of LUTS was to test if combination of the differential effects of the different drug classes would result in synergistic and increased efficacy. The hypothesis that α-blockers and 5-ARIs could work together to provide early relief from symptoms and long-lasting prevention of progression was evaluated by two
landmark studies, namely the Medical Therapy of Prostatic Symptoms (MTOPS) and the Combination of Avodart and Tamsulosin (ComBat).

The MTOPS study contributed substantially to our understanding of the role of combination therapy for LUTS/BPH [19]. With a mean follow-up of 4.5 years, MTOPS showed that the risk of long-term clinical progression was reduced by 66% with combined therapy (vs. placebo) and to a greater extent than with either finasteride or doxazosin monotherapy (34 and 39%, respectively) [19]. The risks of AUR and need for invasive therapy were significantly reduced by combination therapy (81 and 67%, respectively) and finasteride (68 and 64%, respectively) but not by doxazosin monotherapy compared with placebo. In addition, doxazosin, finasteride and combination therapy all resulted in significant improvements in symptom scores versus placebo but combination therapy was superior to both doxazosin and finasteride alone.

The ComBat study included patients in high risk for progression (Prostate Volume (PV) ≥ 30 ml and prostate-specific antigen [PSA] ≥ 1.5 μg/l) [20]. Reduction of the relative risk of overall disease was significantly greater for the combination treatment (-31.2% compared with dutasteride and -44.1% compared with tamsulosin). Compared with tamsulosin, combination therapy reduced the relative risks of AUR by 67.8%, BPH-related surgery by 70.6% and symptom deterioration by 41.3% after 4 years [20]. In addition, ComBat demonstrated that long-term combination therapy is superior to either α-blocker or 5-ARI monotherapy in improving LUTS and Qmax.

Drug-related adverse events were typical of an α1-blocker and 5-ARI and more frequent during combination treatment than for either monotherapy, but the reported withdrawal rates were similar across the treatment groups.

3. Investigational therapies

3.1 Phosphodiesterase type 5 inhibitors

Epidemiologic studies have shown that the prevalence of coexisting LUTS and ED increases with age, the severity of one condition typically correlates to the severity of the other, and increasing severity typically results in reduced quality of life (QoL). A recent systematic review of the available epidemiological data showed that although fewer than one-third of men in the general population have coexistent LUTS and ED of any severity, most men seeking treatment for either LUTS or ED have both conditions of moderate-to-severe severity [21]. Several pathophysiological theories have been proposed in the literature including alteration of the nitric oxide (NO)-cyclic guanosine monophosphate pathway, enhancement of RhoA–Rho-kinase contractile signalling, autonomic adrenergic hyperactivity, and pelvic atherosclerosis that may explain the action of phosphodiesterase type 5 inhibitors (PDE5-Is) on BPH-related LUTS [22].

All three approved PDE5-Is, namely sildenafil, tadalafil and vardenafil, have been evaluated in large clinical studies for the indication of LUTS suggestive of BPH. A recent meta-analysis of the seven available randomised controlled trials comparing PDE5-Is with placebo was performed [23]. Sildenafil was used in one study, tadalafil in four studies, vardenafl in one study and UK-369003 (a new selective PDE5I, also known as gisadenafil) in another study. In total, 3214 men were randomised and followed up for 12 weeks and 2749 completed the study (1879 and 870 in the PDE5I and placebo group, respectively). Combining the results of those RCTs, it was found that monotherapy with a PDE5-I alone achieved a significant improvement of the International Index of Erectile Function (IIEF) score (+5.5) and IPSS (-2.8), but no significant improvement in Qmax was found (0.00) compared with placebo (Table 1) [23].

In an additional randomised controlled trial not included in the above meta-analysis, Oelke et al. evaluated the efficacy of tadalafil 5 mg or tamsulosin 0.4 mg versus placebo over a 12-week period [24]. It was found that both tadalafil and tamsulosin achieved a significant subjective and objective improvement compared with placebo in terms of IPSS and Qmax at 12 weeks. The IPSS improvement over placebo was -2.1 and -1.5 for tadalafil and tamsulosin, respectively. The corresponding increase in Qmax over placebo was 2.4 and 2.2 ml/s. On the other hand, only tadalafil improved ED in terms of the IIEF–Erectile Function domain. This is the first report ever that a PDE5-I achieves a significant improvement in Qmax compared to placebo, whereas all the previous studies with any of the PDE5-Is showed only small numeric but insignificant increases in Qmax (suggesting that the effect of these agents to bladder outlet obstruction seems to be minimal). Therefore, this new finding needs to be confirmed by more studies. It should be noted that the US Food and Drug Administration recently approved daily tadalafil (5 mg) for the treatment of LUTS secondary to BPH with or without simultaneous ED, and tadalafil is also expected to be officially registered for the treatment of male LUTS in Europe.

A recent randomised, double-blind, placebo-controlled study with a 12-week follow-up investigated the efficacy and safety of mirodenafil in patients with ED [25]. Mirodenafil is a new PDE5-I with a maximum plasma concentration at 1.25 hours, duration of 6 hours and a half-life of 2.5 hours. IPSS and Qmax were evaluated as secondary efficacy outcomes. It was found that, compared with placebo, mirodenafil significantly improved IIEF scores by 4.39 (p < 0.001), IPSS by -3.17 (p < 0.001) and Qmax by 2.26 ml/s (p = 0.001). In addition, the reported adverse effects were mild to moderate without any difference between the mirodenafil and placebo group. However, these results should be interpreted with caution since the mean baseline age, IPSS and Qmax of the mirodenafil patients were 56.9 years and 12.8 and 15.7 ml/s, respectively [25].

The combination of α-blockers with PDE5-Is has also been evaluated. A meta-analysis of the 5 randomised controlled trials on the combination (sildenafil 2, tadalafil 2, vardenafil 1) versus α1-adrenergic blockers alone was performed [23]. The
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Notably, it was found that the combination of PDE5-Is and α-blockers significantly improved IPSS (-1.8) and IIEF score (+3.6) when compared with the use of α-blockers alone. Notably, it was found that the combination of PDE5-Is and α-blockers significantly improved Qmax (+1.5 ml/s) as compared with α-blockers alone [23].

Recently, a randomised, double-blind, placebo-controlled study (not included in the above meta-analysis) after a 2-week run-in (baseline) with tamsulosin 0.4 mg/d investigated the safety and efficacy of tamsulosin vs. tamsulosin plus udenafil 10 mg/day in patients with LUTS/BPH with a 12-week follow-up [26]. There was a statistically significant improvement in Qmax (placebo: +0.07, udenafil: +2.56, \( p = 0.034 \)), irritative-IPSS subscores (placebo: -1.67, udenafil: -3.11, \( p = 0.039 \)) and IIEF (placebo: +0.06, udenafil: +2.61, \( p = 0.030 \)), but no differences in the incidence of common, treatment-related AEs between the two groups [26].

The combination of udenafil and α-blockers in patients with BPH/LUTS and ED who had been undergoing stable α-blocker therapy was evaluated for the first time in an open, prospective, and noncomparative study. Chung et al. gave udenafil (100 mg/d) for 8 weeks to 120 patients who had been treated with α-blockers for BPH. At study end point, IPSS (from 14.3 to 11.5) and IEEF (from 11.9 to 19.3) scores improved significantly compared with baseline values [27]. Limitations of the study included the lack of a placebo group, the fact that udenafil was not taken regularly, and that Qmax was not evaluated.

The most frequent adverse events of PDE5-Is include flushing, headache, gastroesophageal reflux, dyspepsia, back pain and sinusitis. In addition, PDE5-Is seem to interact to some degree with α-blockers, resulting in hypotension; therefore, caution is required based on the products’ labelling [4,28].

### Table 1. Level 1 studies on the use of PDE5-Is in male LUTS.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>FU (weeks)</th>
<th>Treatment arms</th>
<th>Pts</th>
<th>IPSS change vs control</th>
<th>( \delta )Qmax change vs control</th>
<th>IIEF change vs control</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>[23]</td>
<td>12</td>
<td>Placebo</td>
<td>2250</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PDE5-I alone</td>
<td>964</td>
<td>-2.8* [-3.6 to -2.1]</td>
<td>0.0 ml/s [-0.6 to 0.6]</td>
<td>5.5* [4.1 – 6.9]</td>
<td></td>
</tr>
<tr>
<td>[23]</td>
<td>12</td>
<td>α-blocker</td>
<td>107</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PDE5-I + α-blocker</td>
<td>109</td>
<td>-1.8* [-3.7 to 0.0]</td>
<td>1.5 ml/s* [0.9 – 2.2]</td>
<td>3.6* [3.1 – 4.1]</td>
<td></td>
</tr>
<tr>
<td>[24]</td>
<td>12</td>
<td>Placebo</td>
<td>172</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tadalafil 5 mg</td>
<td>171</td>
<td>-2.1 ± 0.6*</td>
<td>+1.2*</td>
<td>4.0 ± 1.0*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamsulosin 0.4 mg</td>
<td>167</td>
<td>-1.5 ± 0.6*</td>
<td>+1.0*</td>
<td>-0.4 ± 1.0*</td>
<td></td>
</tr>
</tbody>
</table>

*Statistical significant vs. control.

There are several LHRH antagonists available, including cetrorelix (CET), degarelix, tevarelix, elagolix and ozarelix.

#### 3.2 LHRH antagonists

Administration of luteinising hormone-releasing hormone (LHRH) antagonists, through their action in pituitary gland, results in serum and intraprostatic testosterone and DHT levels. The idea of using LHRH antagonists in the management of LUTS/BPH was to titrate serum testosterone to a level that would reduce prostate volume without causing adverse effects.

There was only a favourable trend on the IPSS, as compared to placebo in a subgroup of patients with large prostate glands (AEtarna Zentaris, press release, 17 August 2009). In addition, the drug did not have a significant effect on \( Q_{max} \) or prostate volume versus placebo. In the open-label, safety study Z-041 (528 patients in North America) and the efficacy study Z-036 (420 patients in mainly Europe), adverse events were mostly mild and transient in intensity, and most frequently AEs included hot flushes, nasopharyngitis, injections site pain and headache. Efficacy was assessed using the IPSS which showed an improvement from...
Investigational therapies targeted to the treatment of benign prostatic hyperplasia

A mean score of 21.2 at baseline to 15.6 at week 26. An improvement ≥3 points was reported by 63% of the patients (AEterna Zentaris, press release, 17 August 2009).

Study Z-036 showed that there was no difference between the two drug doses used and placebo in terms of efficacy with 6-point improvement in the IPSS maintained throughout the 52 weeks. There was observation of an improvement in uroflow, both maximum and mean, and in residual volume in all treatment groups (AEterna Zentaris, press release, 7 December 2009). Due to the failure of the study Z-036 to reach its primary endpoint, AEterna Zentaris Announces Termination of Agreement with sanofi-aventis U.S. for the Development, Commercialization and Licensing of Cetrotrelix in Benign Prostatic Hyperplasia (AEterna Zentaris, press release, 18 December 2009).

Recently, the influence of CET (either alone or in combination with a growth hormone-releasing hormone antagonist) on animal models of BPH was investigated. Rick et al. showed that CET reduces mRNA levels of inflammatory cytokines IFN-γ, IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, IL-15 and IL-17 and growth factors EGF, FGF-2, FGF-7, FGF-8, FGF-14, TGF-β1 and VEGF-A in Wistar rat prostate and can lower prostate weights at doses which do not induce castration levels of testosterone [31]. In addition, the combination of growth hormone-releasing hormone antagonist JMR-132, given at a dose of 40 µg daily, and CET, given at a dose of 0.625 mg/kg, caused a marked shrinkage of prostate (30.3%) in a BPH model in rats [32].

### 3.2.2 Teverelix
Teverelix was also evaluated in men with LUTS/BPH. Results have been published as abstracts. In a Phase II, randomised, double-blind, placebo-controlled trial, teverelix was administered subcutaneously as 2 doses each of 60 mg 48 hours apart. IPSS decreased over time until study completion at 16 weeks [33]. This improvement was statistically significant compared to placebo (6.3 vs. 1.1, respectively), while the drug was well tolerated. In a Phase II, randomised, double-blind, placebo-controlled trial, teverelix was given as two single subcutaneous injections (30 mg or 60 mg 12 weeks apart). Improvement in IPSS was transient and not clinically significant following the first injection [34]. After the second dose IPSS was significantly reduced and sustained for until the last visit at 28 weeks. No difference was found between the two doses, indicating that the 30 mg repeated at appropriate intervals may be clinically effective.

### 3.2.3 Ozarelix
A Phase II randomised, double-blind, placebo-controlled, multicentre, dose-ranging study evaluated the impact of ozarelix on LUTS [35]. Compared with placebo, ozarelix in a dose-dependent manner improved the IPSS score and peak flow rate without affecting the IIEF sexual function inventory. Improvement was durable up to the end of the 6 months observation period, while the lowest recorded serum testosterone did not reach the castrate level and was achieved with the highest doses of ozarelix [35].

#### 3.2.4 Degarelix
Degarelix has been investigated in two Phase II clinical trials but results are awaited. Table 2 displays the trials for the evaluation of LHRH antagonists for LUTS/BPH and their current status.

### 3.2.5 Elagolix
The safety, tolerability, pharmacokinetics and pharmacodynamics of elagolix were assessed in a Phase I single dose. Elagolix effectively reduced testosterone production when compared to placebo. A second study (2006) showed that a dose-related reduction of testosterone was achieved and that two weeks of elagolix is generally safe and well tolerated in healthy males (Neurocrine Bioscience, Press release 4 February 2009). No clinical trial for the effect of elagolix in male LUTS is being currently underway.

#### 3.3 NX-1207
NX-1207 is a new therapeutic protein of proprietary composition with selective pro-apoptotic properties. It has been demonstrated to induce focal cell loss in prostate tissue through apoptosis, leading to prostate tissue shrinkage [36]. NX-1207 0.25 mg/ml is administered by transrectal intraprostatic injection with ultrasound guidance using a no. 22 gauge needle. A total of 5 ml is injected into each lobe of the transition zone of the prostate. Treatment is performed on outpatient basis without the need of sedation or analgesia, or catheterisation, with patients reporting only minimal discomfort [36].

Two US Phase II trials confirmed positive safety and efficacy results from two earlier US Phase I/II studies, showing that NX-1207 offered symptom improvement in 3 months after the injection compared to placebo and finasteride (Table 3) [37,38]. Preclinical animal toxicology and safety studies showed no evidence of toxicity or other safety concerns for NX-1207. Few adverse events reported from the clinical studies were related to the transrectal procedure [36]. Interestingly, long-term blinded follow-up (up to 5 years) of patients in Phase II studies of NX-1207 demonstrated a sustained symptom improvement in half of the patients without the need of other medical or surgical treatments since their initial treatment [36].

Two Phase III studies are underway to define the true efficacy, safety and mechanism of action of this novel approach to treat BPH. The first Phase III study is a multicentre prospective randomised parallel-group placebo-controlled double-blind clinical evaluation of NX-1207 for the treatment of BPH which is currently recruiting patients (NCT00945490). This study will evaluate the safety and efficacy of a 2.5-mg dose of NX-1207 for the treatment of BPH as compared to placebo. The second Phase III study is a multicentre, prospective, open-label clinical safety evaluation of...
reinjection of NX-1207 for the treatment of BPH. This trial is designed to demonstrate the safety and efficacy of a second transrectal intraprostatic injection of NX-1207 given to men with BPH who previously received an injection of NX-1207 in an earlier US clinical trial (NCT01438775). Nymox announced the completion of recruitment on 11 July 2012. These initial data are encouraging, but the results of the ongoing large Phase III trials are awaited in order to define the potential role of NX-1207 for the management of symptomatic patients with BPH.

3.4 PRX302

PRX302 is a modified form of proaerolysin, a highly toxic bacterial pore-forming protoxin that requires proteolytic processing by PSA for activation [39].

Denmeade et al. published the results of an open-label Phase I dose-escalation trial (15 patients) and a Phase II volume-escalation study (18 patients) that evaluated the safety and efficacy of intraprostatic PRX302 with a 12-month follow-up [40]. After administration of local anaesthesia, PRX302 was injected transperineally under TRUS guidance using a 22-gauge needle. In the Phase I study, 3 – 4 deposits of 0.25 ml of PRX302 were made with each injection approximately 1 cm apart as the needle was withdrawn. In the Phase II study, prostate volume was calculated by TRUS, and cohorts of patients were given six equally divided deposits of PRX302 at a concentration of 3 mg/ml in a total injected volume that was 10, 20 or 30% of the total prostate volume. Overall, PRX302 treatment resulted in an 8 – 10 reduction in IPSS values in the majority of patients, with the duration of treatment effect lasting up to 1 year [40]. Sixty percent of men in the Phase I study and 64% of men in the Phase II study treated with PRX302 had >30% improvement compared to baseline out to day 360. The percentage of patients showing >20% reduction at day 360 was 36 and 63% for the Phase I and II studies, respectively. Patients receiving >1 ml of PRX302 per deposit had the best response overall. No dose-limiting toxicities were reported and adverse events were mild to moderate and transient in nature (frequency was the most common in both studies) without an adverse impact on sexual function [40]. However, these promising results are limited by the small sample size and multiple dose levels, urging the need for larger studies.

### Table 2. Clinical trials on LHRH antagonists in men with BPH without published results.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Purpose</th>
<th>Type</th>
<th>ID number</th>
<th>Status</th>
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<td>Ozarelix</td>
<td>Efficacy and safety of ozarelix 15 mg. given IM 2 weeks and the duration of improvement for up to 6 months</td>
<td>Phase II/III randomised, double-blind, placebo-controlled trial</td>
<td>NCT00427219</td>
<td>Completed</td>
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<td>Ozarelix</td>
<td>Efficacy of ozarelix in men with LUTS as assessed by IPSS at week 14</td>
<td>Phase II randomised, double-blind, placebo-controlled trial</td>
<td>NCT00743184</td>
<td>Terminated</td>
</tr>
<tr>
<td>Degarelix</td>
<td>The potential of four different doses of degarelix to treat BPH with only a short transient lowering of the serum testosterone concentration to or below the castration level defined as 0.5 ng/ml</td>
<td>Phase II open-label study</td>
<td>NCT00527488</td>
<td>Completed with results but no statistical analysis has been provided</td>
</tr>
<tr>
<td>Degarelix</td>
<td>Efficacy of three different doses of degarelix (dose finding) in men with LUTS</td>
<td>Phase II randomised, double-blind, placebo-controlled trial</td>
<td>NCT00947882</td>
<td>Completed</td>
</tr>
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</table>

### Table 3. Phase II studies on NX-1207.

<table>
<thead>
<tr>
<th>Ref.</th>
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<th>Treatment arms</th>
<th>Pts</th>
<th>∆AUASI from baseline</th>
<th>∆Q\text{max} from baseline (ml/s)</th>
<th>Type</th>
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<td>Placebo</td>
<td>62</td>
<td>6.5</td>
<td>1.5</td>
<td>RCT</td>
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<tr>
<td></td>
<td></td>
<td>NX-1207 2.5 mg</td>
<td>113</td>
<td>11.0*</td>
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<tr>
<td></td>
<td></td>
<td>NX-1207 5.0 mg</td>
<td>113</td>
<td>8.7*</td>
<td>NA</td>
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<tr>
<td></td>
<td></td>
<td>NX-1207 10.0 mg</td>
<td>113</td>
<td>8.1</td>
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<tr>
<td>[38]</td>
<td>90</td>
<td>Finasteride</td>
<td>24</td>
<td>4.13</td>
<td>2.4</td>
<td>RCT</td>
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<td></td>
<td></td>
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<td>9.71*</td>
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<tr>
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*Statistical significance vs. control.
NA: Not available.
Sophiris Bio, Inc. recently announced the results of a multicentre, double-blind, placebo-controlled Phase Ib study (TRIUMPH) of PRX302 in males with moderate-to-severe BPH (press release 9 October 2012). The study demonstrated that patients treated with PRX302 had a statistically significant improvement in IPSS from baseline when compared to placebo at 3 months post-treatment (9.1 vs 5.8, p < 0.05). Data at 12 months post-treatment are expected to be released later this year.

A double-blind, multicentre, placebo-controlled Phase II study is being conducted to evaluate the safety, tolerability and efficacy of a single transrectal intraprostatic treatment of PRX302 for LUTS due to BPH compared to placebo (NCT01454349). Patient enrollment has been completed. Patients were randomised to PRX302 or placebo within one of the four dose cohorts (single intraprostatic injection with an ascending dose per cohort of 0.75, 1.5, 3.0 and 6.0 mg/ml) in this transrectal study. The primary endpoint of the study is to evaluate the 3-month safety and tolerability of escalating doses of PRX302. The safety data from the transrectal route of administration will be compared with the safety profile obtained from the previously conducted studies utilising the transperineal route. Patients will be followed for up to 12 months. Results are awaited with great interest.

3.5 BONT/A
Botulinum toxin type A (BoNT-A), an exotoxin produced by *Clostridium botulinum*, acts at acetylcholinergic synapses to block the release of the neurotransmitter acetylcholine resulting in decrease of target muscle tone [41]. The use of BONT/A, for the treatment of LUTS due to BPH, has attracted the increased interest of the urological community. Animal studies have shown that intraprostatic BoNT/A downregulates the expression of α-1A-adrenoceptor, thus affecting the dynamic component of LUTS/BPH [42,43]. In addition, apoptosis of prostate has been described in both humans and animals resulting in prostate volume reduction [42,44,45]. On the other hand, glandular atrophy has been documented only in animal studies but not in human prostate [42,44,46].

In an excellent review of the available studies (until 2010) on the use of intraprostatic injection of BONT/A for LUTS/BPH, Marchal et al. summarised the evidence on the clinical efficacy and safety of this treatment [47]. They identified 6 RCTs and 18 prospective, observational studies where BONT/A was administered either transperineally or transrectal or transurethral in doses ranging from 100 to 600 U. An improvement in IPSS from the baseline levels was found in 20 studies and this reduction was statistically significant in 13 studies. The overall mean IPSS reduction was 10.8 ± 2.66 points [47]. Similarly, Qmax increased in all series reaching statistical significance in 14 studies with a mean post-treatment increase of 6.6 ± 15.6 ml/s. The reduction in prostate volume varied between the different series, and was statistically significant in 18 studies with a mean decrease of 22.4 ± 20.2 ml. Interestingly, PSA reduction was not consistent over the different series, and only in 10 series there was a significant difference with an overall mean drop of 1.15 ± 0.9 ng/ml [47]. The duration of the effects of treatment was also variable, ranging from 3 to 30 months and coinciding in every case with the maximum duration of follow-up. The main reported complications after treatment included dysuria, haematuria, epididymitis, prostatitis and grade 2 – 3 events (unspecified) among 35% of patients in the series. The injection of BONT/A had no impact on sexual function. However, it was acknowledged that there was a wide variation between the reviewed studies in terms of cohort sizes, doses administered, inclusion criteria, follow-up time, definition of retreatment and losses to follow up.

A noncomparative, two-stage, Phase II study evaluated treatment success (defined as improvement in American Urological Association symptom index by at least 30% and/or improvement in Qmax by at least 30% from baseline to 3 months after treatment) and safety of two different doses (100 and 300 U) of BONT/A administered transrectally [48]. Patients were followed for 12 months. Each dose met the predefined 3-month success criteria. The mean AUASI for men in the 100 U dose arm improved by 7.1 points at 3 months and by 6.9 points at 12 months (baseline 18.8), and for men in the 300 U dose arm AUASI improved by 8.9 points at 3 months and 7.2 points by 12 months (baseline 19.5). Qmax in men in the 100 U dose arm increased by 2.5 and 2.2 ml/s at 3 and 12 months, respectively, while the corresponding increase in men treated with 300 U was 2.6 and 2.3 ml/s [48]. The frequencies of AEs and serious AEs were similar for the two dose arms. The overall incidence of serious AEs was 9% including three cases of urosepsis related to the BONT/A injection.

Recently, the results from a Phase II trial on the efficacy of different doses of BONT/A (100, 200 and 300 U) versus placebo in men with LUTS/BPH have been published [49]. This is the largest placebo-controlled study conducted to date since 380 patients were randomised and 351 and 265 completed the 12- and 72-week follow-up, respectively. Notably, there was a change in the route of administration (from transperineal to transrectal) and in injection volume during the study. Significant reduction from baseline in IPSS at week 12 (primary endpoint) was recorded in all groups, including placebo, with no significant between-group differences due to the large placebo effect [49]. Similarly, QoL, Qmax and prostate volume were improved in all the treatment groups, including placebo. Interestingly, in an exploratory post hoc analysis, a significant reduction in IPSS versus placebo at week 12 was observed with BONT/A 200 U in men previously treated with α-blockers. Treatment with BONT/A was well tolerated and the occurrence was comparable across the treatment groups. Most of the AEs were local and related to the treatment procedure while in addition no sexual dysfunction was reported. Table 4 displays the clinical outcome of the studies on BONT/A for the management of LUTS/BPH.

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**Table 4**

<table>
<thead>
<tr>
<th>Dose (U)</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Change</th>
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<tbody>
<tr>
<td>100</td>
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<td>200</td>
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<td>300</td>
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</table>

**Notes:**
- Baseline and Week 12 data are expressed as mean (SD).
- Change is calculated as post-treatment compared to baseline.
In the future, we need to better understand the mechanism of action, and standardise both technique and doses, while more high-quality randomised studies against established Minimally Invasive Treatment (MITs) and/or medical treatments with longer follow-up are required before BONT/A is licensed for the treatment of BPH.

3.6 Other drugs

3.6.1 MCS-2

MCS-2 is an investigational botanical drug (multi-carotenoids composition) for the relief of symptoms of BPH. In a Phase II study, MCS-2 achieved a significant improvement in IPSS with low risk of adverse events. MCS-2 is currently evaluated by an adaptive, Phase IIb/3, double-blind, randomised, placebo-controlled study which is recruiting patients (NCT01002417). Phase IIb will evaluate the 0 mg (placebo), 15 mg and 30 mg MCS-2 in terms of dose response and determine the optimal dose. Phase III will use the determined dose to assess the efficacy and safety of MCS-2 as compared to placebo in a treatment-naïve men with LUTS due to BPH. In addition, a Phase III, double-blind, randomised, placebo-controlled study will investigate the efficacy and safety of MCS-2 (30 mg/d) in treating LUTS/BPH in treatment-naïve population (NCT01002664).

There are also two open-label extension Phase III studies (NCT01002274 and NCT01002222) of studies MCS-2-TWN-a and MCS-2-US-a to further assess the long-term safety and efficacy of MCS-2. No placebo arm is planned in those studies which are currently recruiting patients. Subjects can take lycopene-containing vegetables and fruits during this open-label extension study, but they are advised to refrain from extra source of lycopene supplementation.

3.6.2 Elocalcitol

Elocalcitol is a synthetic derivative of vitamin D3 that regulates cell proliferation and apoptosis via its binding to the vitamin D receptor. Available data suggest that eocalcitol reduce the static component of BPH by inhibiting the activity of intraprostatic growth factors downstream of the androgen receptor, the dynamic component by targeting the RhoA/ROCK pathway in prostate and bladder cells, and the inflammatory component by targeting the NF-kappa B pathway [50].

A Phase IIb study evaluated the efficacy of three different therapeutic regimens of elocalcitol in terms of IPSS, Qmax and reduction of prostate volume after 6 months treatment in men with BPH. Elocalcitol 150 µg/d was identified as the optimal dose that achieved a statistically significant reduction in prostate volume and improvement in Qmax and IPSS compared to placebo [51]. However, results from a Phase IIb urodynamic double-blind, placebo-controlled trial in patients with overactive bladder showed that elocalcitol failed to meet the primary endpoint (significant change in bladder volume at the first involuntary detrusor contraction) following 4 weeks of treatment (Bioxell, press release, 8 April 2009). Based largely on these data, BioXell decided to terminate all further clinical developments of elocalcitol. However, given the novel mechanism of action and the efficacy profile, elocalcitol is still under investigation as a potential therapy for LUTS. Recently, a preclinical study investigated the effects on bladder function of combining elocalcitol and tolterodine in rats with outflow obstruction [52]. It was found that the combination had additive beneficial effects on obstruction-related functional changes in this experimental model. If these findings will be confirmed in humans, the use of elocalcitol with antimuscarinics could improve efficacy in obstruction-related LUTS.

3.6.3 LY500307

LY500307 is a potent, selective estrogen receptor β agonist. In vitro, LY500307 induces apoptosis in both prostate epithelial and stromal cell lines. In a mouse model, oral administration of LY500307 for 14 days reduced prostate weight without any significant change in circulating testosterone concentrations or seminal vesicle/testes weights [53]. A Phase II 24-week study was conducted to evaluate LY500307 in men with LUTS due to BPH. Doses up to 25 mg (1 mg, 3 g, 10 mg and 25 mg) were well tolerated. The study was terminated due to insufficient efficacy (NCT01097707).

3.6.4 Etonogestrel

Etonogestrel is a synthetic biologically active metabolite of the synthetic progestin desogestrel which binds with high affinity to progesterone receptors in the target organs. In orally administered doses of 150 and 300 µg, it causes low or slightly
below normal testosterone levels (but well above castrate levels) that may improve LUTS associated with BPO without hypogonadal side effects [54]. A Phase II, randomised, double-blind, placebo-controlled trial was conducted to investigate the efficacy and safety of etonogestrel tablets in men LUTS suggestive of BPH. The study has been terminated for business reasons (NCT00651807).

5. Expert opinion

The desired goals of treatment of LUTS/BPH are sustained, clinically significant improvement in symptoms and QoL and/or slowing or preventing the progression of the condition. The present review showed that there are several new therapies under investigation in trials that may be emerging in the management of LUTS due to BPH. The reasons for this continuing interest in research include the high prevalence of the condition and the unmet expectations of patients and physicians regarding the efficacy of available therapies.

Research has focussed on the understanding of the underlying pathophysiological mechanisms and natural history of LUTS/BPH. Many potential targets for future drugs have been evaluated. However, increasing evidence suggests that pathogenesis of this condition is multifactorial, indicating that the combination of available and emerging new drug classes should also be investigated.

It is obvious that there is a wide variation in the degree of mature of each therapy.

Some drugs have novel mechanisms of action that have proved their efficacy in preclinical studies but confirmation and further assessment in humans are required. Other drugs have been assessed in Phase III studies but they still have a long track ahead of them before they can be adopted in clinical practice. Time and high-quality studies will decide which of these potential drugs will fade away without fulfilling the initial promises. On the other hand, PDE5-Is are ready to claim their position in the armamentarium of BPH treatment. Tadalafil has been licensed in USA and approval is expected to be granted in Europe soon.

In the future, research will aim not only at the discovery of new therapies, but also at the evaluation of durability of available medications, and at the identification of factors (clinical or molecular) that will allow tailoring of treatment in order to achieve maximal efficacy. Interestingly, the route of application and thus the concept of working mechanism differ significantly between several classes of drugs: direct intraprostatic application or oral administration. Whereas the latter also addresses an extraprostatic cause of the conditions, the intraprostatic delivery of treatment clearly has a focus at the prostate as the sole cause of male LUTS. This is, however, not directly in line with the current concepts and developments in this field. In general, urologists have taken distance from a pure surgical approach to treat patients with the so-called ‘male LUTS’ since we have learned by now that this may not only result in unsatisfactory outcomes but also into possible and undesirable side effects. Moreover, frequently extraprostatic causes may play a significant role. Consequently, we should aim to tailor our treatment to the specific underlying pathophysiology. If, however, we are not in the position to determine the exact cause of the origin of the complaints in each individual patient, we should aim to offer the best first-line treatment which results in the alleviation of male LUTS with low adverse side effects. Obviously, the classical α-blockers and/or 5ARIs meet those requirements, whereas the PDE5 inhibitors are the new kid on the block that add another dimension to that.
Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.


★★ The European Guidelines introduce the term male LUTS and provide recommendations on the treatment.


★★ The American Guidelines on BPH management.


★★ This landmark study contributed substantially to our understanding of the role of combination therapy for LUTS/BPH.


★★ A high level of evidence study that provides support for the long-term use of dutasteride and tamsulosin combination therapy in men with LUTS at increased risk of progression.


★★ A recommended-to-read meta-analysis of all the available randomized controlled trials (RCTs) comparing PDE5-Is with placebo and of the RCTs comparing the combination (PDE5-Is plus α1-adrenergic blockers) versus α1-adrenergic blockers alone.


★★ The first ever report that a PDE5-I achieves a significant improvement in Qmax compared to placebo.
Investigational therapies targeted to the treatment of benign prostatic hyperplasia


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* An excellent review on NX-1207. This paper presents in detail all the available studies.


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Affiliation
Stavros Gravas1 & Jean JMCH de la Rosette2

1Author for correspondence
1University of Thessalia,
Department of Urology,
Larissa, Greece

2University of Amsterdam,
AMC University Hospital,
Academic Medical Center,
Department of Urology,
Meibergdreef 9, 1105 AZ Amsterdam Z-O,
The Netherlands
Tel: +31 20 5666030;
Fax: +31 20 5669585;
E-mail: j.j.delarosette@amc.uva.nl