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Therapeutic Options

FOCUS ON BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is a histologic diagnosis referring to smooth muscle and epithelial cell proliferation within the transition zone of the prostate.[1] BPH can technically only be diagnosed after the prostate is biopsied and the specimen examined under a microscope.[2] In contrast, benign prostatic enlargement is a clinical diagnosis that can be made on digital rectal examination.[2]

The prevalence of BPH increases significantly with age. Greater than 50 per cent of men will have BPH at 60 years of age, whereas approximately 90 per cent of men will have BPH by age 85.[2] Fortunately, not everyone with BPH will be symptomatic; bothersome symptoms are estimated to affect about 30 per cent of men.[2] For those affected, however, impact on quality of life can be significant.[1] As symptom severity does not correlate well with the degree of hyperplasia, and because other conditions can cause similar symptoms, the clinical syndrome associated with BPH is often referred to as male lower urinary tract symptoms (LUTS).[3]

SYMPTOMATOLOGY & COMPLICATIONS

An enlarged prostate gland has been proposed to contribute to male LUTS via two primary mechanisms: (1) direct bladder outlet obstruction (static component), and (2) increased smooth muscle tone and resistance (dynamic component).[1] Based on these mechanisms, male LUTS are commonly classified as either obstructive/voiding symptoms or storage/irritative symptoms[1,2,4] (see Box 1).

Potential complications of chronic bladder outlet obstruction secondary to BPH include renal insufficiency, urinary retention, recurrent urinary tract infections, and bladder stones.[1,5]

ASSESSMENT & DIAGNOSIS

According to recent Canadian guidelines for the management of BPH, assessment of symptom severity and bother is essential in the initial evaluation of a man presenting with LUTS.[6] A formal assessment of symptoms, including their impact on quality of life, is also recommended as part of the initial diagnostic workup, as well as to monitor symptom evolution and evaluate response to treatment.[3,6] Such an assessment can be done using the International Prostate Symptom Score (IPSS) or American

Box 1 – Classification of male LUTS[2,4]

Obstructive/voiding symptoms
- Hesitancy
- Weak urine flow
- Intermittent urine flow
- Straining
- Incomplete emptying

Storage/irritative symptoms
- Frequency
- Urgency
- Urge urinary incontinence
- Nocturia

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Urological Association Symptom Index (AUA-SI).[6] Both tools use the same seven questions (available online at http://www.usrf.org/questionnaires/AUA_SymptomScore.html) to assess the frequency of storage and voiding symptoms on a six-point scale (from 0 to 5, with higher numbers indicating increased frequency); based on the sum of the scores for each question, BPH severity is classified as follows:

- 0–7 = mild;
- 8–19 = moderate; and
- 20–35 = severe.[3,7]

For purposes of assessing treatment response, a three-point improvement in total score is considered meaningful.[8]

Further to the seven questions regarding symptom frequency, the IPSS also asks a single quality of life question to assess the degree of bother associated with LUTS: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?"[8]

In addition to symptom assessment, a focused physical examination including a digital rectal exam is considered a mandatory part of the diagnostic workup for BPH.[6] Urinalysis is required to rule out non-BPH diagnoses that may cause LUTS, and other tests may also be required (refer to the online version of the Canadian guidelines[6] for details [see References, below, for URL]).

It is notable that a variety of medications can cause or exacerbate LUTS (see Box 2), and this should be kept in mind during patient assessment.

Box 2 – Some medications that can contribute to LUTS[3,9]

Androgens
- Testosterone

Anticholinergics
- Atropine
- Benztropine
- Flavoxate
- Hyoscine
- Oxybutynin
- Scopolamine

Antidepressants
- Amitriptyline
- Doxepin
- Nortriptyline
- Trimipramine

Antihistamines
- Brompheniramine
- Chlorpheniramine
- Cyproheptadine
- Hydroxyzine
- Dimenhydrinate
- Diphenhydramine

Antipsychotics
- Fluphenazine
- Loxapine

Muscle relaxants
- Baclofen
- Cyclobenzaprine

Opiates
- Codeine
- Hydromorphone
- Meperidine
- Methadone
- Morphine
- Oxycodone

Sympathomimetics
- Ephedrine
- Phenylephrine
- Pseudoephedrine
- Terbutaline

MANAGEMENT

The primary goals of BPH treatment are to improve symptoms and quality of life and lower the risk of disease progression.[10] The main treatment strategies include watchful waiting (with or without lifestyle modification), pharmacological therapies, and surgical therapies.[2,6,11] Information regarding these approaches is presented below.

Watchful waiting & lifestyle modification

Current Canadian[6] and U.S.[1,8] guidelines recommend a "watchful waiting" approach (i.e., active surveillance, but no active treatment) for patients with mild LUTS (IPSS/AUA-SI ≤7) secondary to BPH. Watchful waiting is also appropriate for those with moderate or severe BPH-related LUTS (IPSS/AUA-SI ≥8) who are not bothered by their symptoms and have no complications of bladder outlet obstruction.[1,8]

Various lifestyle changes (see Box 3) may also be suggested in combination with watchful waiting, although not all are supported by high quality evidence.[6]

Pharmacotherapy

Pharmacological approaches are generally reserved for men with moderate or severe (IPSS/AUA-SI ≥8), bothersome LUTS.[6,12] The primary place in therapy of the various treatment alternatives, as well as other pertinent information about the medications, is summarized in Table 1. It is notable that the comments in Table 1 do not generally discuss adverse effects of the treatment options; however, such information is provided in the U.S.[1,8] and European[5] guidelines (see References, below, for URLs).

Presently, the main medical treatment options are the alpha-1 adrenoreceptor antagonists (alpha-blockers) and the 5-alpha reductase inhibitors (5ARIs).[2] It is notable that these agents and others offer symptomatic relief only and are not curative; therefore, therapy may be life-long.[2]

Treatment response and adverse effects should be assessed after four to six weeks in patients treated with alpha-blockers or anticholinergics.[10,12] As onset of effect is slower for 5ARIs, first follow-up is recommended after three to six months.[10,12] All patients should continue to be evaluated every six to 12 months.[12]

Surgery

Surgical approaches are warranted when bothersome symptoms have not responded to conservative management and drug therapy, or when complications of BPH are present.[1,10,12]

A detailed discussion of the various surgical approaches to BPH, including minimally invasive procedures, is beyond the scope of this review. Readers interested in further information on surgical therapies

Box 3 – Lifestyle changes for LUTS[6,8,9]

- Modification or restriction of fluid intake (particularly prior to bedtime)
- Avoidance of excessive intake of caffeinated/alcoholic beverages or spicy foods
- Adjustment/avoidance/monitoring of some drugs* (e.g., diuretics)
- Timed or organized voiding (bladder retraining)
- Pelvic floor exercises
- Avoidance or treatment of constipation
- Increased exercise

* See Box 2

TABLE 1 – SOME MEDICATIONS USED TO TREAT MALE LUTS[1,5,6,10,12-14]

Treatment Option/Drug	Usual Daily Dose*	Primary Place in Therapy	Comments
Alpha-blockers • Alfuzosin • Doxazosin • Tamsulosin • Terazosin	 10 mg 2–8 mg 0.4 mg 5–10 mg	First-line treatment for moderate-to-severe BPH-related LUTS	• All agents in class appear to be equally effective in appropriate doses • Typically reduce IPSS by ~35–40%† and increase Q_{max} by ~20–25%; efficacy does not depend on prostate size • Improvements may be noted in hours to days; full effects apparent within a few weeks; duration of efficacy appears to be maintained over at least 4 years • Clinical impact of formulation (e.g., immediate vs. sustained release, etc.) is modest • Do not alter the natural progression of disease • Doxazosin and terazosin require dose titration and blood pressure monitoring
5-α reductase inhibitors • Dutasteride • Finasteride	 0.5 mg 5 mg	Appropriate treatment for moderate-to-severe BPH-related LUTS associated with prostate enlargement	• Both agents in class appear to be equally effective • Typically reduce IPSS by ~15–30%, decrease prostate volume by ~18–28%, and increase Q_{max} by ~1.5–2 mL/s after 2–4 years of treatment; efficacy depends on prostate size‡ • Improvements generally seen after a minimum treatment duration of 6–12 months • May alter the natural progression of disease through a reduction in risk of acute urinary retention and need for surgery • Should not be used for BPH-related LUTS without prostate enlargement • Result in decreased PSA levels,§ which needs to be considered for prostate cancer screening
Anticholinergics‖ • Darifenacin • Oxybutynin • Solifenacin • Tolterodine • Trospium chloride	 7.5–15 mg 5–30 mg¶ 5–10 mg 4 mg 40 mg	Appropriate for moderate-to-severe BPH-related LUTS where bladder storage symptoms predominate and there is no elevated PVR urine**	• Efficacy data from RCTs are limited for men with LUTS; although storage symptoms appear to decrease in the majority of patients, statistical significance vs. placebo was not demonstrated in most trials • Caution is advised in men with bladder outlet obstruction due to the theoretical risk of decreased bladder strength and resultant urinary retention or elevated PVR urine
Alpha-blocker + 5-α reductase inhibitor	See individual agents	Appropriate treatment for moderate-to-severe LUTS associated with prostate enlargement	• Combination therapy significantly improves symptom scores and increases Q_{max} compared with either monotherapy option, although benefits may not be seen until at least 9 months of treatment†† • The combinations tested in clinical trials include: dutasteride plus tamsulosin, or finasteride plus alfuzosin, doxazosin, or terazosin • Successfully treated patients can be given the option to discontinue the alpha-blocker after 6–9 months of therapy; if symptoms recur, the alpha-blocker should be restarted
Alpha-blocker + anticholinergic	See individual agents	May be useful for moderate-to-severe LUTS where symptoms remain after monotherapy with either drug‡‡	• Combination therapy has been shown to reduce frequency, nocturia, and IPSS compared with alpha-blockers or placebo; combination therapy has also been shown to reduce urgency and urge incontinence and increase quality of life§§ • Use combination cautiously in men suspected of having bladder outlet obstruction

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TABLE 1 – SOME MEDICATIONS USED TO TREAT MALE LUTS[1,5,6,10,12-14] *(continued)*

Treatment Option/Drug	Usual Daily Dose*	Primary Place in Therapy	Comments
Phosphodiesterase inhibitors • Sildenafil • Tadalafil • Vardenafil	 NA NA NA	Not currently recommended for BPH-related LUTS outside of clinical trial settings	• All agents in class have reduced IPSS in RCTs; storage and voiding symptoms decreased equally during treatment; improvements in quality of life have also been demonstrated compared with placebo • Insufficient information is available about combinations with other LUTS medications
Complementary and alternative medicines	NA	Not currently recommended for BPH-related LUTS	• Available data do not suggest any clinically meaningful effects of saw palmetto on BPH-related LUTS; however, further trials are in progress • There is a paucity of published, high quality data regarding single extracts of stinging nettle

BPH = benign prostatic hyperplasia; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; NA = not applicable; PSA = prostate specific antigen; PVR = post-void residual; Q_{max} = maximum urinary flow rate; RCT = randomized controlled trial

* Doses listed are for the oral route of administration.
† Demonstrated in controlled studies, after a run-in period.
‡ Finasteride may not be more efficacious than placebo in patients with baseline prostate volume <40 mL. Dutasteride appears to be efficacious in patients with baseline prostate volume between 30 mL and 40 mL, but symptom improvement is quicker and more pronounced with in men with higher baseline prostate volume.
§ PSA levels are reduced by ~50% after 6–12 months of treatment.
‖ Also referred to as muscarinic receptor antagonists.
¶ Dose varies according to formulation used.
** Use with caution in patients with a PVR urine >250–300 mL.
†† Based on data from a study evaluating the combination of tamsulosin and dutasteride.
‡‡ Combination may be most appropriate for patients with persistent bladder storage symptoms while on alpha-blocker monotherapy.
§§ Based on data from a study evaluating the combination of tamsulosin and tolterodine, although benefits likely represent class effects.

should consult the online versions of the guidelines[1,5,6,8] (see References, below, for URLs).

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