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Pharmacology of the lower urinary tract: update on LUTS treatment

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***Abstract*:** The number of compounds used in the pharmacological treatment of lower urinary tract symptoms (LUTS) of patients who do not respond to conservative measures has been relatively stable during the last decade, with the exception of the introduction of the new class of β3 adrenoceptor agonists. However, different combinations have been investigated, and the long-term use of these compounds has raised new concerns about adherence and safety. This review summarizes the current state of pharmacology for LUTS, and presents a thorough discussion of the possible challenges concerning their future use. In this narrative review, we analyze the most recent articles related to LUTS pharmacotherapy, after an initial review of mechanisms of bladder function relevant in present clinical practice. The main problems with pharmacotherapy in LUTS are associated with its moderate efficacy, low persistence on treatment, and the incidence of short- and long-term adverse events (AE) associated with some compounds. The long-term AE, such as cognitive impairment in the elderly vulnerable patients associated with antimuscarinic drugs or persistent erectile dysfunction in sexually active men after treatment with 5-α-reductase inhibitors (5-ARI), are some of the problems addressed in this review. Combination therapy taking advantage of the synergistic mechanisms of action between some classes of compounds may overcome AE associated with dose escalation. LUTS pharmacotherapy offers moderate results to most patients but not a full cure. The use of combination drugs to achieve better clinical results, reduce AE and improve both efficacy and adherence, will be used more frequently in the future. The recently raised concern on potential long-term irreversible AE associated with some of these drugs, like antimuscarinics and 5-ARI, are critically important and require further investigation.

Keywords: BPH, combination therapies, LUTS, OAB, oral pharmacotherapy, update

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Introduction

The lower urinary tract (LUT) is responsible for efficient low-pressure urine storage with normal sensation and perfect continence, and periodic, complete voluntary emptying. This system is composed of the bladder, the bladder outlet, the urethra, and the pelvic floor. Their function is synergic and coordinated by a complex innervation that includes the central and the peripheral nervous system.[1]

Abnormalities at any of these levels may result in bladder disorders, which can be classified roughly as storage and voiding dysfunctions. A disturbed storage function can, at least theoretically, be improved by agents decreasing detrusor activity or increasing its relaxation, and/or increasing outlet resistance.[2] Improvement of a disturbed voiding function is presently limited to agents that decrease outlet resistance. No drugs for clinical use are available to increase detrusor contractility in patients with symptomatic detrusor underactivity.

This review aims to update the actual pharmacotherapy for LUT symptoms (LUTS). Despite intense investigation into LUT pharmacology, there is an obvious stagnation in the number of drugs currently available for monotherapy. Additionally, available drugs, in general, have relatively low efficacy and low persistence on treatment, two drawbacks that combination therapy attempts to overcome. Another growing

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concern is the possibility that the long-term use of some drugs might cause permanent adverse events (AE), including impairment of cognition among vulnerable elderly subjects.

With this in mind, the first part of the work will review the mechanism of action of the drugs licensed to treat LUTS related to bladder outlet obstruction (BOO), to overactive bladder (OAB), and stress urinary incontinence (SUI). Due to the lack of drugs for clinical use in detrusor underactivity, this LUT dysfunction will not be addressed further.

Many other pathways have been identified as relevant to the control of urinary function. In the future, different pathways may result in new drugs, like the P2x3 receptor antagonist,[3] or even gene therapy.[4] For readers interested in the many pathways and receptors involved in bladder function that are not mentioned or explored in this paper, the authors recommend the review by Soler *et al*.[5]

Receptors and intracellular pathways relevant to licensed drugs used in LUTS management

The function of the LUT is dependent upon the activity of the smooth muscle in the bladder and striated muscles present in the urethral sphincter and pelvic floor. These structures are a functional unit controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors.[2,6] However, licensed drugs act only on three classes of receptors, among all those potentially involved in the control of detrusor and bladder outlet activity: the muscarinic receptors, the β3 adrenoceptors, and the α1 adrenoceptors.[2]

Two muscarinic receptor subtypes were identified in the bladder smooth muscle cells. The M2 are the most numerous receptors in detrusor but it is the less expressed M3 subtype that plays the key role in detrusor contraction.[7] The M2 and M3 muscarinic receptors have also been identified in sensory fibers and in the urothelium, but their role in the regulation of overall bladder function is not fully understood.[8] The M2 muscarinic receptors act *via* a G_i type receptor decreasing intracellular cyclic AMP (cAMP), which leads to inhibitory-type effects by decreasing intracellular calcium, inhibiting the voltage-gated $Ca^{2}+$ channels and ultimately increasing the efflux of K^+ ions, promoting smooth muscle relaxation. The M3 muscarinic receptors are G_q-coupled receptors that mediate upregulating the phospholipase C (PLC) and inositol trisphosphate (IP3) cascade, with consequent increase in intracellular calcium, leading to the smooth muscle contraction.[2,9]

Several studies have revealed that three subtypes of β adrenoceptors are present in the detrusor – β1, β2, and β3 –the latter being the subtype that predominates in both normal and pathological (neurogenic) bladders.[2,10,11] The conventional mechanism of action of β3 agonists implicates the activation of adenyl cyclase, with the formation of cAMP, leading to detrusor relaxation. However, an immunohistochemical study of the human bladder demonstrated expression of only the β3 adrenoreceptor in cholinergic terminal nerve endings, suggesting a possible role for this receptor in the release of acetylcholine.[12] Surprisingly, no β3 adrenoceptor expression was seen in smooth muscle cells, questioning the classical mechanism described above involving adenyl cyclase. The role of the β3 adrenoceptor expressed in sensory fibers is, as yet, unclear, although one might expect a modulation of bladder sensory input.[13]

The third type of receptor targeted by licensed drugs is the α1 adrenoceptors, especially the α1A subtype that predominate in the bladder neck and the prostatic stroma.[14] These receptors are transmembrane glycoproteins and are responsible for bladder neck and prostatic tone by released norepineprine. Once activated, a heterotrimeric G protein, G_q, activates PLC, causing an increase in IP3 and calcium, leading ultimately to the activation of protein kinase C. This cascade is responsible for maintaining smooth muscle tone.[1,6]

Regarding intracellular pathways, the first enzyme to be used as a target for LUTS improvement was 5-α-reductase (5AR). This enzyme converts testosterone to dihydrotestosterone (DHT), a potent androgen that regulates prostate metabolism. The rationale to decrease DHT levels with 5AR inhibitors (5-ARI) is to reduce prostate volume and prevent further prostate growth.[15] LUTS improvement is not expected to be a direct consequence of enzyme inhibition. Rather, one expects that prostate shrinkage will improve urine flow and, therefore, will reduce LUTS.

Another relevant enzyme in LUTS pharmacology is phosphodiesterase 5 (PDE5). Inhibitors of PDE5 (PDE5i) improve erectile function by increasing the concentration and prolonging the

activity of intracellular cGMP in cavernous smooth muscle, resulting in reduced muscle tone. In the bladder and the prostate smooth muscle, it is acknowledged that PDE5i also promote smooth muscle relaxation. Also, other effects might be expected, including an increase in bladder oxygenation, a reduction in collagen accumulation, a decrease of afferent nerve activity, and a reduction of potential local inflammatory activity.[16]

Duloxetine, a dual norepinephrine (NE) and serotonin (5-HT) reuptake inhibitor, is licensed to treat SUI in males and females. Both NE and 5HT receptors are abundant in spinal cord areas associated with LUT function, especially around the Onuf nucleus located in the sacral segments, which houses the nerves controlling the external urethral sphincter. An increase in the activity of these neurons was shown to enhance the resting tone and contraction strength of the urethral striated sphincter.[17] New compounds are being enrolled into clinical studies after positive results in animal models. At the moment, no other drugs acting on the central nervous system (CNS) are licensed to treat LUTS. However, some receptors may have some relevance. Gamma-aminobutyric acid (GABA) receptors exert an inhibitory effect on sensory fibers in the spinal cord. Drugs like baclofen and gabapentin, with agonist effect on these receptors,[18] have been used off label to treat urinary incontinence (UI) in spinal cord injured patients. However, large clinical trials were never carried out. The ubiquitous distribution of GABA receptors is a serious drawback in terms of AE. However, this can be overcome by the intrathecal administration of the drugs.

Antimuscarinics (anticholinergic drugs)

The 2019 *European Association of Urology* (EAU) guidelines recommend antimuscarinic drugs as a first-line option for adults with OAB storage symptoms when conservative measures fail. A clear preference for extended-release (ER) formulations is stated.[19] Antimuscarinics can be divided according to their molecular characteristics into a tertiary and quaternary amine, with trospium and propantheline being the only quaternary drugs. The difference between them is mostly in their lipophilicity and molecular size, which influences their ability to cross the blood-brain barrier and to pass into the CNS. Some tertiary amines, like darifenacin, have an active transporter out of the CNS. In terms of receptor selectivity, darifenacin is the only drug that can be considered M3 selective.[20] The majority of antimuscarinic drugs are metabolized by the cytochrome p450 enzyme system, and, for that reason, carry the risk of drug interactions by causing enzyme inhibition or enzyme induction. Generally, these drugs and their metabolites are not extensively excreted through urine, and, for that reason, in renal insufficiency, there is no need to adjust the therapeutic dose. Trospium is the exception. As a quaternary amine, it is not metabolized by the cytochrome P450 enzyme system and is eliminated extensively by the kidney.[21] All antimuscarinics are contraindicated in untreated narrow-angle glaucoma. Studies performed with current antimuscarinics showed that they provide relevant, albeit moderate, clinical benefit over placebo. Clinical benefits include a reduction of micturition frequency, urgency, incontinence episodes, and the number of pads used, and improvement of quality of life (QoL). The effect on nocturia was very limited or non-existent.[22–24] Some studies, including meta-analysis and head-to-head trials, comparing antimuscarinic drugs showed some advantages of solifenacin over tolterodine ER and fesoterodine over tolterodine ER.[20,25–27] A placebo control study, evaluating darifenacin clinical efficacy, concluded that, although having better efficacy than placebo, the results showed similar efficacy to placebo-controlled studies enrolling other antimuscarinics. Despite these studies, EAU guidelines were not able to indicate a first-line antimuscarinic. A recent meta-analysis of studies that used continence as an outcome revealed that these drugs have limited efficacy in terms of cure of UI. Overall, the study showed that, for all the antimuscarinic drugs, 8–10 need to be treated to have one patient cured.[26]

When treatment with an antimuscarinic is ineffective, the dose-escalation of antimuscarinics is a recommended alternative.[28] A meta-analysis published in 2012 summarizing a total of 76 trials evaluating the efficacy and safety of antimuscarinics concluded that the gain in efficacy with dose escalation was, however, inevitably accompanied by a higher incidence of typical anti-muscarinic AE.[27] Another alternative is to switch from one antimuscarinic to another. However, the CONTROL trial showed that cycling one antimuscarinic to another does not decrease the OAB symptom burden in patients who did not respond to the first drug prescribed.[29]

Most of the antimuscarinic drugs used in LUTS treatment have been investigated in predominantly female or female-only cohorts. However, the necessity of treating men with OAB symptoms led investigators to access the use of antimuscarinic drugs in men. One study evaluating the safety of tolterodine *versus* placebo in men with urodynamically demonstrated BOO concluded that tolterodine was well tolerated. Also, the latter study demonstrated that the urinary flow rate was unaltered, with no evidence of clinically meaningful changes in voiding pressure or urinary retention in the tolterodine arm.[30] The majority of similar randomized controlled trials (RCT) in men had a short duration (12 weeks), and most used tolterodine 4 mg as the antimuscarinic drug. Generally, antimuscarinic drugs significantly reduce voiding frequency and urge incontinence compared with placebo. Nocturia and International Prostate Symptom Score (IPSS) were also numerically reduced although not reaching statistical significance. The increase in post-void residual (PVR) volume greater than 25cc *versus* 0cc in the placebo, or the incidence of acute urinary retention (AUR), was in general similar in the antimuscarinics and placebo arms.[30] One should, however, keep in mind that only patients with low PVR volumes at baseline were included in these studies. These drugs should, therefore, be prescribed with caution in elderly men, and regular evaluation of PVR urine is advised.

The most-reported AE are related to the widespread distribution of muscarinic receptors. Dry mouth is the most common and may affect up to one-third of patients. Many patients will also refer to constipation, blurred vision, and fatigue. In terms of antimuscarinic AE, meta-analyses found similar rates in all types of drugs except oxybutynin, which had a distinctive higher rate.[31] The incidence of AE, whatever the drug used, increases with age.[32] The use of antimuscarinics in elderly patients is a major concern, due to the cognitive dysfunction that may be associated with cumulative doses of drugs with anticholinergic effects.[33] One study demonstrated that patients taking anticholinergic drugs who were clinically evaluated annually during treatment had increased brain atrophy and cognitive decline (although in this study the majority of subjects were using antihistamines and gastrointestinal tract antispasmodics).[34] A study in diabetic patients showed that those taking solifenacin, oxybutynin, and tolterodine had increased risk of dementia, with oxybutynin having the highest risk among the three.[35] It may, however, be recalled that solifenacin was tested in patients with mild cognitive dysfunction during three periods of 21 days and no cognitive decline was detected during exposure to solifenacin.[36] The cognitive effects of fesoterodine in elderly patients were also investigated in 12-week studies without any evidence of short-term cognitive deterioration in the mini-mental state examination.[37,38] An observational study with patients older than 70 years with OAB, evaluating safety and efficacy of solifenacin in flexible doses, also did not show any relevant effects on brain function evaluated by the mini-mental state test.[38,39]

The main problem with antimuscarinic therapy is the low rate of persistence on treatment.[40] EAU guidelines could not identify one particular antimuscarinic drug that could be pointed out as offering better persistence. The most common causes of abandoning therapy are the lack of efficacy and the incidence of AE.[31] Risk factors to discontinue antimuscarinic therapy include younger age and male gender.[40] Immediate release (IR) formulation drugs present shorter persistence on treatment, with half of patients stopping the treatment within the first 3 months.[41] Although the persistence on treatment with ER formulations is slightly higher, the rates observed upon prescription in European and North American countries are still disappointing.

β3 adrenoceptor agonists

This new class of drugs is now a first-line pharmacologic treatment option to patients in whom OAB storage symptoms are refractory to conservative measures.[28]

In phase II and III clinical trials;[42,43] mirabegron 25 mg (available in some countries) and 50 mg once a day improves LUTS, including frequency and urgency incontinence. The initial findings were corroborated by systematic reviews and network meta-analysis of RCTs.[44] A head-to-head trial between mirabegron 50 and solifenacin 5 mg showed similar symptomatic improvements in daily episodes of frequency, urgency, and urge UI (UUI).[45] A sub-analysis of a phase III trial showed that mirabegron 50 mg is effective in patients refractory to antimuscarinic medication.[43] A study based on UK prescriptions showed that 50% of the patients will maintain the β3 adrenoceptor agonist more than 100 days over tolterodine 4 mg

ER.[46] Moreover, a real-life observational study among patients prescribed mirabegron 50 mg showed a persistence rate of 54% at 12 months, accompanied by meaningful improvements in QoL and health status.[47] Another study, comparing the persistence of mirabegron 50 mg and antimuscarinic in Canadian patients, performed by Wagg, also verified a higher adhesion rate with mirabegron at 12 months.[48] In general, the persistence with mirabegron at 12 months varies from 40% to 53%, while the antimuscarinics class ranges from 14% to 38%.[45] In all studies, the difference in terms of persistence profile is statistically relevant in favor of the β3 adrenoceptor agonist (β3-AR).

The efficacy and safety of mirabegron in males were studied by Nitti *et al.* in work directed to evaluate the safety of the drug in men with urodynamic demonstrated BOO. In a 12-week study, mirabegron 50 mg did not impair detrusor pressure or maximum flow rate (Qmax) compared with placebo.[49] In 2018, a new prospective, multicentric placebo-controlled study, evaluating the effects of mirabegron 50 mg in men with OAB symptoms during 12 weeks improved LUTS while showing a safety similar to that of placebo.[50]

Head-to-head comparisons between mirabegron and antimuscarinics are lacking. The relative efficacy of the two classes has been, however, investigated by systematic reviews. Efficacy of mirabegron 50 mg and most antimuscarinics for control of incontinence and urinary frequency seems to be similar. However, solifenacin 10 mg monotherapy and combination of solifenacin 5 mg plus mirabegron 25/50 mg may be more efficacious than the β3-AR agonist for some outcomes.[44]

In terms of AE, β3-AR has a better profile than antimuscarinic drugs, in phase III trials, the incidence of AE was very similar to that of placebo. A recent meta-analysis showed that Mirabegron 50 mg was significantly better tolerated regarding dry mouth, constipation, and urinary retention than antimuscarinics.[45,47] Mirabegron is contraindicated only in patients with severe uncontrolled hypertension (systolic ⩾180 mmHg or diastolic ⩾110 mmHg). However, in a head-to-head trial between mirabegron 50 mg and solifenacin 5 mg, changes in blood pressure were similar.[45] The concern of a potential effect on blood pressure originated from a dose-responsive elevation in blood pressure of approximately 3–4 mmHg in phase I studies. However, in subsequent phase II and III studies, blood pressure elevation was irrelevant and similar to those observed in the placebo arm.

Mirabegron, being devoid of cholinergic effects, is now recommended by EAU guidelines as a preferable pharmacological treatment in elderly OAB patients with, or at risk of developing, cognitive changes.[19] A *post hoc* analysis of pooled phase III data showed that mirabegron 25 or 25 mg caused improvements in frequency and incontinence in patients above 65 or 75 years of age that were numerically similar to those observed in the overall population.[36]

Mirabegron 25 mg, with the possibility of escalation to 50 mg, was compared against placebo in a 12-week study in patients over 65 years of age, in the Pillar study.[51] It was concluded that mirabegron significantly reduced micturition frequency and UI episodes over placebo. AE were mild. No hypertension found. Also, the Montreal cognitive assessment (MoCA) test that spots mild cognitive changes did not detect any change in the patients that received mirabegron. A recent large pooled study by Chapple *et al.* comparing AE between mirabegron and antimuscarinics also stated that AE was more common in those under antimuscarinics action (21.4%) than under mirabegron treatment (17.0%). The most significant differences were in the dry mouth and constipation rates in the elderly (⩾75 years).[52] The cardiovascular safety of mirabegron was specifically evaluated in a pool of 13,000 subjects, and no evidence of higher risk for cardiovascular diseases in the mirabegron group was seen.[53] These findings point to some β3-AR advantages over antimuscarinics in terms of safety.

Other β3 selective agonists are being developed and compared in terms of efficacy and safety in placebo-controlled trials. At the moment, solabegron and vibegron have concluded already phase IIB and phase III, respectively, and more molecules are currently in *in vitro* and animal studies. Based on results from Japanese phase III trials, vibegron received approval in Japan for the treatment of OAB. A placebo-controlled study showed that, at week 12, the frequency of nocturnal voiding was reduced from baseline both for vibegron 50 and 100 mg groups. The mean volume of nocturnal voids and the volume of the first nocturnal voiding were significantly greater in the vibegron groups than in the placebo group.[54] Tolerability of vibegron was similar to placebo, and no cases of hypertension were reported.

A multicenter randomized, double-blind, placebo-controlled phase IIb study conducted to determine the efficacy and safety of solabegron concluded that β3-AR significantly reduced symptoms in women with moderate to severe OAB and that the drug was safe *versus* placebo.[55]

α1 adrenoreceptor antagonist (α-blockers)

α-blockers agents are the drugs used most commonly for male LUTS treatment, whether or not related to benign prostatic enlargement (BPE). According to EAU guidelines, α-blockers are considered the first-line drug treatment for men with moderate-to-severe LUTS. Drugs available include alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin. Indirect comparisons between a1-blockers and limited direct comparisons demonstrate that all α-blockers have similar efficacy.[56] Placebo-controlled studies have shown that the IPSS can be reduced by 35–40%.[57] However, one must realize that total IPSS does not indicate if the improvement results from a decrease in voiding or storage symptoms. It is well known that α-blockers are more effective in improving voiding symptoms. Many patients will maintain persistence storage symptoms that may require drug combination (see below). α1-blockers neither reduce prostate size nor prevent AUR, in long-term studies.[56,58] Analysis of the tamsulosin arm of the COMBAT study,[59] and a meta-analysis with terazosin, suggest that, in the long term, treatment α-blockers might be slightly more effective in decreasing IPSS in men with small than in men with large prostate glands.[60,61]

The last approved α-blocker was silodosin, a super-selective α1 subunit A blocker, with 162-fold greater affinity for the α1-A subunit than for the α1-B subunit of the adrenergic receptor and about a 50-fold greater affinity for α1-A than for α1-D adrenergic receptor.[57] However, systematic analyses of placebo-controlled studies show that all non-selective α1-A-blockers and silodosin have very similar efficacy in reducing symptoms and improving urinary flow. A head-to-head trial between silodosin 8 mg against tamsulosin 0.4 mg in patients older than 50 years showed that silodosin was not inferior to tamsulosin in improving both storage and voiding LUTS. The superiority of silodosin 8 mg over tamsulosin 0.4 mg could be demonstrated only in the capacity to reduce bothersome symptoms related to nocturia (>2 episodes) in further *post hoc* analysis.[62]

Qmax improvement after the α-blocker is moderate. EAU guidelines estimate an average increase of around 20–25%.[63] A recent meta-analysis by Fusco *et al*. evaluated urodynamic outcomes in patients with LUTS related to benign prostatic enlargement (LUTS/BPE). The primary endpoint was the BOO index (BOOI), and secondary endpoints were Qmax and detrusor pressure. It was concluded that α-blockers improve moderately Qmax and decrease BOOI, in patients in men with urodynamically demonstrated BOO.[64]

Common side effects of α-blockers are dizziness, rhinitis, headache, asthenia, and postural hypotension. The latter is not observed with silodosin, which, on the other hand, induces a much higher incidence of dry ejaculation than the non-selective α-blockers. The fewer cardiovascular side-effects of silodosin can be relevant when deciding the α-blocker for elderly patients with concomitant cardiovascular comorbidities. On the other hand, the high incidence of dry ejaculation with silodosin does not favor the use of this agent in sexually active younger males.[57]

Although being a drug with several years of prescription, mainly in older men, the debate on whether α-blockers, especially tamsulosin, could increase the probability of mental impairment was recently raised. The rationale is that CNS would be impaired by the blockade of a1-adrenoceptors in the brain. Evidence supporting the link between tamsulosin and dementia was found in a study by Duan *et al*., in 2017, comparing the incidence of cognitive impairment in men using tamsulosin with men taking other BPE-medication. After a median period of 20 months of follow up for all cohorts, the results indicated that men taking tamsulosin had a higher incidence of mild-to-moderate dementia, with statistical significance (incidence: 31.3 *versus* 25.9/1000 person-years; hazard ratio: 1.17). The effect of tamsulosin on cognitive function was described as dose related. The only drug with a similar incidence of dementia was alfuzosin ($p = 0.39$).[65] This study was strongly criticized. A response, in *European Urology* in 2018,[66] pointed out the high probability of selection bias, since the safest cardiovascular profile of tamsulosin led physicians to prescribe the drug in men with more comorbidities, with an increased probability of already having some degree of dementia. At the same time, the time of follow up was relatively short to determine the association so clearly, particularly for a

compound that has a minimum penetrance in the blood-brain barrier – although this could be questionable. A Korean nationwide population-based study from 2019, involving approximately 60,000 patients undergoing different α-blockers (tamsulosin, doxazosin, alfuzosin, terazosin) re-accessed this issue, calculating the incidence of *de novo* dementia in these patients after longer exposure, with a median duration of 50 months.[67] No association between α-blockers and dementia was found. The authors concluded that BPE medication was not associated with an increased risk of developing dementia in men. Nevertheless, In the future, high-quality prospective studies are warranted to elucidate the possible relationship between BPE medication and cognition.

Adherence to medical therapy shows a clear decrease with time. In a large Italian data basis with over a million patients, the proportion of those who continued α-blockers up to 10 months was 70%, This rate decreased to 35% at 12 months. In men who received a prescription for at least 6 months, the 1-year adherence was 29%.[68] In a US database, the percentage of men persisting on medication for ⩾4 years was 48%.[69]

5α-reductase inhibitors

Only two 5-ARI available for clinical use; these two differ in their activity against 5-AR isoenzymes. Finasteride inhibits preferentially type II 5-AR isoenzymes and prevents, by 70%, the conversion of testosterone to DHT. Dutasteride inhibits both types I and II isoenzymes, preventing 95% conversion of testosterone to DHT.[70] Despite these different profiles, there are no relevant clinical differences between them. In a head-to-head comparative trial between the two drugs, the conclusion was that, in terms of LUTS improvement, Qmax, and prostate volume variation, the drugs had similar efficacy at 1 year follow up.[71,72]

Clinical effects of 5-ARI are seen after a minimum treatment duration of at least 6–12 months.[59] After 2–4 years of treatment, 5-ARI reduce IPSS by 15–30%, increase Qmax by 1.5–2.0 ml/s, and reduce prostate volume by 18–28%.[73] 5-ARIs decrease prostatic specific antigen (PSA) by 50% within 6–12 months.[71] 5-ARIs show little efficacy in patients with prostates smaller than 40 ml.

A very important feature of the 5-ARI is that, contrary to α-blockers, these drugs can change the natural history of BPH, reducing the risk of long-term complications like AUR and BPE-related surgery. This is particularly evident in patients with large prostate glands and high total serum PSA. Reflecting this information, EAU guidelines recommend 5-ARI in men with moderate-to-severe LUTS, prostate volume over 40 ml, and an increased risk of disease progression.

Regarding AE profile, both finasteride and dutasteride exhibit similar profiles. Up to 10% of patients report sexually related events, like erectile dysfunction (ED), decreased libido, and decreased volume of ejaculate. In placebo-controlled trials, the incidence of these AE in the active arm was nearly twice the incidence in the placebo arms.[74] Some alarms concerning the non-reversibility of sexual AE were recently raised. A study in 2017 evaluated the risk of developing persistent ED (ED for more than 90 days after stopping 5-ARI) in men undergoing medical therapy with 5-ARI. In this study, persistence ED affected one-third of the men who complained of ED during exposure to the 5ARIs. This percentage represents 1.4% of men with 5-ARI exposure (0.1 mg of finasteride, 5 mg of finasteride or Dutasteride) who developed *de novo* persistent ED. The long duration of exposure to 5-ARI was the most accurate predictor of persistent ED, from all the risk factors accessed.[75] Interestingly, a recent pre-clinical study, in rats, also concluded that long-term 5-ARI medication can result in persistent ED.[76] Further prospective studies are warranted, since they may restrict the use of these drugs in the future. A critical aspect of the efficiency of 5ARIs is long-term adherence to the medication. EAU guidelines strongly highlight discussion of this aspect with candidates for the medication to obtain the ideal effect. However, in real life, long-term adherence is low. An Italian database shows that the proportion of patients who continued 5ARIs up to 10 months does not reach 60%, and is only 18% at 1 year.[68]

A recent retrospective study by Sarkar *et al.*, involving more than 80,000 subjects diagnosed with prostate cancer (PCa), evaluated the use of 5-ARI previous to prostate cancer diagnosis, and its possible prognostic role. They considered the use of 5-ARI in at least in the 12-months before the diagnosis, and compared PCa characteristics in patients with and without previous 5-ARI (with and without AB). This retrospective study reinforces the hypothesis that 5-ARI delays PCa diagnosis and worsened PCa outcomes, reinforcing

the need to perform a prospective study in this area and the need to establish guidelines in PCa screening in this subset of patients.[77]

Phosphodiesterase 5 inhibitors

Since 2002, after the first study suggesting beneficial effects of PDE5i in LUTS/BPE, multiple studies have been published using PDE5i drugs alone or in combination with α-blockers for the treatment of male LUTS. Until now, only tadalafil 5 mg once daily has been licensed. A meta-analysis of 12 studies, seven placebo-controlled, with 3214 men, and 5 studies on the combination of PDE5i with α-blockers with 216 men, was carried out.[78] Although the conclusions were limited by the short, 12-week, duration of the studies, the use of PDE5i alone was associated with a significant improvement in both IPSS score and International Index of Erectile Function (IIEF) score, although no changes in Qmax were observed. The association of PDE5i and α-blockers was superior to α-blockers alone in improving IPSS score, IIEF score, and, unexpectedly, also increasing Qmax.[78] The latest 12-week prospective study comparing tadalafil 5 mg, tamsulosin 0.4 mg once daily and placebo for 12 weeks revealed similar improvements in IPSS in both tadalafil and tamsulosin groups. As one could expect, the improvement of the IIEF score was observed only in the tadalafil arm. Qmax increased significantly after either tadalafil or tamsulosin.[79] In 2019 EAU guidelines, it is strongly recommended to use PD5i in men with moderate-to-severe storage and voiding LUTS with or without ED.

Plant extracts

This class of agents includes a heterogeneous group of plant extracts, either from a single plant or from preparations obtained from two or more plants. The most widely used plants are *Cucurbita pepo* (pumpkin seeds), *Hypoxis rooperi* (South African star grass), *Pygeum africanum* (bark of the African plum tree), *Secale cereale* (rye pollen), *Serenoa repens* (syn. *Sabal serrulata; saw palmetto*) and *Urtica dioica* (roots of the stinging nettle).[80]

The mechanism supporting for using these products remains unclear. It had been suggested that plant extracts have anti-inflammatory properties or could inhibit the conversion of testosterone to DHT. A placebo-controlled study with *S. repens* in patients with chronic prostatitis, showed that patients who received the plant extract had less histological and immunohistochemical signs of prostatic inflammation.[81] The randomized Complementary and Alternative Medicine for Urological Symptoms (CAMUS) study, compared the effect of *S. repens* administration during 72 weeks on serum PSA levels and found no differences between patients that received the plant extract or the placebo, failing to demonstrate a robust effect on the DHT pathway.[82]

The CAMUS trial did not show a difference between *S. repens* and placebo in changes in IPSS scores.[83] However, a meta-analysis of available studies found that treatment with *S. repens* reduced nocturia and improved Qmax compared with placebo, and had efficacy similar to that of tamsulosin and short-term 5-ARI treatment for relieving LUTS. A Cochrane meta-analysis on *Pygeum africanum* suggested that men treated with this plant material were twice as likely to report symptom improvement compared with placebo.[84] However, it should be borne in mind that many comparative studies enrolled patients with very mild IPSS scores at baseline. Due to all of these contradictory data, the EAU guidelines do not give any specific recommendations for phytotherapy in the management of male LUTS.

Noradrenaline and serotonin reuptake inhibitor

Duloxetine, in a posology of 40 mg twice daily is the only approved drug to treat SIU in females ineligible, or waiting, for surgical treatment.[19] Duloxetine was evaluated as a pharmacologic treatment for female SUI or mixed UI (MUI) in three different studies. One reported a cure rate for UI in 10% of patients.[85] No improvement in QoL was found in a study using incontinence QoL (I-QoL) as a primary endpoint. A more complex study, comparing duloxetine, 80 mg daily, with pelvic floor muscle therapy (PFMT) alone, PFMT with duloxetine, and placebo, concluded that duloxetine was superior in reducing incontinence compared with PFMT or no treatment.[86] Two open-label studies, with a follow-up of at least 1 year, evaluated the long-term effect of duloxetine. Treatment discontinuation due to a high incidence of AE was common in all studies. The most common AE are nausea and vomiting (at least 40% of patients), dry mouth, constipation, dizziness, insomnia, somnolence and fatigue, and potential risk of suicide.[87,88]

Duloxetine was also investigated in men suffering from post-prostatectomy incontinence. One high-quality RCT showed that the drug can speed up continence but does not increase the final number of patients fully continent.[88]

A new compound of this class, litoxetine, is under study in an ongoing clinical trial enrolling women with MUI. This drug is an oral selective 5-HT reuptake inhibitor and a multifunctional 5-HT agonist–antagonist. Animal studies data confirmed the potential of this drug in humans. The study started in 2017, and, although there are no published results in terms of efficacy, litoxetine seems to have a good safety profile in patients without a recent history of mental health disease.[89]

Combination therapies

The rationale of using combination therapies is to take advantage of different mechanisms of action to obtain higher treatment efficacy, eventually using lower doses and decreasing potential AE related to dose escalation. Generally, combination therapies should be used as second- or third-line pharmacological options. Despite general evidence that they increase efficacy, the combined administration of two drugs is more expensive for patients.

Antimuscarinic plus β3 adrenoceptors agonist

Taking into consideration the distinct mechanism of action of antimuscarinics and β3-AR, several studies have investigated the combined administration of the two drugs in OAB patients when monotherapy is ineffective. Two strategies were investigated, the add-on and the fixed combined modality.[90,91]

The comparing combination treatment (Solifenacin plus Mirabegron) with one treatment alone (Solifenacin; BESIDE) study, conducted in patients with incontinence resistant to solifenacine 5 mg concluded that adding mirabegron 50 mg to solifenacin 5 mg was more effective in reducing urinary frequency and UUI than the escalation of solifenacine monotherapy to 10 mg. Also, the combination therapy also avoided the increment of AE such as dry-mouth and constipation observed with the escalation of solifenacin.[90] On the other side, a multicenter, randomized study in Japan (MILAI II) evaluated patients initially treated with mirabegron 50 mg and persistence of OAB symptoms.[92] These patients were randomized to receive mirabegron 50 mg/day plus an antimuscarinic (solifenacin 5 mg, propiverine 20 mg, imidafenacin 0.2 mg, or tolterodine ER 4 mg) with the potential to double the antimuscarinic dose (except for tolterodine) at week 8. It was concluded that all combination treatments brought significant improvements in all efficacy parameters, including the total OAB symptom score (OABSS). Overall, 80.2% of patients experienced at least one treatment-emergent AE, with similar rates for all drugs.

The efficacy and safety of combinations of mirabegron and solifenacine compared with monotherapy and placebo in patients with OAB (SYNERGY) study evaluated fixed combinations of mirabegron and solifenacin. The study, with a 12-week duration randomized patients to placebo, to monotherapy with mirabegron or solifenacin, or different fixed-dose combinations of mirabegron (25 mg or 50 mg) with solifenacin (5 mg). The results showed improvements in efficacy compared with the respective monotherapies, with effect sizes generally consistent with an additive effect.[93] Following the SYNERGY study, the SYNERGY II was reported in 2018.[91] In this study, the combination of solifenacin 5 mg and mirabegron 50 mg was compared with monotherapy with mirabegron 50 mg or solifenacin 5 mg. After 2 weeks of placebo run-in, patients were distributed into three groups and remained in therapy for 12 months. The results supported previous studies that indicated a better efficacy and a good safety profile of the combination therapy in long-term use. In terms of efficacy, the combination therapy was statistically superior to monotherapy in the primary and most secondary endpoints. In terms of AE, cardiovascular and urinary events were the most common and they were generally comparable with solifenacin monotherapy.

α1-blocker plus antimuscarinic

As male LUTS very often include voiding and storage symptoms,[94] a combination of α-blockers and antimuscarinic drugs find a rationale to relieve storage symptoms that persist after α-blocker medication. Two strategies were investigated: the add-on and the fixed combination. In the add-on therapy, antimuscarinics are added to α-blockers in patients with persistent storage symptoms. Several studies demonstrated a significant reduction of LUTS scores and improvement of QoL

after adding the antimuscarinic drug. No acute urinary retention was observed even in patients with urodynamically proven mild or moderate BOO. The combination of the antimuscarinics did not affect significantly urine flow or PVR volume.[95–98] Two studies evaluated the fixed combination of tamsulosin 0.4 mg and solifenacin 6 and 9 mg *versus* tamsulosin alone and placebo in men with moderate-to-severe LUTS.[95,99] The results of these studies showed that the combination of solifenacin 6 mg and tamsulosin significantly improved storage and voiding symptoms, as well as QoL parameters, over placebo. In a 52-week extension of the initial studies, clinical efficacy was maintained while urinary retention occurred in only 1.1% of the patients, with only 0.7% of them requiring a permanent catheter.[100,101] A study by Barkin *et al.*, from Canada,[102] evaluated the persistence of medical therapy with an α-blocker alone *versus* α-blocker and antimuscarinic, in patients with HBP and storage symptoms, at 12 months. In this study, patients on combination therapy remained more days in treatment – although the difference was not statistically significant against monotherapy. The authors concluded that the additional medication burden did not have a negative effect on therapy adherence.[102] A total of 1891 men in the Netherlands receiving an α-blocker plus an antimuscarinic in fixed-dose or concomitant therapy showed that the median time to discontinuation was significantly longer with the fixed combination (414 *versus* 112 days; $p < 0.0001$). Persistence at 12 months was 51.3% *versus* 29.9%, respectively.[103]

Currently, the use of muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms is strongly recommended by EAU guidelines.[28]

α1-blocker plus β3 adrenoceptor agonist

The rationale of using the combination of α-blockers with β3-AR is the same as the combination of α-blockers with antimuscarinic drugs, the persistence of storage symptoms following an initial period of α-blocker monotherapy. β3-AR antagonist receptors may be more attractive to physicians than antimuscarinics, following the safety demonstration by Nitti *et al.*[49] To evaluate the add-on therapy with tamsulosin and mirabegron, 536 patients with BOO and OAB were enrolled in a double-blinded, placebo-controlled study in Japan. Patients in the tamsulosin group (0.2 mg) who received mirabegron 50 mg had lower urinary frequency and a lower score in the OABSS. Combination therapy AE were rare and the incidence of urinary retention was similar in both groups.[104]

A recent 12-week, phase IV, randomized, double-blind, multi-center study, the PLUS study,[105] was carried out to access the efficacy and safety of this combination with tamsulosin doses of 0.4 mg used in Europe and North America. After a run-in period of 4 weeks, men were randomized to placebo or mirabegron 25 mg with escalation to 50 mg at week 4. The primary endpoint, the change from baseline to end of treatment in the number of micturitions per day confirmed the superiority of the combination therapy. The combination therapy was safe. In particular, no changes in PVR volume or Qmax were found, and the risk of AUR was similar between the two arms.

In 2019 EAU guidelines, the use of β3-AR in men with moderate-to-severe LUTS who maintain bladder storage symptom has a weak recommendation, reflecting the paucity of studies.

α1-blocker plus 5α-reductase inhibitor

The distinct mechanisms of action of α-blockers and 5-ARI lead to the investigation of combination therapy. Two large trials were performed to compare the effects of monotherapy *versus* combination therapy: the medical therapy of prostatic symptoms study (MTOPS) and the combination of avodart and tamsulosin (CombATs) study (the latter without a placebo arm). The two studies differ in the mean prostate volume at baseline, in the CombAT study being greater than in MTOPS (55.0 ml *versus* 36.3 ml).[106] Nevertheless, both studies have demonstrated the superiority of combination therapy over monotherapy in preventing symptomatic progression, risk of AUR and BPE-related surgery.[59,61] Today, combination therapy with α-blockers and 5-ARI is recommended by the EAU guidelines for patients with moderate-to-severe LUTS and an increased risk of disease progression (higher prostate volume, higher PSA serum concentration, advanced age, higher PVR, lower Qmax). Combination therapy should be used only when long-term treatment (more than 12 months) is intended, and patients should be informed about this. Adherence to the combination therapy seems to be directly correlated with the severity of BPE symptoms, the more severe the symptoms, the higher the adherence rate to the combination treatment. In a

nationwide Korean database, adherence to the combination was 36% at 6 months and 28% at 12 months. Data also suggested that patients were more adherent to combination therapy than monotherapy. In the Italian database, adherence was 34% at 6 months but only 9% at 12 months.[68] A review article by Barkin, based on MTOPS and CombAT, showed the acceptability of combination therapy of dutasteride/tamsulosin in fixed-dose over monotherapy, based on the number of study participants that requested continuation of the treatment, suggesting superior adherence to the combination therapy.[107]

According to some studies, the timing of initiating combined therapy is important to clinical outcomes. Results from a prospective study indicated that patients initiating ARI5 earlier than 30 days after α-blocker had a lesser probability of clinical progression, AUR, and BPE-surgery than patients who delayed the introduction of the A-RI5. For each 30-day delay in adding 5-ARI to α-blockers, the average probability of overall clinical progression was 21.1%, the risk of AUR was increased by 18.6%, and prostate-related surgery was increased by 26.7%. More prospective studies are needed to corroborate these findings.[108]

In men with moderate LUTS under combined therapy, the discontinuation of the α1-blocker after 6, 9, or 12 months of combination therapy may deteriorate their LUTS.[107,109]

The disadvantages of combination therapy are the increased cost and the increased incidence of side-effects – characteristics of both classes of drugs.[106]

Conclusion

The high prevalence of LUTS in the population above the age of 40 years requires the frequent prescription of drugs. Therefore, functional urologists and physicians, in general, require a solid knowledge of LUT pharmacology, and on the efficacy and safety of licensed drugs.

The introduction of β3-AR will progressively challenge the use of antimuscarinics in monotherapy. The use of combined pharmacotherapy will slowly increase to enhance efficacy and reduce potential AE related to dose escalation.

Strategies to improve adherence need to be implemented in clinical practice, taking into consideration the low persistence seen in most drugs in use for LUTS treatment. In this context, phenotyping patients may help select the ideal treatment for the right patient.

The development of new drugs to treat LUTS is major proof that innovation and better solutions are needed for the pharmacological treatment of LUTS.

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The authors declare that there is no conflict of interest.

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