CLINICAL PRACTICE

Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 59-year-old man with a history of benign prostatic hyperplasia and lower urinary tract symptoms comes for care. He has been receiving doxazosin at a dose of 4 mg daily (his only medication) for the past 2 years, with minimal improvement. He continues to have nocturia, a weak urinary stream, and urinary frequency (voiding eight times per day). How would you manage this case?

THE CLINICAL PROBLEM

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Benign prostatic hyperplasia, a histologic diagnosis, is a condition that occurs with aging; the prevalence increases from 25% among men 40 to 49 years of age to more than 80% among men 70 to 79 years of age.[1] Although many men with histologic findings of benign prostatic hyperplasia and even anatomically enlarged prostates due to this condition have no symptoms, more than 50% of men in their 60s to as many as 90% of octogenarians present with lower urinary tract symptoms.[2] These symptoms are further classified as obstructive voiding or bladder storage symptoms. Obstructive voiding symptoms include urinary hesitancy, delay in initiating micturition, intermittency, involuntary interruption of voiding, weak urinary stream, straining to void, a sensation of incomplete emptying, and terminal dribbling. Storage symptoms include urinary frequency, nocturia, urgency, incontinence, and bladder pain or dysuria.

Among men with lower urinary tract symptoms in the placebo group of a randomized trial of medical therapy for benign prostatic hyperplasia, clinical progression (defined as worsening lower urinary tract symptoms, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection) occurred in 14% of the men over a follow-up period of 5 years. Rates of progression increase with older age, increased severity of lower urinary tract symptoms, larger prostate size, increased prostate-specific antigen (PSA) levels, and decreased rates of urinary flow.[3,4] In 2007, a total of 1.9 million visits to physicians' offices and more than 202,000 visits to the emergency department led to a primary diagnosis of benign prostatic hyperplasia, and 120,000 prostatectomies were performed for the disorder.[5]

The pathophysiology of benign prostatic hyperplasia remains incompletely understood. The development of the histologic features of benign prostatic hyperplasia is dependent on the bioavailability of testosterone and its metabolite, dihydrotestosterone.[6] A congenital lack of 5α-reductase results in a vestigial prostate gland,[7] and castration in a man leads to glandular atrophy and regression of lower urinary tract

KEY CLINICAL POINTS

BENIGN PROSTATIC HYPERPLASIA AND LOWER URINARY TRACT SYMPTOMS

- Lower urinary tract symptoms — including obstructive symptoms (e.g., urinary hesitancy and weak stream) and bladder storage symptoms (e.g., urinary frequency and nocturia) — occur in more than half of men in their 60s and increase with age.
- Watchful waiting is appropriate for men with mild symptoms.
- For men with moderate-to-severe symptoms, bothersome symptoms, or both, the benefits and risks of medication should be discussed.
- Pharmacologic options are an α-adrenergic-receptor blocker, a 5α-reductase inhibitor (if there is evidence of prostatic enlargement or a PSA level >1.5 ng per milliliter), a phosphodiesterase-5 inhibitor, or antimuscarinic therapy; the first three have proven efficacy as monotherapy.
- Combination therapy with an alpha-blocker and a 5α-reductase inhibitor is more effective than monotherapy with either agent but has more side effects.
- The addition of antimuscarinic therapy may be useful in men with clinically significant storage symptoms that are not controlled with the use of an alpha-blocker alone.

symptoms.[8] In addition to levels of endogenous testosterone and dihydrotestosterone,[9] other physiological markers associated with an increased risk of benign prostatic hyperplasia include high levels of dehydroepiandrosterone and estradiol,[9] insulin-like growth factors,[10] and inflammatory markers (e.g., C-reactive protein).[11-13] Additional risk factors include black (vs. white) race,[14] obesity,[15] diabetes,[16] high levels of alcohol consumption,[17] and physical inactivity[18]; mechanisms underlying these associations remain poorly understood.

Normal micturition requires that the bladder detrusor muscle relax between voidings and contract to overcome resistance of the bladder outlet (i.e., the prostate and bladder neck) during voiding.[19,20] Benign prostatic hyperplasia, when accompanied by anatomical enlargement of the prostate gland, can lead to static bladder-outlet obstruction; this is the most commonly cited basis for lower urinary tract symptoms[21] (Fig. 1). Bladder obstruction may also arise from a dynamic process mediated by the α-adrenergic axis.[22] Bladder detrusor hyperactivity, mediated by M2- and M3-type muscarinic receptors, contributes to lower urinary tract symptoms in approximately 15% of men.[23,24] Studies also suggest a role for nonmuscarinic targets (e.g., phosphodiesterase-5 in bladder and prostatic smooth muscle) in the pathogenesis of lower urinary tract symptoms.[24,25]

STRATEGIES AND EVIDENCE

EVALUATION

Evaluation begins with a complete medical, neurologic, and urologic history to rule out causes of lower urinary tract symptoms other than benign prostatic hyperplasia and bladder dysfunction. This evaluation includes consideration of excess fluid and caffeine intake and the use of diuretics or medications with antihistaminic effects that may weaken bladder detrusor function. In some cases, lower urinary tract symptoms resolve with replacement of a diuretic by a nondiuretic antihypertensive agent. A digital examination of the prostate should be performed and a PSA measurement obtained, since in rare cases, obstruction is due to a bulky prostate cancer; referral to a urologist is warranted if results are abnormal. A urinalysis should be ordered to screen for urinary tract infection and to look for hematuria, which might indicate urolithiasis or cancer of the kidney, bladder, or prostate.[26] Urinary tract infections should be treated before initiation of other therapy. If the patient reports a sense of incomplete bladder emptying or has a palpable bladder on abdominal examination, a postvoiding residual urine measurement should be obtained to rule out "silent" urinary retention (normal residual urine volume, <100 ml).[27] Referral to a urologist should be considered for patients

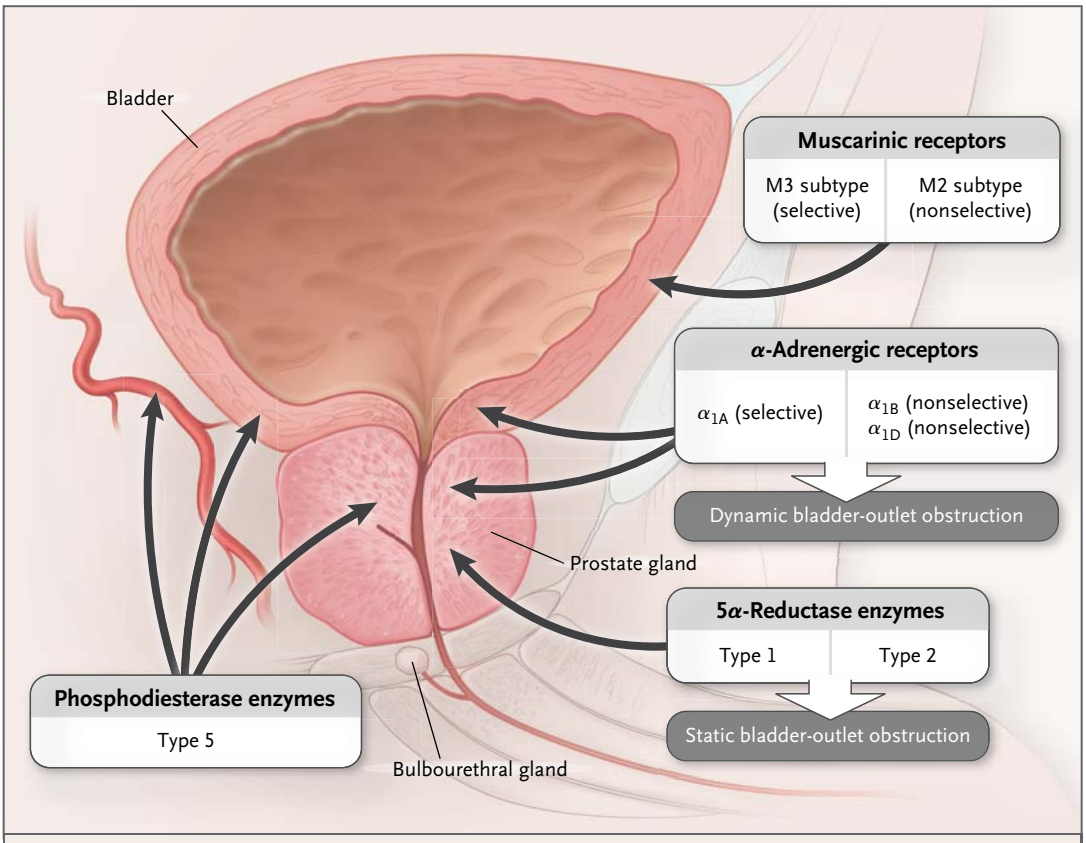

Figure 1. Mechanisms of Action and Targets for Intervention in Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms.

Lower urinary tract symptoms due to an overactive bladder, a bladder-outlet obstruction, or both may be treated pharmacologically. Selective agents have target receptors that are predominantly localized to the bladder and prostate. In contrast, nonselective agents may have more systemic effects.

with complicated lower urinary tract symptoms (Table 1 and Fig. 2). For uncomplicated cases, initial management in the primary care setting is reasonable.

Evaluation should also include the use of the American Urological Association Symptom Index (AUASI), a validated, self-administered, quantitative measure of the severity of lower urinary tract symptoms (on a scale of 0 to 35, with 0 indicating no symptoms and 35 indicating the most severe symptoms) and the extent to which the patient is bothered by these symptoms[28] (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The AUASI score guides management and provides a reliable quantitative measure of response to therapy; a minimum of a 3-point change (either an increase or a decrease) is considered a clinically important difference.[29]

MANAGEMENT

In men with mild or no symptoms (AUASI score, <8) or who are not bothered by their symptoms, watchful waiting is recommended.[30] This involves annual assessment with the AUASI, physical examination, and review of the patient's history for any new indications for treatment or referral to a urologist (Table 1 and Fig. 2). At each follow-up evaluation, the patient should be asked whether his lower urinary tract symptoms have become sufficiently bothersome that he would like to consider taking medication.

Pharmacologic treatment should be routinely discussed with patients who have moderate-to-severe symptoms (AUASI score, ≥8), bothersome symptoms, or both, with attention to the benefits and risks of various options[30] (Fig. 2 and Table 2). Therapy is generally prescribed at the discretion of the patient with the goal of improving urinary

symptoms, limiting progression of lower urinary tract symptoms, or both; there are few absolute indications for intervention (Table 1). Four classes of medication have shown efficacy: α-adrenergic–receptor blockers, 5α-reductase inhibitors, antimuscarinic agents, and phosphodiesterase-5 inhibitors. Patients should receive a medication for a sufficient time (Table 2) before deeming it ineffective.

Table 1. Indications for Referral to a Urologist.*

Complicated lower urinary tract symptoms
History of prostate cancer
Elevated PSA level
Hematuria
Bladder stones
Bladder cancer
Urethral stricture
Spinal cord injury
Parkinson's disease
Stroke
Prostatitis
Urinary retention
Recurrent or persistent urinary tract infections
Failure of medical therapy
Patient's preference for nonpharmacologic treatment
Absolute indications for intervention
Renal compromise due to urinary retention
Bladder stones
Persistent or recurrent urinary retention
Chronic urinary tract infections

* PSA denotes prostate-specific antigen.

α-Adrenergic–Receptor Blockers

Initially developed as antihypertensive agents, α-adrenergic–receptor blocking agents (alpha-blockers) exert their effect by blocking sympathetic adrenergic-receptor–mediated contraction of the prostatic smooth-muscle cells and bladder neck (Fig. 1).[22] Alfuzosin, doxazosin, tamsulosin, terazosin, and silodosin are approved by the Food and Drug Administration (FDA) for the treatment of lower urinary tract symptoms in men. As a class, alpha-blockers are subdivided on the basis of their degree of selectivity for the α_1-receptor subtype (Table 2). Terazosin, doxazosin, and alfuzosin are nonselective (i.e., they block α_1-receptor subtypes equally). The wide distribution of $\alpha 1_B$ and $\alpha 1_D$ receptors in vascular and central nervous system tissues explains their common side effects (e.g., hypotension, fatigue, and dizziness).[22] Tamsulosin and silodosin block α_{1A}-adrenergic receptors better than α_{1B}-adrenergic receptors and are considered to be selective for the α_1-receptor subtype, although their side-effect profiles are generally similar to those of the nonselective agents.[22]

In randomized trials involving men with symptomatic benign prostatic hyperplasia, defined primarily by the presence of moderate-to-severe lower urinary tract symptoms and in some studies by decreased urinary flow rates, alpha-blockers have been associated with clinically important decreases in the AUASI score (4 to 6 points).[31-33] Effects on symptoms are observed within 1 week after treatment has been initiated. Adjustment to the highest dose without side effects is necessary for nonselective alpha-blockers (Table 2).

5α-Reductase Inhibitors

5α-Reductase inhibitors, which block the conversion of testosterone to its active metabolite, dihydrotestosterone, shrink the prostate and reduce further prostatic growth. There are two FDA-approved 5α-reductase inhibitors: finasteride inhibits the type 2 5α-reductase isoenzyme, leading to decreases in serum dihydrotestosterone levels by 70 to 90%, whereas dutasteride blocks both type 1 and type 2 5α-reductase isoenzymes, reducing dihydrotestosterone to levels that approach zero. Both agents have been shown in randomized, placebo-controlled trials to reduce prostate size by as much as 25% and to decrease lower urinary tract symptoms over a period of 2 to 6 months, with total AUASI scores decreasing by 4 to 5 points[34] in men with larger prostates (>30 g).[34] In a direct comparison, the effects of finasteride and dutasteride were similar.[35]

Although inclusion criteria for the trials of these medications have varied, a prostate size of more than 30 g, measured with the use of ultrasonography, was typically applied. Given the inconvenience of ultrasonographic testing and the reasonable correlation of prostate size with PSA level, a PSA level of more than 1.5 ng per milliliter is recommended as a surrogate criterion for initiating therapy with 5α-reductase inhibitors.[36] Prostate size is generally underestimated on digital examination.[37]

Side effects of both 5α-reductase inhibitors

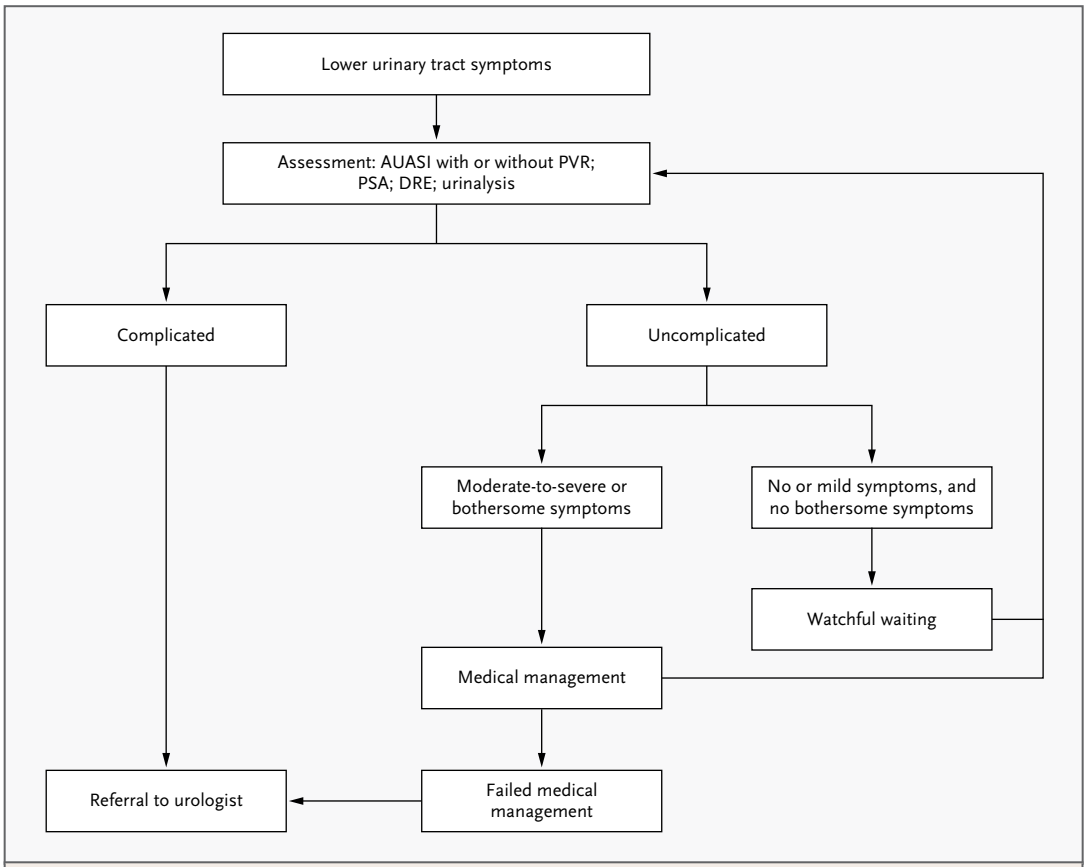

Figure 2. Management of Lower Urinary Tract Symptoms.
AUASI denotes American Urological Association Symptom Index, DRE digital rectal examination, PSA prostate-specific antigen, and PVR postvoiding residual urine volume.

include decreased libido, erectile dysfunction, decreased ejaculation, and gynecomastia.[34,38] In trials assessing whether finasteride or dutasteride could prevent prostate cancer,[38,39] treatment with either agent resulted in an absolute reduction in the risk of prostate cancer of up to 6 percentage points, but it was also associated with an increased risk of moderate-to-high-grade prostate cancer (Gleason score, ≥7). (A higher Gleason score, which ranges from 6 to 10, indicates a more aggressive histologic form of prostate cancer.) The FDA has revised the labels for these agents to include information about this risk (Table 2). If prostate cancer is suspected or the PSA level begins to increase during therapy, the patient should be referred to a urologist.[40] 5α-Reductase inhibitors reduce PSA concentrations by approximately 50% after 6 months; this effect must be taken into account in the interpretation of PSA tests performed for cancer detection.[34]

In a randomized, placebo-controlled trial comparing an alpha-blocker (doxazosin), a 5α-reductase inhibitor (finasteride), and the combination of the two, type 1 5α-reductase inhibitors (with or without an alpha-blocker therapy), but not alpha-blocker therapy alone, significantly reduced rates of secondary outcomes of urinary retention and the need for invasive therapy for benign prostatic hyperplasia (relative risk reduction with combination therapy vs. placebo, 81% vs. 67%).[3]

Combination of α-Adrenergic–Receptor Blockers and 5α-Reductase Inhibitors

In the trial noted above, combination therapy was superior to either agent alone in reducing the risk of clinical progression of benign prostatic hyperplasia, defined as worsening lower urinary tract symptoms, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection (relative risk reduction vs. pla-

cebo, 66%).[3] Rates of abnormal ejaculation, peripheral edema, and dyspnea were more common with combination therapy than with either agent alone, but these conditions were relatively uncommon even in the combination-therapy group (on average, ≤5 cases per 100 person-years).[3]

A trial of dutasteride and tamsulosin corroborated the benefit of combination therapy over single-agent therapy.[41] However, many men do not require combination therapy, and the higher rates of adverse effects and greater costs (as compared with single-agent therapy) must be weighed against the benefits. It is reasonable to begin treatment of lower urinary tract symptoms with a single agent, assess the effectiveness, and adjust the dose (if a nonselective alpha-blocker is used), and then replace the agent with a second agent or add a second agent as needed.

Antimuscarinic Therapy

Antimuscarinic agents inhibit muscarinic receptors in the detrusor muscle, thereby decreasing the overactive-bladder component of lower urinary tract symptoms. Several antimuscarinic agents have been approved for voiding dysfunction: darifenacin, solifenacin, trospium chloride, oxybutynin, tolterodine, and festosterodine. Antimuscarinic agents such as darifenacin and solifenacin are classified as selective if they primarily affect the M3-type muscarinic receptors in the bladder detrusor smooth muscle.[24] In contrast, M2-type muscarinic receptors are also located in the salivary glands, cardiovascular system, brain, and intestinal tract; this explains the distribution of adverse effects associated with nonselective antimuscarinic agents. Differences in the safety profile with regard to selectivity have not been studied extensively in men.

Although the American Urological Association (AUA) guidelines state that antimuscarinic therapy may benefit the subgroup of men who have predominantly storage symptoms, data are lacking to provide support for the efficacy of this class of drugs as monotherapy. In randomized trials involving men with clinically significant storage symptoms (e.g., ≥8 voidings per day), the addition of antimuscarinic therapy (vs. placebo) to alpha-blocker therapy resulted in significant reductions in storage symptoms (decrease in total AUASI storage-subscale scores, 2 to 4 points),[42-44] whereas antimuscarinic therapy alone has not been shown to result in a clinically significant benefit.[43]

Antimuscarinic therapy did not appear to increase the risk of acute urinary retention in the trials noted above, which included men with postvoiding residual urine volumes of less than 250 ml. Given the lack of data for men with greater postvoiding residual volumes, it is recommended that the baseline postvoiding residual volume be checked before antimuscarinic therapy is instituted. Effects on symptoms occur within 2 weeks; side effects include dry mouth, dry eyes, and constipation.

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 inhibitors, initially approved for the treatment of erectile dysfunction, may also improve lower urinary tract symptoms. Phosphodiesterase-5 is present (in addition to male reproductive tissue) in prostatic tissue, particularly in the transition zone, bladder detrusor, and vascular smooth-muscle cells relating to the urinary tract.[25] Inhibition of phosphodiesterase-5 results in increases in cyclic AMP and cyclic guanosine monophosphate, leading to smooth-muscle relaxation, and may also have antiproliferative effects in prostatic and bladder smooth-muscle cells.

Only tadalafil has received FDA approval for the treatment of urinary symptoms. In a randomized, placebo-controlled trial involving men with lower urinary tract symptoms for at least 6 months, a 5-mg dose of tadalafil resulted in an average decrease in the AUASI score of 2.8 points at 6 weeks and 3.8 points at 12 weeks.[45] Efficacy was shown as early as 4 weeks.[46] Common side effects (Table 2) are usually transient but may occur with a delayed onset.

Other Therapies

Although the use of herbal supplements such as saw palmetto (*Serenoa repens*) for benign prostatic hyperplasia has been increasing, available trial data do not support the efficacy of such supplements,[47-49] and their use is not endorsed by the guidelines of the AUA.

For men who are not interested in medical therapy, who have unacceptable side effects, or who do not have a response to medical therapy, surgical intervention, such as microwave thermotherapy or transurethral resection of the prostate, is an option. The use of laser technology and bipolar transurethral resection of the prostate, as compared with standard transurethral

Table 2. Medical Treatment of Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms.

Agent	Recommended Daily Dose*	Minimum Duration for Adequate Effect†	Common Side Effects‡	Precautions
Alpha-blockers§		2–4 wk	Erectile dysfunction, abnormal ejaculation, Dizziness and syncope, hypotension, fatigue, nasal congestion, headache, dry mouth and dry eye	Class effect: intraoperative floppy iris syndrome¶ (www.fda.gov/Safety/MedWatch/SafetyInformation/ucm197087.htm)
Selective				
Tamsulosin	0.4–0.8 mg			
Silodosin‖	8 mg			
Nonselective				
Terazosin	1–20 mg			
Doxazosin	1–8 mg			
Alfuzosin	10 mg			
5α-Reductase inhibitor		2–6 mo	Erectile dysfunction, abnormal ejaculation, gynecomastia, decreased PSA level	Class effect: increased risk of high-grade prostate cancer (www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258529.htm)
Finasteride	5 mg			
Dutasteride	0.5 mg			
Antimuscarinic agents**		12 wk	Constipation, dyspepsia, dry mouth and eyes, headache	Contraindicated for narrow-angle glaucoma; cognitive impairment possible with selective tertiary amines that cross blood–brain barrier; urinary retention possible
Selective				
Darifenacin	7.5–15.0 mg			
Solifenacin	5–10 mg			
Nonselective				
Trospium	40 mg (20-mg dose twice/day)			
Oxybutynin	2.5–20.0 mg			
Tolterodine	2–4 mg (1-mg or 2-mg dose twice/day)			
Festosterodine	4–8 mg			
Dual-drug products		2–6 mo	Erectile dysfunction, abnormal ejaculation, gynecomastia, dizziness, hypotension, headache, decreased PSA level	Same as class effects for alpha-blockers and 5α-reductase inhibitors
Dutasteride–tamsulosin	0.5 mg dutasteride and 0.4 mg tamsulosin			

Phosphodiesterase-5 inhibitor		4 wk	Headache, indigestion, back pain, flushing, nasal congestion	Concomitant use of α-adrenergic blockers or organic nitrates with a phosphodiesterase inhibitor can cause symptomatic hypotension
Tadalafil	2.5–5.0 mg			

* The recommended daily dose with an acceptable side-effect profile for adults is given. Long-acting formulations of doxazosin, oxybutynin, trospium, and tolterodine are available with different dosages than those listed.

† The recommended minimum duration for determining whether medication is efficacious, assuming an acceptable side-effect profile, is listed.

‡ Less commonly reported class side effects are as follows: for selective alpha-blockers, insomnia, blurred vision, and abdominal pain; for 5α-reductase inhibitors, hypotension, peripheral edema, somnolence, dyspnea, and rhinitis; for antimuscarinic agents, nausea, abdominal pain, diarrhea, influenza, dizziness, asthenia, dry eyes, urinary retention, peripheral edema, depression, cough, and hypertension; and for phosphodiesterase-5 inhibitors, diarrhea, pain in the limbs, myalgia, and dizziness.

§ Selective agents are those in which the antagonist of α_{1A}-adrenergic receptors is greater than that of α_{1B}-adrenergic receptors; nonselective agents block all α_1 receptors equally. Terazosin and doxazosin require dose adjustment over a period of 2 weeks. Failure to adjust the dose may lead to an insufficient dose or systemic effects on blood pressure.

¶ The intraoperative floppy iris syndrome, which consists of intraoperative miosis, a flaccid iris, and prolapse of the iris during cataract surgery, has been reported in men receiving alpha-blockers, particularly tamsulosin. However, discontinuation of this medication has not been shown to decrease the incidence of this syndrome. Men should be asked about planned cataract surgery, and those who are planning to undergo cataract surgery should not initiate treatment with alpha-blockers until after the surgery.

‖ Moderate renal impairment requires a dose reduction of silodosin to 4 mg daily.

** Selective agents are those in which M3 receptors are inhibited selectively; these are also tertiary amines, which can cross the blood–brain barrier. Cognitive impairment has been reported with these agents, and they should therefore be used with caution in patients who have or are at risk for cognitive disorders. A dose reduction of solifenacin, trospium, festosterodine, and tolterodine is necessary in patients with renal or hepatic impairment, and a dose reduction of darifenacin, solifenacin, festosterodine, and tolterodine is necessary in patients who are receiving CYP3A4 inhibitors.

resection of the prostate, has resulted in lower rates of adverse effects such as erectile dysfunction.[50,51] A detailed discussion of surgical therapies is beyond the scope of this article.

AREAS OF UNCERTAINTY

A better understanding is needed of modifiable risk factors for the development and progression of lower urinary tract symptoms. Data are lacking from randomized trials assessing the benefits and risks of combining a phosphodiesterase inhibitor with other approved medications for lower urinary tract symptoms and the effects of this therapy on the progression of symptoms.

GUIDELINES

The AUA published updated guidelines for the management of benign prostatic hyperplasia in 2010,[30] and the European Association of Urology published its updated guidelines in 2004.[52] The recommendations provided below are consistent with these recommendations except for the use of phosphodiesterase-5 inhibitors, which was not addressed by either body.

In contrast to the guidelines of the AUA, which recommend a urinalysis but no other routine testing for evaluation of patients with lower urinary tract symptoms, the guidelines of the European Association of Urology recommend routine measurement of serum creatinine and PSA levels, the urinary flow rate, and the postvoiding residual volume as part of the evaluation.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has benign prostatic hyperplasia and lower urinary tract symptoms with an inadequate response to a submaximal dose of an alpha-blocker. His AUASI score should be calculated; his history suggests that he has at least moderate symptoms.

A reasonable approach would be to increase the dose of doxazosin as tolerated up to 8 mg. If symptoms are still bothersome, a 5α-reductase inhibitor can be added as long as the PSA level is higher than 1.5 ng per milliliter (indicating prostatic enlargement). Another option, particularly if the patient also had erectile dysfunction for which he desired treatment, would be to pre-

scribe a phosphodiesterase-5 inhibitor (currently only tadalafil is approved for these symptoms), since this agent could address both problems. Alternatively, an antimuscarinic agent might be added, given trial data showing a greater reduction in storage symptoms with combination antimuscarinic and alpha-blocker therapy as compared with alpha-blocker monotherapy.

Referral to a urologist is recommended for complicated cases or for patients with clinically significant lower urinary tract symptoms whose response to medical therapy is deemed by the patient to be inadequate. For patients who are not interested in therapy, watchful waiting is recommended to monitor the patient for progression of lower urinary tract symptoms and urinary retention.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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