Bladder Outlet Obstruction and Overactive Bladder in Males

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Emanuele Rubilotta

6.1 Definition

Bladder outlet obstruction (BOO) is a generic term indicating a pathological condition of obstruction during voiding. BOO is a urodynamic condition characterized by increased detrusor pressure and reduced urine flow rate during micturition (high detrusor pressure/low peak flow) [1, 2]. In men, BOO often results from benign prostate obstruction (BPO) which may be related to the benign prostate enlargement (BPE), with histological feature such as benign prostate hyperplasia (BPH) [3, 4]. In addition to prostate obstruction, in males several conditions can lead to BOO, such bladder neck dysfunctions, urethral stricture, poorly relaxed urethral sphincter, urethral sphincter dyssynergia, neurological diseases.

Overactive bladder syndrome (OAB) is defined as urinary urgency, usually with frequency and nocturia, with or without urgency urinary incontinence [2, 4]. Detrusor overactivity (DO) is the urodynamics observation of OAB, characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked [1]. Although OAB prevalence is similar in both sexes, anatomical and physiological differences in the lower urinary tract system of men and women may explain some different underlying mechanisms which lead to this disorder. In males, the main causes are bladder outlet obstruction, neurological diseases, medications, uncontrolled diabetes [5].

E. Rubilotta (✉)
Department of Urology, A.O.U.I. Verona, Verona, Italy
e-mail: emanuele.rubilotta@aovr.veneto.it

M. Balzarro, V. Li Marzi (eds.), *Non-Neurogenic Bladder Dysfunctions*, Urodynamics, Neurourology and Pelvic Floor Dysfunctions,
https://doi.org/10.1007/978-3-030-57393-5_6

6.2 Epidemiology

The association between BOO and OAB has been recognized in several studies [5]. The main epidemiological reports showed that males OAB prevalence ranges from 10.8% to 27.2% [6–10]. The coexistence of OAB and BOO is described up to 50% in males with LUTS, while DO is urodinamically confirmed in the half of these men [11–13]. The overall rate of persistent OAB after medical or surgical treatments for BOO is described up to 50% [14–16].

6.3 Pathophysiology

The proposed pathophysiological mechanisms underlying the development of OAB in males with BOO include the myogenic, neurogenic, and urothelial factors [17]. All these pathological causes may provoke denervation from ischemia, changes in the bladder wall, and modifications in neural control of bladder contraction induced by BOO [17–22]. A decrease in blood flow has been recognized only in the dysfunctional bladders of males with BOO, but not in the balanced detrusor muscles [19, 22]. Thus, the reduction in blood flow to the bladder seems an essential cause of the pathological detrusor contractility. The main explication of the diminution of blood flow is linked to the effect of the raised intravesical pressure during micturition, or the increased tissue pressure of hypertrophied bladder wall during filling. Denervation induced by ischemia has a lot of consequences. An effect of the parasympathetic denervation is the supersensitivity to acetylcholine that leads to stronger and more intense detrusor contractions [21–25]. The sympathetic stimulation is also affected by BOO [26–28]. The sympathetic system stimulation is increased by BOO, and a shifting in the predominant subtype of a-adrenoreceptors has been recognized (from a1a to a1d) [29, 30]. Furthermore, the sympathetic system may be relevant in the progression to DO and OAB through the Rho-kinase pathway. BOO upregulates the RhoA/Rho-kinase pathway which produces an increase in phosphorylation of the myosin light chain, leading to increase in contractility of the detrusor smooth muscle cells, and consequently to OAB [31]. Bladder outlet obstruction can also provoke changes in cell-to-cell contacts between detrusor smooth muscle cells. Protrusion of cell junctions and ultraclose abutments have been demonstrated in cells of patients with BOO. Abnormal cell-to-cell signaling can induce segmental contractions, evoke afferent nerve activity, increase afferent noise, and trigger micturition reflex [29, 30]. The reorganization of the spinal micturition reflex due to BOO has been proposed as a mechanism of developing DO and OAB [31, 32]. The hypertrophy of both bladder afferent and efferent neurons in BOO conditions is associated with an increase of the expression of NGF in the bladder and in the sacral autonomic centers, leading to facilitation of the spinal micturition reflex [33]. This reflex is thought to be mediated by bladder sensory unmyelinated C-fibers which transmit sensations of bladder fullness, urgency, pain. NGF has a relevant effect in bladder sensory C-fibers by promoting their sprouting in the central nervous system, by changing receptor expression in sensory fibers, and by decreasing their threshold of response to the

normal stimulation [34]. The hypersensitivity of these C-fibers causes a rise in the local release of neurotransmitters as tachykinins and other peptides. The consequences in the bladder wall are bladder smooth muscle contraction, facilitation of neural transmission and increase vascular permeability [35–37]. Thus, all these properties of bladder sensory nerve suggest that the increased afferent activity in men with BOO can induce detrusor overactivity causing OAB [34].

Recent increasing data has suggested that urothelium can have a part in the pathophysiological mechanism leading to OAB [38]. There are several evidences that the urothelium is not just a passive barrier, but is also a responsive structure that is capable of detecting thermal, mechanical and chemical stimuli [39, 40]. The urothelium synthesizes and releases acetylcholine (Ach) which differs widely from that of neurons with respect to the molecular components of ACh synthesis and release machinery [41]. Urothelial cells express ion channels similar to stretch activated (mechanosensitive) channels in nervous tissue and these channels may play a role in mechanotransduction in the lower urinary tract. The epithelial sodium channel (ENaC) has been implicated in several processes including transduction of mechanical and nociceptive stimuli [42]. The transient receptor potential vanilloid 1 (TRPV1), a Ca^{2+}-permeable, non-selective cation channel, which has a prominent role in nociception, is present in urothelial cells and underlies their sensitivity to vanilloid compounds [43, 44]. Transmitters released from the urothelium may alter the excitability of afferent nerves and affect detrusor muscle contractility [40]. Absence of the urothelium may cause an increase in the spontaneous activity of detrusor. Thus, a chronic urothelial injury leads to both an increase urinary frequency and a decrease voiding volume, and can play an important pathophysiological role in the development of OAB [45].

6.4 Diagnosis

6.4.1 General Considerations

The concomitance of BOO and OAB should be supposed in males reporting urinary symptoms of both storage and voiding phase. In these males, the diagnostic approach should lead to evaluate whether these urinary symptoms are related to BOO or to other conditions, such detrusor underactivity (DUA) or neurological diseases. Furthermore, it is essential to assess whether storage symptoms correspond to those of the OAB syndrome and whether they are secondary to a BOO condition or to an idiopathic OAB syndrome. Males affected by BOO usually report voiding symptoms and some storage symptoms, as nocturia, followed by urgency and urgency incontinence, while men with OAB most commonly refer urgency and frequency [22]. Thus, often the storage symptoms are the same, but the order of severity reported by patients may change. For these reasons, it is essential to use a proper and accurate diagnostic methodology, and several useful diagnostic tools, in the investigation of these males to clearly determine the association between BOO and OAB [46].

The medical history is the basic step to identify the potential causes of lower urinary tract symptoms (LUTS) in men. The evaluation of patient's comorbidities, current medications, lifestyle habits may aim to better characterize the clinical condition [46, 47].

Physical examination should focus suprapubic area, external genitalia, perineum and lower limbs, urethral discharge, meatal stenosis, phimosis, penile cancer. Digital rectal evaluation helps to assess prostate volume, to exclude prostate cancer or prostatitis [46, 47].

The use of validated symptom score questionnaires, such International Prostate Symptom Score (IPSS) [48], The International Consultation on Incontinence Questionnaire (ICIQ-MLUTS) [49], Overactive Bladder Questionnaire (OAB-q) [50], International Consultation on Incontinence Questionnaire Overactive Bladder (ICIQ-OAB) [51] is recommended [46, 52]. Symptoms scores are helpful in quantifying LUTS and identifying which type of symptoms are predominant, but they are not disease, or age-specific [46].

Bladder diary is an essential investigation tool for men with suspected coexisting BOO and OAB [2]. Parameters resulting from bladder diary comprise daytime and nighttime voiding frequency, urgency episodes, urgency urinary incontinence episodes, volume per void, total voided volume, the rate of urine production during night (nocturnal polyuria index), fluid intake, use of pads, activities during recording. A duration of 3-days-long bladder diary is recommended [46, 53]. An accurate bladder diary may explain a lot of the urinary symptoms and aid in the diagnosis of symptoms related to BOO and/or OAB. Frequency and urgency episodes can be properly assessed leading to a correct diagnosis of OAB. Nocturia can be differentiate from nocturnal polyuria avoiding incorrect diagnosis and inappropriate treatments [54, 55].

Urinalysis, prostate specific antigen (PSA) and measurement of renal function should be taken [56, 57].

The evaluation of post-void residual (PVR) of urine is recommended in the baseline assessment [46], unless the diagnostic accuracy of this measurement is low. Indeed, the PVR threshold of 50 mL corresponds to the positive predictive value (PPV) of 63% and to the negative predictive value (NPV) of 52% for the prediction of BOO [58]. A high baseline PVR is associated with an increase risk of symptoms progression [59, 60]. High PVR volumes can be a consequence of voiding obstruction and/or impaired detrusor contractility, so they may indicate some pathological bladder emptying conditions such BOO or DUA. Anyway, this parameter cannot be used to achieve a differential diagnosis between these conditions [61–63]. Thereby, PVR measurement can be an aid in the patient's evaluation, but should always be consider only as one of the diagnostic steps in the overall assessment.

Uroflowmetry (UF) is a non-invasive urodynamic investigation recommended in the initial evaluation of males with urinary symptoms suggestive of bladder outlet obstruction [46]. The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably and is substantially influenced by threshold values, such voided volumes lower than 150 mL or higher than 500 mL [64]. Indeed, the optimal contractile function of detrusor muscle fibers is reached with a bladder filling ranging between

150 and 500 mL, which avoid an under- or overstretching of the muscle fibers. Uroflowmetry specificity can be improved by repeated flow rate testing [1, 2]. A peak flow (Q_{max}) threshold of 10 mL/s has a specificity of 70%, a PPV of 70% and a sensitivity of 47% for BOO. The specificity using a threshold Q_{max} of 15 mL/s is 38%, the PPV 67% and the sensitivity 82%. If Q_{max} is >15 mL/s, physiological compensatory processes mean that BOO cannot be excluded [65]. Anyway, this non-invasive urodynamic evaluation is unable to discriminate the underlying mechanisms of pathological voiding, such bladder outlet obstruction or detrusor underactivity.

Invasive urodynamics is the most accurate investigation for males with urinary symptoms suggestive of OAB and BOO [1]. Invasive urodynamics comprise a cystometry which may uncover signs of the OAB, and pressure-flow studies which allow to reveal bladder outlet obstruction and to distinguish BOO from DUA. During the filling phase of the examination it is possible to detect involuntary detrusor contractions, corresponding to detrusor overactivity (DO), occurring with or without contemporary sensory urgency [5]. In symptomatic patients, involuntary detrusor contractions are detected only in almost 50% of the cases. The urodynamic diagnosis of BOO is characterized by the increased detrusor pressure associated to the decreased urinary flow during voiding. BOO has to be differentiated from DUA, which is described by the decreased detrusor pressure during voiding, coupled to the decreased urinary flow [5]. Accepted nomograms exist to aid in the differential diagnosis. Abrams-Griffith nomograms was developed on the model of urethral resistance relation (URR) [66] and was followed by the Schäfer nomograms which was based on the passive urethral resistance relation (PURR) [67, 68], a simplified model of the Griffith's URR. According to URR, as bladder pressure rises, the flow rate will be zero until the intrinsic bladder pressure equals the intrinsic urethral pressure. At this point, flow will start and the flow rate will rise rapidly with further increases in the intrinsic bladder pressure. If pairs of simultaneously measured values of detrusor pressure and flow rate are plotted against one another throughout the course of a micturition event, a curve is obtained that shows the resistance to flow independent of detrusor function, representing the urethral resistance relation. The Abrams-Griffith nomograms boundary were: unobstructed, equivocal, and obstructed [69, 70]. The PURR curve describes the relationship between pressure and flow during the period of lowest urethral resistance (i.e., during complete relaxation), and therefore defines the lowest urethral resistance during a single voiding event [71]. The PURR was the first attempt to quantify relevant features of the voiding cycle describing the interplay of detrusor capability and bladder outlet resistance. In Schäfer nomogram this linear PURR (LinPURR) curve was divided into seven zones labeled 0 to VI corresponding to increasing grades of obstruction: grades 0 and 1, no obstruction; grade 2, equivocal or mild obstruction; grades 3–6, increasing severity of obstruction. The limit between grades 2 and 3 corresponds to the boundary between equivocal and obstructed in the Abrams-Griffiths nomogram. The linear PURR also allows for the assessment of detrusor contractility, independent of obstruction, divided in: strong, normal, weak, and very weak [72]. Based on the Griffith models, an ICS nomogram was developed, recommended for the diagnosis of BOO [73, 74]. ICS nomograms uses the bladder outlet obstruction index

(BOOI) represented by the equation: BOOI = P_{det} @ Q_{max} − 2 Q_{max}. According to this nomogram, males are divided into obstructed, equivocal, and unobstructed according to their BOOI: BOOI > 40 = obstructed; BOOI 20–40 = equivocal; and BOOI < 20 = unobstructed. To assess detrusor contractility, in addition to the contractility zones of the Schäfer nomogram, an index for bladder contractility can be calculated from the contractility groups derived from the Schäfer nomogram [75]. The bladder contractility index (BCI) is represented by the following formula: BCI = P_{det} Q_{max} + 5 Q_{max}. Using this formula, contractility can be divided into strong >150, normal 100–150, and weak <100. Thus, the analysis of a complete urodynamic examination, with the aid of these nomograms, is the most accurate investigation to diagnose detrusor overactivity and bladder outlet obstruction. To date, urodynamics is not routinely recommended in the diagnosis of men with LUTS, due to its invasiveness and costs, but it is indicated when the non-invasive urodynamic investigations fail for a definite diagnosis [46].

6.5 Management

6.5.1 General Considerations

For most men with LUTS, there is an overlap of both obstructive voiding symptoms and storage symptoms. Patients management should be tailored according to the type, the severity and the bother of the LUTS. The management of these men may include conservative treatments, pharmacological therapy, and surgical procedures. Each of these approaches has advantages and risks. The conservative management may be the first step. This therapeutic approach has no side effects, but it is effective in a minor part of the patients, mainly in males with LUTS less bothersome. Pharmacological treatments are effective and have mild/moderate side effects, representing the most common first-line therapeutic approach. Surgical procedures should be offered to males nonresponders to conservative and/or pharmacological treatments, with bothersome symptoms and/or more severe clinical conditions, after accurate counseling.

6.6 Conservative Treatments

6.6.1 General Considerations

Behavioral modifications should be proposed to males with BOO and OAB as a first-line therapy or to enhance concomitant treatments. Several data support this clinical approach to these patients [76].

Behavioral management should be offered mainly to men with low/moderate LUTS, minimally bothered by their symptoms. These conservative treatments include lifestyle advices such as reduction of fluid intake, avoidance/moderation of intake of caffeine or alcohol, bladder retraining, revising the medical therapy and optimizing the time of administration or substituting drugs for others with fewer

urinary effects, breathing and perineal exercises, mental tricks to take the mind off the bladder and toilet, treatment of constipation, providing necessary assistance in case of dexterity impairment, mobility or mental state, improve reassurance and education on the patient's clinical condition [77, 78].

6.7 Pharmacological Treatments

6.7.1 General Considerations

In males, due to the high prevalence of benign prostatic obstruction and the related obstructive urinary symptoms, the diagnosis of OAB may be often neglected. Thereby, a therapy for voiding obstructive symptoms is usually offered, while proposed therapy for OAB symptoms is not often advised [79].

6.7.2 α1-Blockers and 5α-Reductase

The main pharmacological treatment for males with BOO is represented by α1-blockers, with or without association of 5α-reductase (type 1 or type 2) [46]. The pharmacological mechanism of α1-blockers is to inhibit the effect of endogenously noradrenaline on smooth muscle cells in the prostate, and thus reduce prostate tone and BOO [80, 81]. The 5α-reductases are generally used in case of prostate volume higher than 40 mL. The androgen effect of these agents on the prostate is mediated by dihydrotestosterone, which is converted from testosterone by the enzyme 5α-reductase, a nuclear-bound steroid enzyme [82]. Both these treatments, α1-blockers and 5α-reductase, in mono- or combination therapy, have good results mostly on voiding symptoms, with improvement of IPSS score up to 50% and Q_{max} up to 40%, and can reduce also storage symptoms [83]. Long-term data (4 years) showed that combination treatment is superior to monotherapy for improvement of symptoms and Q_{max}, and superior to α1-blocker alone in reducing the risk of AUR or need for surgery [59, 84, 85]. Several data demonstrated that combination therapy significantly reduces the risk of disease progression [59, 84, 85]. The adverse events observed during combination treatment were those typical of α1-blockers and 5-ARIs, but the rate of side effects was significantly higher for combination therapy [59, 84, 85]. Combination therapy should be offer in long-term treatment (more than 1 years) and to men with moderate-to-severe LUTS, at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, higher PVR, lower Q_{max}) [86].

6.7.3 Antimuscarinic Agents and Beta-3 Adrenoreceptors

The main drugs used for OAB symptoms are antimuscarinic [79, 87]. Recently, Beta-3 agonist have been introduced in the clinical practice [88–91]. The antimuscarinic mechanism is as following: the detrusor muscle is innervated by

parasympathetic nerves whose main neurotransmitter is acetylcholine, which stimulates muscarinic receptors (M-cholinoreceptors) on the smooth muscle cells. Muscarinic receptors are also present on other cell types, such as bladder urothelial cells, epithelial cells of the salivary glands, or the peripheral or central nervous system. Five muscarinic receptor subtypes (M1–M5) have been described, of which M2 and M3 are predominant in the detrusor. The M2 subtype is more numerous, but the M3 subtype is functionally more important in bladder contractions in healthy humans [92, 93]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system [94, 95]. The following muscarinic receptor antagonists are licensed for treating OAB/storage symptoms: darifenacin hydrobromide (darifenacin); fesoterodine fumarate (fesoterodine); oxybutynin hydrochloride (oxybutynin); propiverine hydrochloride (propiverine); solifenacin succinate (solifenacin); tolterodine tartrate (tolterodine); and trospium chloride. Transdermal preparations of oxybutynin have been formulated and evaluated in clinical trials [96, 97]. Literature data showed that in men storage symptoms significantly decreased after therapy with antimuscarinic agents, with a low complications rate [15, 98–100]. Antimuscarinic drug trials generally show approximately 3–10% withdrawals, which is similar to placebo. Drug-related adverse events include dry mouth (up to 16%), constipation (up to 4%), micturition difficulties/acute urinary retention (up to 3%), nasopharyngitis (up to 3%), and dizziness (up to 5%) [15, 96–100]. Despite the high prevalence of storage symptoms in men with LUTS, and the efficacy of antimuscarinic agents with low side effects/complications, men are usually treated with BPH drugs rather than those specific for OAB [79]. An explication is that some patients may improve storage symptoms by the administration of the first-line therapy alone, represented usually by α1-blockers alone. Another reason may be the perception that these drugs may cause a high increase of PVR and/or acute urinary retention (AUR). However, published placebo-controlled, open-label and active-comparator studies showed that anticholinergics are not associated with a substantial increase in risk of AUR. A 12 week safety study on men with mild-to-moderate BOO showed that tolterodine increased the PVR (49 mL vs 16 mL) but not AUR (3% in both arms) [15]. The urodynamic effects included larger bladder volumes at first detrusor contraction, higher maximum cystometric capacity, and decreased bladder contractility index, while Q_{max} was unchanged. Thus, this trial indicated that short-term treatment with antimuscarinics in men with BOO is safe [15]. Other several well designed, placebo-controlled studies, with longer follow-up, have evaluated the combination of alpha-blockade and antimuscarinic therapy in men [101–103]. All these studies showed a significant improvement in LUTS, and in OAB symptoms, with a very low rate of AUR ranging from 0.9% to 1.8%. Data obtained by RCTs and systematic reviews showed also that males underwent combination therapy had no relevant reduction in maximum flow, nor significant increase in AUR rate, but higher incidence of other side effects [101–111]. A recent RCT investigated the safety, in terms of maximum detrusor pressure and Q_{max}, of solifenacin (6 or 9 mg) associated with tamsulosin in men with LUTS and BOO, compared with placebo [112]. The

combination therapy was not inferior to placebo for the primary urodynamic variables, and Q_{max} was increased vs placebo [112]. In a meta-analysis of sixteen studies with 3548 patients with BPH/OAB, initial combination treatment of an α1-blocker with anticholinergic medication improved storage symptoms and QoL compared to α1-blocker monotherapy, without causing significant deterioration of voiding function [106]. There was no difference in total IPSS and Q_{max} between the two groups. Effectiveness of combination therapy was found primarily in men with moderate-to-severe storage LUTS [107]. Long-term use of combination therapy has been reported in patients receiving treatment for up to a year, showing symptomatic response is maintained, with a low incidence of AUR [108]. NEPTUNE Study showed in men with moderate-to-severe storage symptoms, voiding symptoms, and PVR < 150 mL, the reduction in symptoms using combination therapy, associated with patient-relevant improvements in health-related quality of life (HRQoL) compared with placebo and α1-blocker monotherapy [109]. The European Urological Association guidelines recommend the use of combination therapy—α-blockers and antimuscarinic agents—in males with moderate-severe storage symptoms due to the relevant improvement of storage symptoms and the low rate of complications. Anyway, it is strongly recommended to not offer this combination therapy in males with PVR > 150 mL [46].

Beta-3 adrenoceptors (mirabegron) are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation [88–91]. A meta-analysis of the RCT studies demonstrated that mirabegron was significantly effective in treating the symptoms of OAB, including frequency, urgency and urgency urinary incontinence [88–91], and in improving patient perception of treatment benefit [113]. Anyway, the men enrolled in these studies were only up to 30%. Complications on voiding phase have been reported as very low (about 1%) [88–91, 113]. Beta-3 adrenoreceptors tolerability was reported higher respect to antimuscarinic, with a discontinuation rate lower than that recorded for the antimuscarinic agents. Anyway, long-term studies on the efficacy and safety of mirabegron in men of any age with LUTS are not yet available.

Larger data and studies on the use of mirabegron in combination with other pharmacotherapeutic agents for male LUTS are pending. To date, few data on combination therapy are available from two studies [114, 115]. In an RCT evaluating add-on therapy with mirabegron for OAB symptoms persisting after treatment with tamsulosin 0.2 mg daily in men with BPO, combination therapy was associated with greater improvements in OAB symptom score, in the urinary urgency and daytime frequency and storage subscore of the IPSS, and in the QoL index compared to monotherapy with tamsulosin [114]. A prospective analysis of 50 elderly men showed that mirabegron add-on therapy was effective for patients whose persistent LUTS and OAB symptoms were not controlled with α1-blocker monotherapy, without causing negative effects on voiding function [115]. Further data on long-term efficacy and safety of beta 3-adrenoreceptors and on combination therapy are needed.

6.7.4 Phosphodiesterase 5 Inhibitors

Phosphodiesterase 5 inhibitors (PDE5Is) have been recently assessed in the treatment of men with LUTS, but only tadalafil 5 mg once daily has been licensed for this therapy [46]. PDE5Is increase intracellular cyclic guanosine monophosphate, thus reducing smooth muscle tone of the detrusor, prostate and urethra. Nitric oxide and PDE5Is might also alter reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder [116]. Moreover, chronic treatment with PDE5Is seems to increase blood perfusion and oxygenation in the lower urinary tract [117]. Finally, PDE5Is could reduce chronic inflammation in the prostate and bladder [118]. Anyway, the exact mechanism of PDE5Is on LUTS remains unclear. Several RCTs have demonstrated that PDE5Is reduce IPSS, storage and voiding LUTS, and improve QoL. However, maximum flow rate did not significantly differ from placebo in most trials [119–122]. A meta-analysis on phosphodiesterase 5 inhibitors showed that PDE5Is improved IPSS and IIEF score, and slightly increase maximum peak flow [123]. The meta-analysis was based on five RCTs (two studies with tadalafil 20 mg, two with sildenafil 25 mg, and one with vardenafil 20 mg), showing that combination therapy significantly improved IPSS score (−1.8), IIEF score (+3.6), and Q_{max} (+1.5 mL/s) compared with α-blockers alone. An open-label urodynamic study of 71 patients showed improvements in both voiding and storage symptoms, confirmed by improvements in BOO index (61.3–47.1; $p < 0.001$), and resolution of DO in 15 (38%) of 38 patients. Maximum flow rate improved from 7.1 to 9.1 mL/s ($p < 0.001$) and mean IPSS from 18.2 to 13.4 [124]. Anyway, long-term experience with tadalafil in men with LUTS is limited to one trial with a short follow-up of 1 year [121]. A combination of PDE5Is and α-blockers has also been evaluated. The effects of tadalafil 5 mg combined with finasteride 5 mg were assessed in a 26-week placebo-controlled RCT [125]. The combination of tadalafil and finasteride provided an early improvement in urinary symptoms ($p < 0.022$ after 4, 12 and 26 weeks), with a significant improvement of storage and voiding symptoms and QoL. Combination therapy was well tolerated and improved erectile function. The main side effects of PDE5I reported were flushing, gastroesophageal reflux, headache, dyspepsia, back pain, and nasal congestion, with a discontinuation rate of 2% [126]. Phosphodiesterase 5 inhibitors are contraindicated in patients using nitrates, the potassium channel opener nicorandil, or the α1-blockers doxazosin and terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (<3 months) or stroke (<6 months), myocardial insufficiency (New York Heart Association stage >2), hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if anterior ischemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5Is [123]. The use of PDE5Is can be indicated in men without specific cardiovascular risk factors, with moderate-to-severe LUTS, with or without erectile dysfunction to improve LUTS and quality of life, but not, or only slightly, the maximum peak flow.

6.7.5 Plant Extracts: Phytotherapy

Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits [46]. There are single plant preparations (mono-preparations) and preparations combining two or more plants in one pill (combination preparations). The most widely used plants are *Cucurbita pepo* (pumpkin seeds), *Hypoxis rooperi* (South African star grass), *Pygeum africanum* (bark of the African plum tree), *Secale cereale* (rye pollen), *Serenoa repens* (syn. Sabal serrulata; saw palmetto) and *Urtica dioica* (roots of the stinging nettle) [127]. Possible relevant compounds include phytosterols, ß-sitosterol, fatty acids, and lectins [127]. In vitro, plant extracts can have anti-inflammatory, anti-androgenic and estrogenic effects; decrease sexual hormone binding globulin; inhibit aromatase, lipoxygenase, growth factor-stimulated proliferation of prostatic cells, α-adrenoceptors, 5 α-reductase, muscarinic cholinoceptors, dihydropyridine receptors and vanilloid receptors; and neutralize free radicals [127–129]. The effects in vivo of these compounds are uncertain, and the precise mechanisms of plant extracts remain unclear. Most of the data on these plant extracts regard *Serenoa repens*, *Pygeum africanum*, and *Secale cereale* showing some positive effects on nocturia and maximum flow rate, with only some poor relevant gastrointestinal side effects [130–134]. Thereby, these treatments may be offer only to men with mild urinary symptoms.

6.8 Surgical Treatments

6.8.1 General Considerations

Surgical treatments should be accurately counseled in men with coexisting BOO and OAB. Surgical approach is usually indicated for male nonresponders to pharmacological therapy, not fit for conservative management due to the side effects, or with severe urinary symptoms and/or obstruction condition who request a treatment as resolutive as possible. Patients should be counseled on the possibility that storage symptoms could be persistent or return after surgical procedures.

It is known that surgical treatments (transurethral prostate resection, prostatectomy, laser vaporization, laser enucleation) are well effective on voiding obstructive symptoms, but less successful on the OAB symptoms [46]. Transurethral prostate resection (TUR-P) is still the gold standard, despite the introduction of new endoscopic/surgical techniques [46]. After surgical treatments, in a short-term follow-up (1 year) urgency persist in half of the males, while urgency urinary incontinence continues in one-third of the patients [135]. In long-term follow-up, after transurethral prostate resection (TURP), OAB symptoms returned in up to two-thirds of the males [22]. Detrusor overactivity reduced after surgical procedures to 30% in males assessed at 5-years follow-up. Urodynamic investigations uncovered that long-term failure of surgical treatments was associated with

detrusor overactivity in 64% of the men [136]. Thereby, in males with concurrent BOO and OAB, an accurate counseling should be performed explaining the risk of failure of surgery for the symptoms of overactive bladder, despite the success for the voiding obstructive symptoms.

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