REVIEWS ARTICLE

Developments in the medical treatment of lower urinary tract symptoms in men

García-Mora and L. Reyes-Vallejo

Abstract There have been radical changes over the years in the approach to and understanding of the male patient with lower urinary tract symptoms (LUTS). The simplistic vision that centered on prostate growth has been abandoned and substituted by an integrated approach that includes bladder, renal, neurologic, and bladder outlet function as causal factors. We now know that the bladder pays a crucial role in the presence and characteristics of LUTS and that these problems can be caused by bladder outlet obstruction (BOO) due to the growth of the prostate, as well as to characteristic bladder changes secondary to aging and pelvic ischemia, similar to those observed in women with no type of obstruction.

From this new perspective, we have incorporated numerous drugs into our armamentarium that act on different sites of both the upper and lower urinary tract. The management approach to the patient with LUTS is no longer a strictly surgical one and the disease is viewed as a chronic degenerative pathology that requires integrated management. Surgery remains an option in certain cases, but with the wide variety of available medication we can choose the treatment that best fits each patient.

The aim of our review was to describe an integrated approach to the management of the LUTS patient, presenting all the currently available options, pointing out their advantages and disadvantages. We also attempted to provide a basis for choosing and formulating the combinations enabling the individualized treatment of these patients.

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Introduction

The approach to and understanding of the male patient with lower urinary tract symptoms (LUTS) has radically changed over the years. The simplistic vision centered on prostate growth has been abandoned and substituted by an integrated focus that includes bladder, kidney, neurologic, and bladder outlet function as the origin of the problem. The terminology implicating the prostate gland as the cause of the disease, such as prostate enlargement, prostatism, or prostatic hyperplasia should no longer be used, because they exclude the alterations that are now recognized as the root causes of this pathology. There is substantial evidence that prostate size is not correlated with the quantity of symptoms, and given that there is no causal relation, symptoms should not be attributed to it. Likewise, symptom classification has evolved. In the past, symptoms were referred to as obstructive and irritative. We now know that the correlation between obstructive symptoms and bladder outlet obstruction is very low, and so they should be restated as voiding symptoms. In the case of irritative symptoms, there is no type of irritation within the lower urinary tract in the majority of the patients, and thus a more accurate nomenclature is storage symptoms. Current knowledge recognizes that the bladder plays a crucial role in the presence and characteristics of LUTS and that these problems can be caused by bladder outlet obstruction due to prostate enlargement, as well as to changes in the bladder itself, secondary to aging and pelvic ischemia, similar to what is observed in women with no type of obstruction. Furthermore, another of the most prevalent and bothersome symptoms in men is nocturia, traditionally attributed to prostate problems. Based on epidemiologic studies, it is very clear that nocturia increases with age and this phenomenon is observed to be similar in men and women. The causes of nocturia are varied and age-dependent, but today we know that more than 70% of the cases have their origin in the kidneys, and its underlying cause is excessive nocturnal urine production. This explains why there is no improvement in nocturia in approximately 60% of the patients that have undergone transurethral resection of the prostate.

With this new perspective we have incorporated numerous pharmacologic agents into our armamentarium that act on different sites of the upper and lower urinary tracts, and the management approach to the patients with LUTS is no longer surgical, but rather is one in accordance with a chronic degenerative disease that requires integrated management that occasionally involves a surgical procedure. And thanks to the wide variety of available medications, we can choose an individualized treatment for each patient.

The aim of this review was to offer an integrated perspective and report on the currently available pharmacologic options for managing the patient with LUTS, emphasizing the advantages and disadvantages of each group, as well as providing bases from which to choose and formulate the necessary combinations for each particular case.

Lower urinary tract symptom pathophysiology

A detailed review of the pathophysiology and etiology of LUTS is beyond the scope of the present review. However, it is important to underline certain aspects with respect to this. The presence of urinary symptoms is related to different causes:
1. Bladder outlet obstruction
   a. Prostate growth
   b. Urethral stricture
   c. Primary bladder neck dysfunction
   d. Pelvic floor contractions
   e. Vesical sphincter dysynergia
2. Detrusor underactivity
3. Detrusor overactivity
4. Bladder sensitivity disorders
5. Nocturnal polyuria

In the majority of patients, the clinical spectrum we find is caused by a mixture of the factors listed and treatment should be directed accordingly. An objective determination of the role that each of these elements plays can only be made through multichannel urodynamic studies. Nevertheless, these are not necessary for the initial medical management and can be estimated through clinical findings and basic studies that include the medical history, a micturition diary, uroflowmetry and residual urine measurement, and urinalysis and serum creatinine. Prostate-specific antigen (PSA) determination has the additional role of estimating the risk for prostate cancer; its use can be considered in its context of enabling prediction of the possibility of success and disease progression in this group of patients.  

Pharmacologic groups

α blockers

Alpha blockers represent the most common treatment for patients with LUTS. They act upon the dynamic component of bladder outlet obstruction through the relaxation of the bladder neck and prostate.  There are 3 subtypes of α1 receptors: α1a, which are found in the prostate capsule and bladder neck; α1b, which are found in the vascular smooth muscle; α1d, which are located in the detrusor muscle and in the spinal cord at the sacral level.  The main difference in the distinct drugs of this group lies in their selectivity for each type of receptor. Table 1 lists the different α blockers with some of their prominent characteristics. A meta-analysis carried out by Nickel et al. showed that effectiveness related to maximum flow (Qmax) improvement was similar between the different drugs of this group (+1.32 ml/min over placebo), as well as a decrease in the International Prostate Symptom Score (IPSS) (-1.92 versus placebo). Thus, the choice of a blocker will depend on the profile of adverse effects, which is where there are differences. The most feared adverse effect of this drug group is orthostatic hypotension, with a relative risk over placebo of 2.54 in general. The most selective medications, such as tamsulosin and silodosin, have a lower rate in relation to this problem, showing no statistically significant difference when compared with placebo. However, these 2 drugs have higher retrograde ejaculation rates than the less selective ones.

5-α reductase inhibitors

The 5-α reductase inhibitors (5-ARIs) function by inhibiting the conversion of testosterone into dihydrotestosterone. These drugs are used in the management of prostatic growth due to the fact that the prostate is dependent on dihydrotestosterone during embryonal development. The 2 medications that we have with respect to this are finasteride and dutasteride. Finasteride only blocks the 5-α-reductase type 2, whereas dutasteride blocks both types 1 and 2.

At a 5 mg dose, finasteride achieves a reduction in prostate volume in approximately 21% of patients and its maximum effect is reached at 6 months from therapy commencement. Its impact on the IPSS is 21%, versus -2% of the placebo. On the other hand, dutasteride has shown a suppression of dihydrotestosterone levels of 90.2%, but its effects on IPSS, Qmax, and reduced prostate size are similar to those reported for finasteride. A subgroup analysis of different studies has shown that the patients receiving an actual benefit from 5-ARI management are those with a prostate volume above 30-40 g and with a baseline prostate-specific antigen level above 1.5 ng/ml.

The main use of these medications in clinical practice is in patients at risk for progression to urinary retention or the need for surgery, and these drugs are often used in combination with α blockers (see further ahead). The reduced risk for urinary retention is 57% versus placebo and for need for surgery is 48%; this reduction lasts up to 4 years after beginning treatment.

The adverse effects of 5-ARIs are mainly related to sexual performance. Decreased libido and erectile dysfunction are very common and are an important reason why patients stop taking them. However, these effects have been seen to diminish with time, and after one year they are equal to those observed with placebo.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazosin</td>
<td>0.5-20 mg</td>
<td>Barely selective. Traditional value, is currently used in high blood pressure management</td>
</tr>
<tr>
<td>Terazosin</td>
<td>2-10 mg</td>
<td>Not very selective. Requires dose titration</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>2-4 mg</td>
<td>Not very selective. Requires dose titration</td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>10 mg</td>
<td>Slightly greater affinity for the α1a receptors. Does not require dose titration</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>0.4 mg</td>
<td>α1a and α1d receptor-selective. Fewer vasodilation effects. Higher retrograde ejaculation rate</td>
</tr>
<tr>
<td>Silodosina</td>
<td>4-8 mg</td>
<td>α1a and α1d receptor-selective.</td>
</tr>
</tbody>
</table>

*Not available in Mexico*
Phosphodiesterase type 5 inhibitors

The phosphodiesterase type 5 (PDE-5) inhibitors initially emerged as cardiovascular medications, as did the α blockers. During the initial studies, a very important and unexpected improvement in erectile function was detected, and today this is the main indication for these drugs.¹⁸ As time went by, improvement in LUTS began to be noticed.¹⁹⁻²⁰ This improvement has been demonstrated by numerous studies with all types of inhibitors on the market, and is why they are currently included as part of the therapeutic armamentarium of the main international guidelines for treating LUTS.¹¹ The PDE-5 inhibitors act on the lower urinary tract through different mechanisms. The first is by relaxing the smooth muscle of the prostate capsule through nitric oxide; the second is reducing the hyperactivity of the autonomic nervous system; and the third is by relaxing the detrusor muscle through nitric oxide, inhibiting the rho-kinase, and reducing pelvic ischemia.²¹⁻²⁴

One of the limitations that has been postulated for this group of drugs is that in the majority of studies there has not been a statistically significant improvement in Qmax, compared with placebo. Two situations are worth mentioning in this respect. The first is that the improvement observed with the α blockers or the 5ARIs is not numerically important, whereas it has numerical importance in relation to improvement in symptom perception and in the IPSS, as well as with PDE-5 inhibitors. The second is that a medication that notably improves urodynamic parameters, but not clinical ones, lacks relevance in the management of the patient with LUTS, whereas the medication that offers considerable symptom improvement is a very valuable therapeutic weapon against this disease.

Within this drug group are the sildenafil, vardenafil, and tadalafil molecules. The 3 have been studied for their use in LUTS management, but due to their different half-lives, the only one approved for the management of this pathology is tadalafil at a dose of 5 mg/24 h. All the studies have shown a statistically significant improvement in IPSS that fluctuates between 2 and 3 points, compared with placebo. Oelke et al. found similar improvement in both the IPSS and Qmax and similar results were found in a comparative study with tamsulosin.²⁵⁻²⁶ This improvement was observed, regardless of the presence or absence of erectile dysfunction, as demonstrated by Brock et al.,²⁷ and also regardless of prostate size or symptom severity.²⁸

Antimuscarinics

For a long time, antimuscarinics were thought to be contraindicated in patients with urinary tract symptoms due to the risk for accelerating urinary retention. This idea was promoted by viewing the prostate as the causal organ of LUTS. However, with the advent of new knowledge, it is now understood that a percentage of patients present with bladder problems, regardless of the presence or absence of urinary obstruction, and that bladder function alterations are secondary in those patients that present with bladder outlet obstruction. Therefore, between 40-50% of patients with bladder outlet obstruction present with detrusor overactivity in urodynamic studies that can derive from ischemic changes in the bladder or local factors.¹ The antimuscarinics available today are listed in table 2. The action mechanism of this group is the blocking of the action of acetylcholine on the muscarinic receptors, especially the M3 types. In the past, this block was thought to prevent the activation of the detrusor muscle when acetylcholine stimulated the receptors. Now we know that a large percentage of patients with urinary urgency do not have detrusor overactivity confirmed by urodynamics, and that the mechanism by which they present this symptom is due to the activation of afferent receptors, which are also blocked by the antimuscarinics.²⁹⁻³⁰

The main preoccupation in using antimuscarinics in men was the risk for accelerating urinary retention in the presence of obstruction or detrusor underactivity. Numerous studies have demonstrated the safety of this group of drugs in men.²¹ Abrams et al. evaluated the effect of tolterodine in patients with bladder outlet obstruction,²² finding similar changes in the Qmax in the placebo group and the patients treated with tolterodine, with an increase of 25 cc of residual urine in the placebo group as opposed to 0 in the active treatment group. It is worth noting that the only episode of acute urinary retention presented in the placebo group. This urinary retention rate (0.2%) has been consistently shown in numerous additional studies.³³⁻³⁵

![Table 2: Antimuscarinics](image)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>5 mg</td>
<td>More beneficial than tolterodine, but with mildly severe adverse effects</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1-2 mg</td>
<td>Greater risk for cognitive decline in advanced-age patients</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>5-10 mg</td>
<td>Fewer adverse effects than tolterodine and oxybutynin</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>7.5 -15 mg</td>
<td>Very few effects on the SNC</td>
</tr>
<tr>
<td>Imidafenacina</td>
<td>0.1 to 0.2 mg every 12 h</td>
<td>Orodispersible tablet The newest drug of the group Greater receptor-selectivity in the bladder, with fewer adverse effects</td>
</tr>
<tr>
<td>Trospiuma</td>
<td>20 mg every 12 h</td>
<td>Does not cross the blood-brain barrier and therefore has a favorable safety profile in the elderly</td>
</tr>
<tr>
<td>Fesoterodinea</td>
<td>4-8 mg</td>
<td>Superior efficacy to that of tolterodine, but with more adverse effects</td>
</tr>
</tbody>
</table>

*Not available in Mexico*
The use of α blockers and antimuscarinics as monotherapy has been analyzed in different studies. The most important data is from the TIMES study by Abrams and Kaplan. They found that patients treated with extended-release tolterodine (4 mg) as monotherapy showed important improvement in the IPSS in the score of the questions related to storage, as well as in episodes of urge incontinence. This improvement was only observed in patients with storage symptoms, especially in those patients with small prostates.\textsuperscript{32,36-37} The most common adverse effects in this group of drugs are dry mouth (20-30%), constipation (4-10%), blurred vision, and cognitive decline.\textsuperscript{38}

\textbf{α blockers + 5-α reductase inhibitors}

This is probably the most studied and most widely used combination in the management of patients with urinary symptoms. The most important data are from 4 studies: the PREdict,\textsuperscript{39} the MTOPS,\textsuperscript{40} the Veterans Affairs,\textsuperscript{41} and the COMBAT.\textsuperscript{42-43} The main role of this combination is in patients that have moderate to severe symptoms, with risk factors for disease progression. Improvement in the IPSS, Qmax, and quality of life is greater for the combination than for any monotherapy. However, this is observed only in patients with large prostates, and so should be used just for this group of patients.

When this combination is employed, the use of an α blocker can be suspended, once the maximum effect of the 5-ARI has been reached, in other words, 6 to 12 months afterwards.

\textbf{α blockers + antimuscarinics}

This drug combination has sparked great interest in recent studies. A large percentage of patients that were considered cases of failed medical treatment could be retrieved with this combination. As mentioned above, α blockers have a modest impact on storage symptoms and therefore the addition of an antimuscarinic drug to this group of patients could achieve the desired symptom improvement. In addition, it is important to emphasize that many patients that underwent surgery due to symptom progression can present with unfavorable results, because storage symptoms persist in an important percentage of subjects.\textsuperscript{9}

Tolterodine is the most studied antimuscarinic agent for this combination, usually with tamsulosin. Tolterodine has been evaluated in the TIMES\textsuperscript{44} and ADAM\textsuperscript{45} studies and by Athanasopoulos et al.\textsuperscript{46} The most important data on the tamsulosin and solifenacin combination is found in the NEPTUNE\textsuperscript{46} study, from which a commercial formulation has been developed combining the two drugs.\textsuperscript{47} These studies have shown an improvement in the response rate with the combined treatment, especially concerning storage symptoms, with high safety rates and a risk for urinary retention under 2%.

\textbf{α blocker + PDE-5 inhibitors}

The combination of these 2 drugs has been evaluated in different studies. Both medications act by relaxing the prostate capsule and bladder neck through different mechanisms. Moreover, the PDE-5 inhibitors act on other sites of the lower urinary tract, with the expectation of additional effects. This has been corroborated in all the studies to date in which the combination offers a reduction of 2 additional points on the IPSS, compared with monotherapy with a blockers, as well as an additional improvement of 1.5 ml/s in the Qmax. This is achieved in addition to the obvious improvement in erectile function offered by the PDE-5 inhibitor, and therefore this therapeutic modality can be considered for patients with a poor response to either of the 2 forms of monotherapy.\textsuperscript{48}

\textbf{PDE-5 inhibitors + 5-α reductase inhibitors}

The interest in this combination arose from the need for a treatment that had an impact on disease progression, without having an important effect on the sexual function of the patient. Casabé et al. developed a study to analyze the combination of finasteride and tadalafil.\textsuperscript{49} Their results showed a greater reduction on the IPSS with the combination than with finasteride monotherapy throughout the 26 weeks of the study, with an initial 1.7 points and a final 1 point. This is similar to what the MTOPS and COMBAT studies found, in which the α blockers act at the beginning of the study, while the maximum 5-ARI effect is being reached. Not surprisingly, finasteride monotherapy had a deleterious effect on sexual function. However, in the combination group, the effects of tadalafil were far superior, producing an improvement in the International Index of Erectile Function (IIEF) of 4.7 points, compared with finasteride alone.

These findings make this combination very attractive for patients at risk for disease progression, but who want to improve or maintain sexual function.

\textbf{Integrating concepts, tailoring individualized treatment}

With all the options available today, many different combinations can be made that adapt to the needs of each patient. These combinations or treatment choices are summarized in figure 1, and pertinent combinations can be made based on this information. The following are the most important points to keep in mind:

1. For patients at risk for disease progression, the only drug group that has shown a beneficial effect is the 5-ARI group, and therefore they should be included in the management of these patients.
2. The α blockers and PDE-5 inhibitors offer similar symptom improvement, although the latter is more expensive, and thus the α blockers are a more probable first-line treatment for patients presenting only with urinary symptoms.
3. For subjects without sufficient improvement with PDE-5 inhibitor or α blocker monotherapies, their combination should be considered, as it has been shown to be superior in symptom and Qmax improvement.
4. In patients with erectile dysfunction and urinary symptoms, PDE-5 inhibitor monotherapy is beneficial.
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for the symptoms of both pathologies, reducing both the cost of treatment and polypharmacy, and achieving similar results in the reduction of symptoms of the two entities. Likewise, patients that do not tolerate the adverse effects of the α blockers can be treated with PDE-5 inhibitors with the same results.

5. The antimuscarinics are the cornerstone of storage symptom management, whether as monotherapy or combined with α blockers. Their use in men is safe and the risk for urinary retention is around 1-2%.

6. Nocturia manifests as LUTS, but its approach and management is completely independent and goes beyond the scope of this review. Its treatment is based mainly on desmopressin, which can be combined with any of the abovementioned regimens.

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Conflict of interest

Dr. Reyes-Vallejo is a medical consultant in urology for Eli Lilly, Mexico.

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