



Review

The use of antimuscarinics, phosphodiesterase type V inhibitors and phytotherapy for lower urinary tract symptoms in men



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Abstract Besides the mainstay of α -blockers and 5 α -reductase inhibitors, other forms of medical therapy complete the armamentarium in the treatment of lower urinary tract symptoms (LUTS) in men. These treatments can target specific symptoms as well as associated symptoms that would affect the quality of life of the patients. Many patients are bothered by storage symptoms, more so than the voiding symptoms. Antimuscarinics are efficacious and safe, provided the patients do not have high post void residual urine. Many patients with LUTS also have erectile dysfunction, and phosphodiesterase type V inhibitors are effective in relieving both LUTS as well as erectile dysfunction for such patients. Phytotherapy provides a popular and safe treatment for LUTS, however, the efficacy of the treatment has not been proven in well conducted prospective randomized controlled studies.

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1. Antimuscarinics for lower urinary tract symptoms (LUTS)

1.1. Action and indications

In patients with benign prostatic enlargement (BPE), as high as 50% of them experience storage symptoms [1]. Bladder wall

hypertrophy due to functional overload secondary to bladder outlet obstruction (BOO) might be associated with progressive detrusor denervation, which is thought to play a central role in storage symptoms and detrusor overactivity. Considering the high prevalence of storage symptoms in patients with benign prostatic hyperplasia (BPH), antimuscarinic drugs can be considered to help to ameliorate these symptoms.

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1.2. Combination therapy of antimuscarinic with α -blockers

Because of the presence of voiding/obstructive symptoms, antimuscarinics, when used in LUTS, is usually used in combination with α -blockers. This is also thought to decrease the risks of urinary retention. All studies on α -blocker/antimuscarinic combination therapy have only a short follow-up (usually 12 weeks), and no study assessed the outcomes of this combination for >4 months [2]. Therefore, it is currently unknown if long-term α -blocker/antimuscarinic combination is useful, safe, or effective.

Studies have reported significant international prostate symptom score (IPSS) reductions with α -blocker/antimuscarinic combination instead of α -blocker only, especially the reduction in IPSS storage sub score (questions 2, 4 and 7). A reduction of IPSS of 3 points was observed in 74.4% of patients with oxybutynin add-on but only in 65% of patients receiving placebo add-ons [3]. Another study reported IPSS reduction with the antimuscarinic propiverine was more pronounced in patients with peak flow rate (Q_{max}) < 15 mL/s at baseline. In the TIMES study [4], α -blocker/antimuscarinic combination therapy is noted to improve both IPSS and quality of life (QoL) score.

The addition of antimuscarinics to α -blocker results in no significant differences in Q_{max} , but helps improve 24 h urinary voiding frequency (2.8 vs. 1.7 with tamsulosin alone, 1.4 with tolterodine alone, or 1.6 with placebo) and urgency episodes.

1.3. Antimuscarinic monotherapy

First-line antimuscarinic monotherapy can be instituted in patients with predominantly storage symptoms and without BOO, whereas combination α -blocker/antimuscarinic can be used in patients with concomitant BOO. With antimuscarinic monotherapy, average post void residual urine increased significantly, and no patients develop acute retention of urine. Patients with smaller baseline prostate volume, higher IPSS (storage subset) and higher Q_{max} have significantly higher treatment success rates [5].

1.4. Side effects

In many studies, dry mouth was significantly more common in patients on antimuscarinics. Many studies have also shown that antimuscarinic drugs can be safely used in patients with BOO and that the impact on detrusor contractility during the voiding phase, though present, was limited [6]. The safety of the use of antimuscarinic drugs can be explained by the fact that these drugs act mainly by decreasing the urge and increasing bladder capacity during the filling phase, when there is no activity in the parasympathetic nerves. The drugs block the afferent nerves initiating the micturition reflex, triggered by a tonic release of acetylcholine from the nerves or the urothelium. Being competitive antagonists, the action of these drugs can be reduced during the voiding phase, when there is a massive release of acetylcholine. Hence, this can explain why the currently used dosages of antimuscarinic drugs do not lead to urinary retention [7].

1.5. Recommendations

First-line antimuscarinic monotherapy can be instituted in patients with predominantly storage symptoms and without BOO, whereas combination α -blocker/antimuscarinic can be used in patients with concomitant BOO. There should be caution in the use of antimuscarinic in patients with high post void residual urine (>250 mL).

2. Phosphodiesterase type V inhibitor (PDE5i) for LUTS

2.1. Action and indications

Sexual dysfunction is a common co-morbidity in aging men with LUTS. Although the underlying mechanisms for the relationship between LUTS and erectile dysfunction (ED) have not been fully elucidated, common links such as nitric oxide-cyclic guanosine monophosphate (NO/cGMP) pathway, RhoA/Rho-kinase signaling, pelvic atherosclerosis, and autonomic adrenergic hyperactivity can be potential targets for PDE5i [8]. The sites of action of PDE5i on LUTS include potential targets such as prostate, urethra, bladder and LUTS vasculature. A study evaluating PDE5 tissue distribution and activity in the human prostatic urethra, prostate, and bladder from the same patient indicate that PDE5 is mostly expressed in the muscular compartment with the following rank order of activity: bladder neck more than prostatic urethra more than prostate [9]. This selective distribution of PDE5 in the human body, together with inhibition of the RhoA/Rho-kinase contractile mechanism induced by PDE5i in the bladder could be the rationale for the use of PDE5i treatment to ameliorate the dynamic component (bladder dysfunction, and urethral contractions) of LUTS [10].

2.2. Efficacy

In a meta-analysis of 12 published studies [11], PDE5i is noted to significantly ameliorate IPSS (-2.8 [-3.6 to -2.1]; $p < 0.0001$) and international index of erectile function (IIEF) score ($+5.5$ [$+4.1$ to $+6.9$]; $p < 0.0001$) but not Q_{max} (-0.0 mL/s [-0.6 to 0.6]; $p =$ not significant) when compared with placebo. Meta-regression analysis showed that differences in IPSS score were significantly lower in older and obese patients. The effect of PDE5i on IPSS significantly increased as a function of higher IPSS at baseline, which likely reflects the well-known relationship between higher baseline scores and greater numerical improvements, but similar percentage score improvements.

LUTS treated with PDE5i showed improvement in symptoms (IPSS) as opposed to a small clinically insignificant increase in Q_{max} . The relaxation of the prostate and bladder neck after PDE5i treatment could theoretically improve flow rate, but the concomitant relaxation of the detrusor muscle counteracts this effect, with no final improvement in the Q_{max} [12].

The meta-analysis also showed that the improvement in IPSS after PDE5i depends on age (younger) and body mass index (less obese).

2.3. Combination therapy with α -blockers

In a meta-analysis of studies comparing the effect of α -blockers alone versus the combination of α -blockers and PDE5i, it is noted that the combination of the two medications significantly improved IPSS (-1.8 [-3.7 to 0.0]; $p = 0.05$) and IIEF score ($+3.6$ [$+3.1$ to $+4.1$]; $p < 0.0001$) as well as Q_{\max} ($+1.5$ mL/s [$+0.9$ to $+2.2$]; $p < 0.0001$) when compared with the use of α -blockers alone. A combination of PDE5i and α -blockers can significantly improve Q_{\max} (above 1 mL/s) as compared to α -blockers alone, whereas PDE5i alone cannot increase Q_{\max} as compared with placebo.

2.4. Side effects

Side effects included flushing, gastroesophageal reflux, headache and dyspepsia. Most of the treatment related adverse events were of mild to moderate grade, and overall safety profile of PDE5i was good.

2.5. Recommendations

Currently, the only PDE5i that has been approved by the US Food and Drugs Administration (FDA) and Singapore Health Science Authority (HSA) for treatment of LUTS is tadalafil 5 mg once a day. The current evidence showed that PDE5i alone can help symptoms (IPSS) without significant effect on flow rate (Q_{\max}). It works better in younger, less obese patients. It has additional beneficial effects on erectile functions patients with concomitant ED, and thus can be considered in this group of patients. Combination therapy with α -blockers can in addition, help to improve the flow rate (Q_{\max}).

3. Phytotherapy for LUTS

3.1. Action

Phytotherapy is popular among the public as an over-the-counter treatment for LUTS. However, evidence for its long-term efficacy is lacking. There are more than 100 preparations derived from plants for the treatment of LUTS, the most common being *Serenoa repens* and *Pygeum africanum*. *S. repens* has an anti-inflammatory, anti-androgenic and anti-proliferative effect. *In vitro* study [13] has shown that it has an inhibitory effect on type II 5α -reductase. The action of *P. africanum* is uncertain, but it seems that the prostate cells of BPH patients are more sensitive to the antiproliferative and apoptotic action of the herb than the cells of patients without BPH. Many of the studies on phytotherapy show conflicting results and some were methodologically incorrect.

3.2. Efficacy

A well designed double-blind, placebo controlled randomized trial with 12-month follow-up did not show the superiority of *S. repens* versus placebo in the American Urological Association (AUA) symptoms score, flow rate,

prostate volume, post void residual urine, QoL or PSA [14]. However, another study [15] in China with shorter follow-up (12 weeks) showed improvement in Q_{\max} , but not in other parameters like IPSS.

3.3. Side effects

Phytotherapy is generally well tolerated. In the randomized controlled trial, *S. repens* shows side effect profile similar to that of placebo. It appears to be better tolerated than 5-ARIs in regard to sexual dysfunction.

3.4. Recommendations

As phytotherapy includes a heterogeneous group of compounds with lack of standardization of constituents and doses, and published studies tend to have methodological limitations; no specific recommendations can be made on phytotherapy for the treatment of LUTS.

Conflicts of interest

The authors declare no conflict of interest.

References

- [1] Gosling JA, Kung LS, Dixon JS, Horan P, Whitbeck C, Levin RM. Correlation between the structure and function of the rabbit urinary bladder following partial outlet obstruction. *J Urol* 2000;163:1349–56.
- [2] Fullhase C, Chapple C, Cornu JN, De Nunzio C, Gratzke C, Kaplan SA, et al. Systematic review of combination drug therapy for non-neurogenic male lower urinary tract symptoms. *Eur Urol* 2013;64:228–43.
- [3] MacDiarmid SA, Peters KM, Chen A, Armstrong RB, Orman C, Aquilina JW, et al. Efficacy and safety of extended-release oxybutynin in combination with tamsulosin for treatment of lower urinary tract symptoms in men: randomized, double-blind, placebo-controlled study. *Mayo Clin Proc* 2008;83:1002–10.
- [4] Kaplan SA, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, Guan Z, et al. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *JAMA* 2006;296:2319–28.
- [5] Liao CH, Kuo YC, Kuo HC. Predictors of successful first-line antimuscarinic monotherapy in men with enlarged prostate and predominant storage symptoms. *Urol* 2013;81:1030–3.
- [6] Abrams P, Kaplan S, De Koning Gans HJ, Millard R. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. *J Urol* 2006;175:999–1004.
- [7] Andersson KE. Antimuscarinics for treatment of overactive bladder. *Lancet Neurol* 2003;3:46–53.
- [8] Andersson KE, de Groat WC, McVary KT, Lue TF, Maggi M, Roehrborn CG, et al. Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism(s) of action. *Neuro-urology Urodyn* 2011;30:292–301.
- [9] Fibbi B, Morelli A, Vignozzi L, Filippi S, Chavalmane A, De Vita G, et al. Characterization of phosphodiesterase type 5 expression and functional activity in the human male lower urinary tract. *J Sex Med* 2010;7:59–69.
- [10] Morelli A, Filippi S, Sandner P, Fibbi B, Chavalmane AK, Silvestrini E, et al. Vardenafil modulates bladder

- contractility through cGMP-mediated inhibition of RhoA/Rho kinase signaling pathway in spontaneously hypertensive rats. *J Sex Med* 2009;6:1594–608.
- [11] Gacci M, Corona G, Salvi M, Vignozzi L, McVary KT, Kaplan SA, et al. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with α -blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur Urol* 2012;61:994–1003.
- [12] Tinel H, Stelte-Ludwig B, Hutter J, Sandner P. Pre-clinical evidence for the use of phosphodiesterase-5 inhibitors for treating benign prostatic hyperplasia and lower urinary tract symptoms. *BJU Int* 2006;98:1259–63.
- [13] Vela Navarrete R, Garcia Cardoso JV, Barat A, Manzarbeitia F, López Farré A. BPH and inflammation: pharmacological effects of Permixon on histological and molecular inflammatory markers. Results of a double blind pilot clinical assay. *Eur Urol* 2003;44:549–55.
- [14] Bent S, Kane C, Shinohara K, Neuhaus J, Hudes ES, Goldberg H, et al. Saw palmetto for benign prostatic hyperplasia. *N Engl J Med* 2006;354:557–66.
- [15] Shi R, Xie Q, Gang X, Lun J, Lun J, Cheng L, et al. Effect of saw palmetto soft gel capsule on lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized trial in Shanghai, China. *J Urol* 2008;179:610–5.