

Pharmacological treatment of predominantly storage low urinary tract symptoms (LUTS) in men – a review

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Abstract

Low urinary tract symptoms (LUTS) are common, very bothersome and with increased frequency in aging male population. Apart from voiding symptoms many men are struggling with moderate and severe storage symptoms, which influence dramatically their quality of life. One of the treatment options is pharmacotherapy, where several drug groups are available nowadays – among them α 1-blockers and antimuscarinics. While every group has its advantages and side effects, the combination of those two have shown increased efficacy and acceptable safety when used in the good selected population of patients with combined voiding and storage LUTS.

Keywords

LUTS, voiding, storage, α 1-blockers, antimuscarinics, combination

Introduction

Low urinary tract symptoms (LUTS) in men are bothersome and life quality affecting conditions, having different etiology^[1]. While they are often considered to be only prostate related, it is nowadays widely accepted that many anatomical and functional changes could lead to LUTS – benign prostate hyperplasia (BPH), urethral strictures, neurogenic bladder dysfunction, stones, tumors etc^[2]. (Fig. 1)

LUTS prevalence is above 55% among the population aged >18y.o. and was slightly higher in men than women (62.8% vs. 59.6%; $p = .004$), increasing significantly with age ($p = .001$)^[3]. LUTS can be categorized as storage, voiding, and postmicturition symptoms (Fig. 2) and are present alone or most commonly as a combination of symptoms in every patient^[4]. The etiology for those combinations of symptoms is not always unambiguous, sometimes arising from prostate enlargement or for instance bladder hyperactivity.

Apart from imaging – most often ultrasound, or uroflowmetry and laboratory tests of blood and urine, an important diagnostic tool for investigation of patients with LUTS is the International Prostate Symptom Score (IPSS) which approaches its 30th anniversary^[5]. IPSS can be utilized to measure the severity of lower urinary tract symptoms and is a validated, reproducible scoring system to assess disease severity and response to therapy. The IPSS is made up of 7 questions related to voiding and storage symptoms. A score of 0 to 7 indicates mild symptoms, 8 to 19 indicates moderate symptoms and 20 to 35 indicates severe symptoms. (Table 1)

In some men high IPSS score – more severe symptoms respectively, are due to voiding or the opposite – storage symptoms. An analysis of four important epidemiologic studies—the International Continence Society “Benign Prostatic Hyperplasia” (ICSBPH) study, the EPIC survey, the Boston Area Community Health (BACH) survey, and the Epidemiology of LUTS (EpiLUTS) survey^[6] showed that only 12.1% of the investigated adult male population

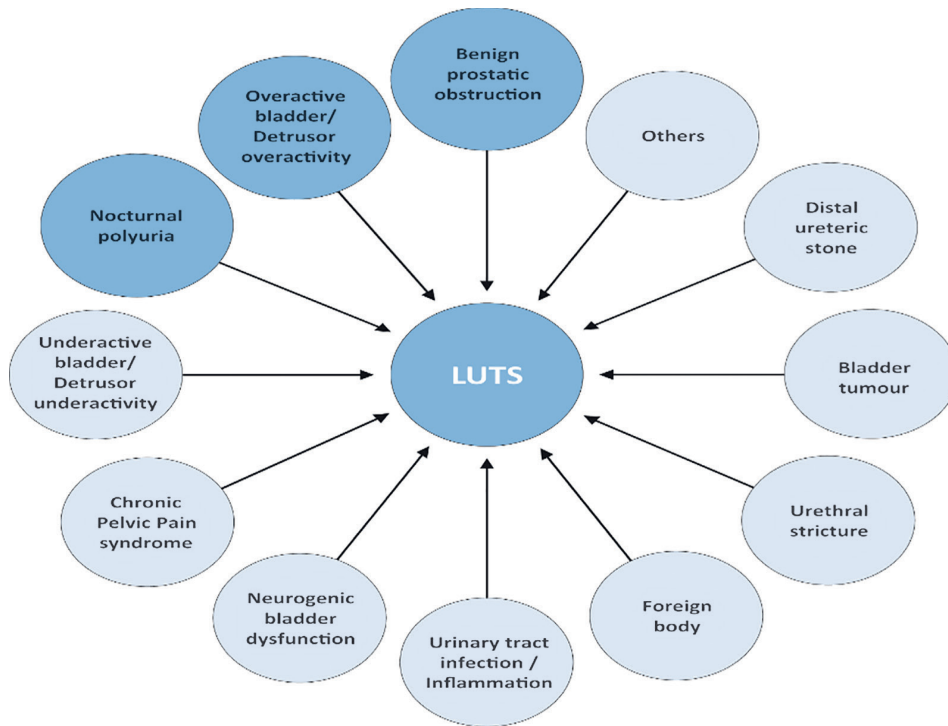


Figure 1. LUTS etiology.

had purely voiding symptoms and 9,1% - storage only. Most of the cases were patients with combined symptoms – 24,3% with all three groups. (Fig. 3) In addition to that Gacci and al [7] report that 46%, almost half of the men with LUTS have also storage component. That means – treating with drugs or surgery only the obstruction will end up with persisting LUTS – the storage ones.

Treatment options

Treatment options for male LUTS include lifestyle changes, pharmacotherapy or surgery. For mild cases where symp-

oms are not bothersome enough for the patient, even watchful waiting is advised [8]. Behavioural and dietary modifications include the following lifestyle advices: reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient (e.g., at night or when going out in public); avoidance/moderation of intake of caffeine or alcohol, which may have a diuretic and irritant effect; use of relaxed and double-voiding techniques; urethral milking to prevent post-micturition dribble; mental tricks to take the mind off the bladder and toilet, to help control overactive bladder symptoms; bladder retraining that encourages men to hold on when they have urgency to increase their bladder capacity and the time between

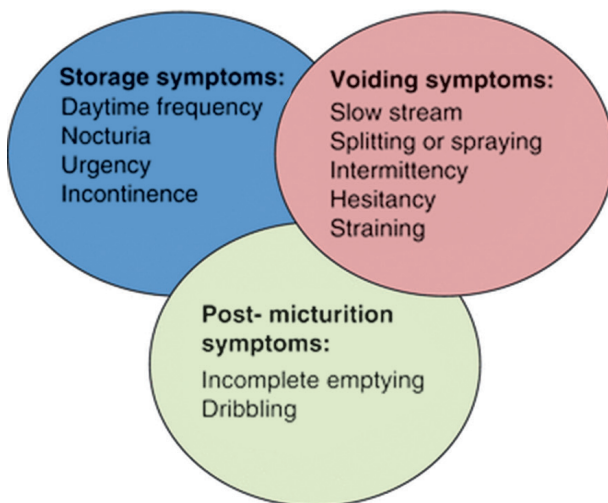


Figure 2. Different groups of LUTS.

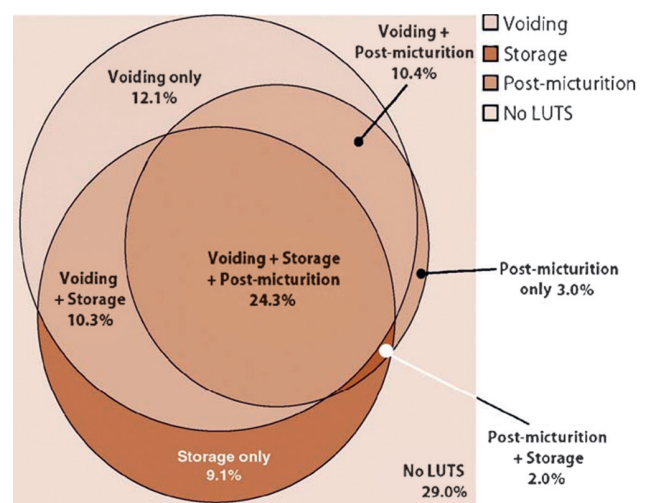


Figure 3. Prevalence of different types of LUTS among adult males.

Table 1. International prostate symptom score (IPSS) questionnaire.

International Prostate Symptom Score (I-PSS)							
<i>In the past month:</i>	<i>Not at All</i>	<i>Less than 1 in 5 times</i>	<i>Less than Half the Time</i>	<i>About Half the Time</i>	<i>More than Half the Time</i>	<i>Almost Always</i>	<i>Your Score</i>
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
7. Nocturia How many times did you typically get up at night to urinate?	None	1 time	2 times	3 times	4 times	5 times	
Total I-PSS Score							
Score:	1-7 Mild		8-19 Moderate		20-35 Severe		
<i>The first seven questions of the I-PSS are from the American Urological Association (AUA) Symptom Index</i>							
Quality of Life Due to Urinary Symptoms							
	<i>Delighted</i>	<i>Pleased</i>	<i>Mostly Satisfied</i>	<i>Mixed</i>	<i>Mostly Dissatisfied</i>	<i>Unhappy</i>	<i>Terrible</i>
<i>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?</i>	0	1	2	3	4	5	6

voids; reviewing the medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects (these recommendations apply especially to diuretics); providing necessary assistance when there is impairment of dexterity, mobility, or mental state; treatment of constipation [9].

Phytotherapy is prescribed in mild to moderate cases when patients want to eliminate the possible side effects of pharmacotherapy. Serenoa repens, pumpkin seeds, pygeum africanum and willow herb are among the historically used herbs. Possible relevant compounds include phytosterols, β -sitosterol, fatty acids, and lectins [10]. In vitro, plant extracts can have anti-inflammatory, anti-androgenic and oestrogenic effects; decrease sexual hormone binding globulin; inhibit aromatase, lipoxygenase, growth factor-stimulated proliferation of prostatic cells, α -adrenoceptors, 5 α -reductase, muscarinic acetylcholine receptors, dihydropyridine receptors and vanilloid receptors; and neutralise free radicals [11]. The in vivo effects of these compounds are uncertain, and the precise mechanisms of plant extracts remain unclear.

Pharmacological treatment include: α 1-Adrenoceptor antagonists (α 1-blockers), 5 α -reductase inhibitors (5-ARI), muscarinic receptor antagonists, beta-3 agonist and phosphodiesterase 5 inhibitors. Their usage in different patients, alone or in combinations, depends on the patients' symptoms, characteristics (age, concomitant therapy and diseases), patients' expectations (i.e. erectile function).

α 1-blockers are available since the 1970s and have fast and significant effect of LUTS in men, especially, but not

only – the voiding compound. They aim to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and obstruction respectively [12]. They are also located in other part of the human body (e.g. urinary bladder and/or spinal cord) which may play a role as mediators of effects. Alpha 1-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and the central nervous system may mediate adverse events. Currently available α 1-blockers are: alfuzosin, doxazosin, silodosin, tamsulosin, terazosin and naftopidil.

There are many trials proving the α 1-blockers efficacy, among them Tamsulosin investigator group, which demonstrated significant improvement in mean change of IPSS and mean change of Q max on uroflowmetry in ml/sec, when comparing placebo and tamsulosin both 0.4mg and 0,8mg [13]. (Fig. 4) This improvement was rapid – in the frame of several weeks.

The most frequent adverse events of α 1-blockers are asthenia, dizziness and orthostatic hypotension because of vasodilating effects. Patients with cardiovascular co-morbidity and/or vaso-active co-medication may be susceptible to α 1-blocker-induced vasodilatation. An adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [14]. α 1-blockers do not adversely affect libido, or erectile function (ED), but often cause abnormal ejaculation (retrograde).

Antimuscarinics were mainly tested in females in the past, as it was believed that LUTS in men were caused by the

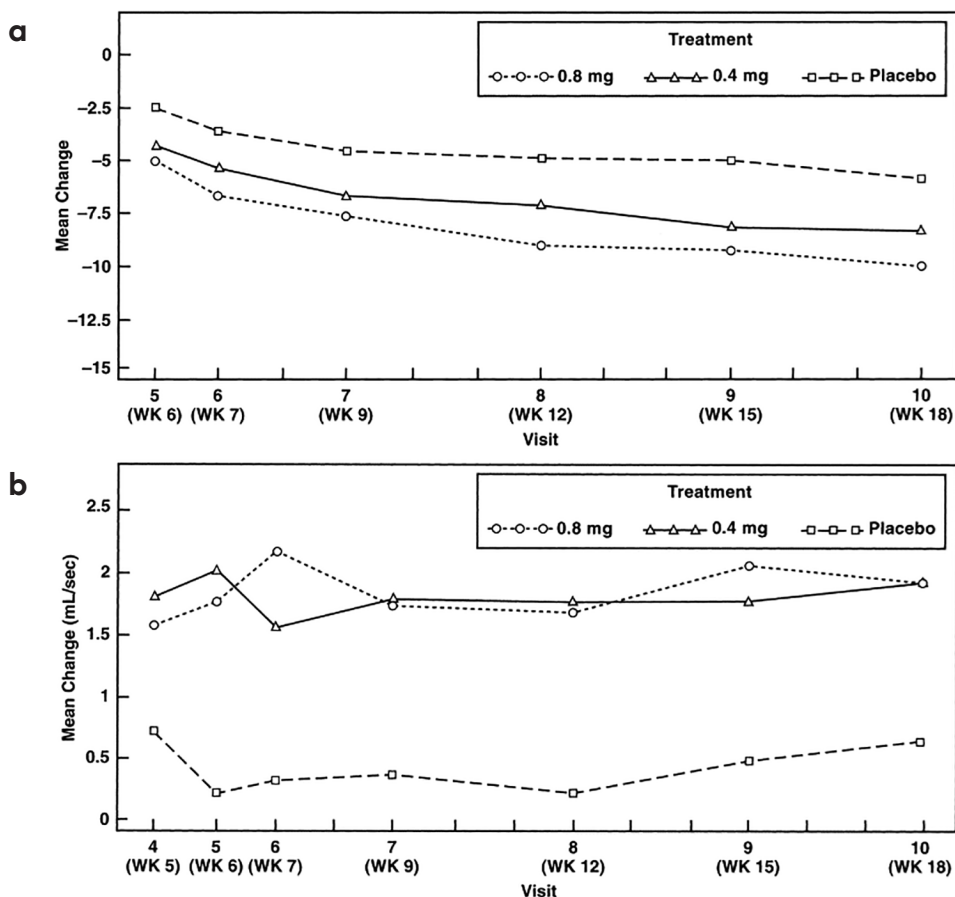


Figure 4. Mean change in IPSS and Qmax Placebo vs Tamsulosin. Tamsulosin Investigator Group.

prostate, so should be treated with prostate-specific drugs. That proved to be wrong, because men do have also bladder beside their prostates. The detrusor 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 in bladder urothelial cells and epithelial cells of the salivary glands. Five muscarinic receptor subtypes (M1-M5) have been described, of which M2 and M3 are predominant in the detrusor. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system [209]. The following muscarinic receptor antagonists are licensed for treating OAB/storage symptoms: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine and trospium chloride. Several studies proved the antimuscarinic effect on male LUTS, especially storage symptoms such as urgency, frequency, incontinence and nocturia, among them Kaplan et al [15] where percentage of positive change from baseline is significant, shown on Fig. 5.

Drug-related adverse events include dry mouth (up to 16%), constipation (up to 4%), micturition difficulties (up to 2%), nasopharyngitis (up to 3%), and dizziness (up to 5%). Theoretically antimuscarinics might decrease bladder strength, which might be associated with increase of post residual volume (PVR) or urinary retention when used in men with obstructive prostate [16].

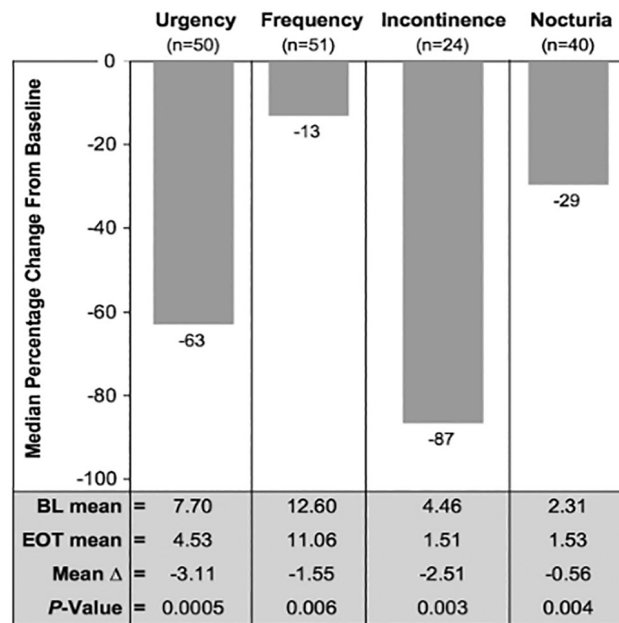


Figure 5. Effect of Solifenacin on storage symptoms in aging men.

A combination between $\alpha 1$ -blockers and antimuscarinics is logical, taking into account their synergy and predominantly pronounced effect of $\alpha 1$ -blockers on voiding and of antimuscarinics on storage symptoms. The NEPTUN study [17] compares the effect of tamsulosin alone vs combination

with solifenacin. Men with IPSS more than 13, and with more than two episodes of urgency per day were included. Mean improvement in IPSS, mean change in the number of micturition per day and mean change of the urine volume per micturition were all significantly better when using combination therapy. (Fig. 6)

This data is supported by the results of EUROPA study when following patient starting combination therapy

Tam/Sol after not sufficient response of monotherapy with Tamsulosin alone. Different aspects of quality of life (QoL) are all significantly better when using combination therapy [18]. (Fig. 7)

Adverse events of both drug classes are seen with combined treatment using α 1-blockers and antimuscarinics. The most common side-effect is dry mouth. Some side-effects (dry mouth or ejaculation failure) may show increased

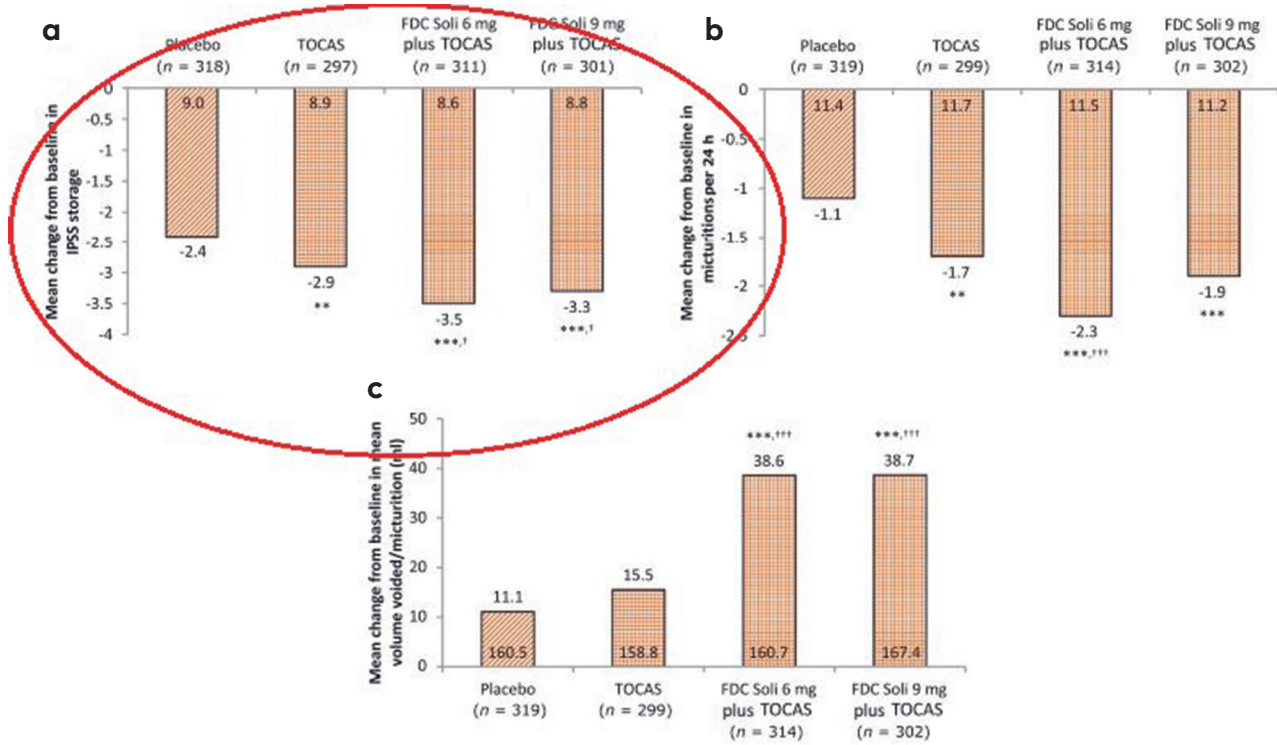


Figure 6. Results of NEPTUN study – placebo vs tamsulosin vs tamsulosin plus solifenacin.

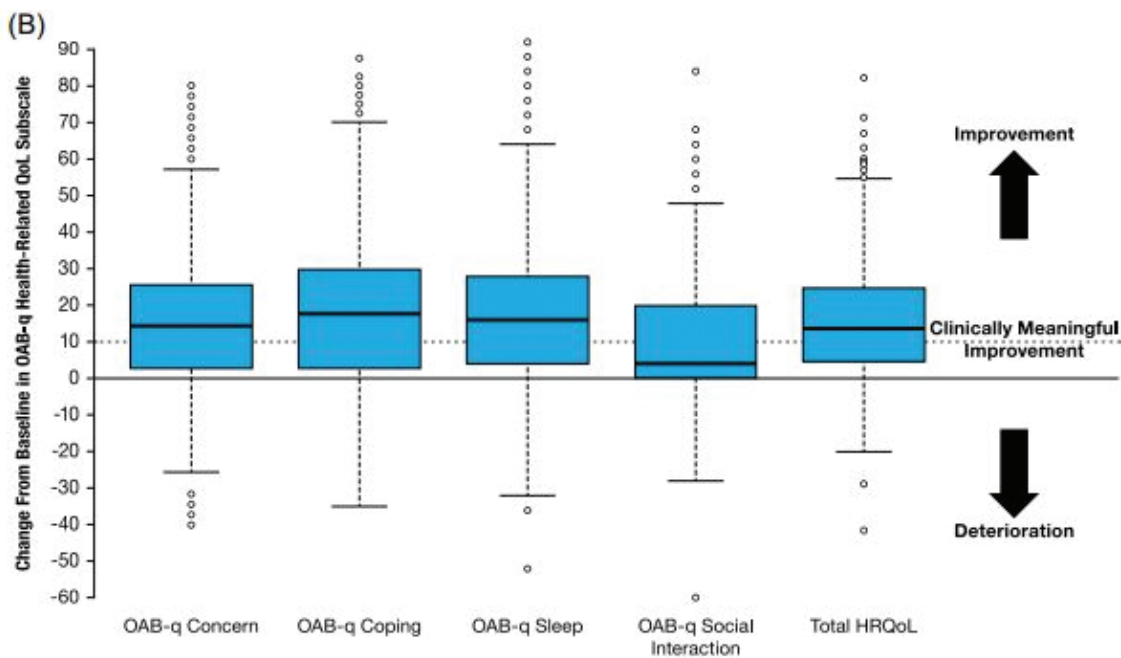


Figure 7. Changed in QoL from baseline (α 1-blockers only) vs added antimuscarinic drug.

incidence which cannot simply be explained by summing the incidence with the drugs used separately. Increased PVR may be seen, but is usually not clinically significant, and risk of acute urinary retention (AUR) is low up to one year of treatment, especially when PVR before treatment is below 150ml^[19].

The effect of some antimuscarinics which cross the blood-brain barrier (i.e. Solifenacin) to the central nervous system can worsen cognitive function especially in older men. Polypharmacy is quite common in elderly and the usage of antimuscarinics in combination with other drugs with antimuscarinic effect should be cautious.

Conclusion

Long-term therapeutic data show that the combination of α 1-blockers and antimuscarinics is much better than the monotherapy for LUTS with regard to storage symptoms and quality of life improves significantly. Side effects of combination therapy are similar to those of both drugs alone. The risk of AUR is small, but combination therapy should be avoided in men with PVR more than 150ml. Caution in elderly patients taking a lot of other drugs and with cognitive decline is advised when using antimuscarinics.

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Additional information

Conflict of interest

The author has declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

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Data availability

All of the data that support the findings of this study are available in the main text or Supplementary Information.

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