Treatment of Overactive Bladder in Elderly Patients: Clinical Considerations

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ABSTRACT: Overactive bladder (OAB) is a highly prevalent disorder among elderly and frail elderly patients, who are frequently polymedicated, suffer from kidney and liver failure and are susceptible to adverse events. Particular attention is, therefore, being given to efficacy and side effects of the treatment in patients older than 75 years. The introduction of newly developed drugs specifically designed for the treatment of OAB is opening new frontiers on this respect. The authors summarize the most recent evidence on this topic.

KEYWORDS: overactive bladder, treatment, elderly patients

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Introduction

According to the International Continence Society, overactive bladder (OAB) is a symptom syndrome defined by the presence of urgency, with or without urgency urinary incontinence (UUI), usually accompanied by frequency and nocturia, in the absence of infections or other obvious pathology.[1] Urgency, a sudden desire to void that is difficult to defer, is the pivotal symptom, but it is very often accompanied by increased daytime micturition frequency (≥8 times/day) and nocturia (≥1 time/night). OAB is associated with UUI in up to 30%–50% of cases.[2,3] OAB frequently progresses over time, therefore many patients who initially suffer from "dry" OAB (without UUI) will develop "wet" OAB, with subsequently increased difficulty.[4] OAB's symptoms often lead to a significant decrease in patient's quality of life (QoL), and specifically in older population, it has been associated with a higher risk of falls and fractures, functional impairment, institutionalization, and depression.[5–7]

The prevalence of OAB in adults ranges from 12% to 17% in Europe, the USA, Canada, and Japan,[8,9] and it increases with age (up to 25% of people aged ≥ 65 years). In the European Prospective Investigation into Cancer and Nutrition (EPIC) study,[8] the prevalence of urgency in men younger than 40 years old was 7.1% and reached 19.1% for those older than 70 years, and in women, it was reported 9.7% for those younger than 40 years and 18.3% for those older than 70 years. With the increase in life expectancy, burden and costs of OAB are expected to increase in the next years. The first-line treatment for OAB is nonpharmacological measures.[10] If these therapies fail, then the next step is to use antimuscarinic drugs or mirabegron, the first β3-receptor agonist approved worldwide recently.

In the literature, we can find different definitions for elderly patients which are as follows:

- Elderly patients: the most common definition is "individuals older than 65 years old,"[11,12] although some authors also consider patients between 61 and 65 years old;[13]
- Frail elderly patients: individuals older than 65 years old with a clinical presentation or phenotype combining impaired physical activity, mobility, balance, muscle strength, motor processing, cognition, nutrition, and endurance (including the feeling of fatigue and exhaustion);[14] patients with multiple comorbidities, functional impairments such as walking or dressing difficulties, and any degree of cognitive impairment;[15]
- Vulnerable elderly patients: individuals with a score of ≥3 on the Vulnerable Elders Survey-13 who have >4 times the risk of death or functional decline over a two-year period versus those with scores <3.[16]

Given that OAB's incidence increases with age, there is a growing interest in the evaluation of the efficacy and safety of the treatment in elderly and frail elderly patients. We can find different opinions on this aspect, ranging from significant reductions in OAB symptoms[17] to a small effect on urinary leakage in the elderly with UUI.[18] There are also some

concerns about the use of antimuscarinics in the elderly due to the possibility of precipitating adverse effects (AEs) such as dry mouth, constipation, increased postvoid residual (PVR) urine, falls, or cognitive impairment.[19,20] Some authors even theorize that OAB in the elderly may be more severe, more likely to be refractory to treatment, or fundamentally different to OAB in younger patients.[21]

In addition, we also have to take into account that elderly patients frequently take many concomitant medications such as antiparkinsonian agents, antihistamines, antiemetics, antipsychotics, antivertigo, cardiovascular (CVS), antidepressants, muscle relaxants, and gastrointestinal drugs with anticholinergic activity.[22] Also, aging is associated with a reduction in first-pass metabolism that can influence the bioavailability of many of these drugs, probably due to a progressive reduction in liver volume and liver blood flow.[23] In contrast, some authors report that there are no significant differences in CYP3A4 activity between young and old populations in in vitro and in vivo studies and that the differences on pharmacokinetics depend more on the genetics than on the age of the patients.[24,25]

The aim of this study was to perform a narrative review summarizing the most recent evidence regarding the treatment of OAB in elderly patients (65 years or older).

Conservative Treatment

The National Institute for Health and Care Excellence (NICE) clinical guideline (CG) 171 recommends giving patients OAB drugs only when the condition has not improved with conservative management alone.[15,26] This guideline is specially addressed at women. Weight loss (if overweight), managing constipation, reducing caffeine intake, bladder training, timed/prompted voiding, pelvic muscle exercises, and biofeedback are all intended to improve bladder control by changing the patient's voiding habits and teaching skills for preventing urine loss with the least risk of harm. This may be challenging to implement effectively in elderly patients with cognitive impairment, mobility disorders, or other debilitating conditions.[27]

Urinary incontinence, especially in the elderly, can be worsened or caused by cardiac failure, chronic renal failure, neurological diseases, obesity, etc., which cause polyuria, nocturia, increased abdominal pressure, or central nervous system (CNS) disturbances.[10] It is possible that the correction of the underlying disease may reduce the severity of urinary symptoms, although little evidence has been published.

Antimuscarinic Treatment

There are five different subtypes of muscarinic receptors in the organism which are as follows[28]:

- M1: These have been found in salivary glands, heart, brain, and eye;
- M2: bladder, gastrointestinal tract, heart, brain, and eye;
- M3: bladder, gastrointestinal tract, salivary glands, heart, brain, and eye;
- M4: brain and eye;
- M5: heart, brain, and eye.

M2 and M3 receptors can be found in the urinary tract with a 3:1 ratio, but M3 receptors are believed to be responsible for detrusor muscle contraction and consequently the most important from a functional perspective.

Antimuscarinic (anticholinergic) drugs are considered the mainstay of treatment for UUI, with several drugs that differ in their pharmacological profiles, pharmacokinetic properties, and formulation. It is recommended to review the therapy after four weeks after the start of each OAB drug treatment (through a telephone interview or face-to-face consultation).[15,26]

Cognition and antimuscarinic treatment. As previously mentioned, all five muscarinic receptor subtypes are present in the brain, and they are involved in higher cognitive processes such as learning and memory (M1 receptors play an important functional role in this regard).[28] M2 receptors are located throughout the brain, and the levels of M3 receptors are low. Muscarinic cholinergic receptor (mAChR) neurotransmission in the CNS is involved in human cognitive function including attention and working memory.[29] The affinity of the different anticholinergic drugs for the muscarinic receptors will influence the possible adverse events appearing in the patients.

It has also been described that the antagonism of muscarinic M1 and M2 receptors in the brain is also dependent on the drug concentration within the CNS, which is determined by the balance between drug penetration through the blood–brain barrier (BBB) and efflux.[30] Elderly patients are believed to be especially vulnerable due to age-related changes in drug elimination, increased BBB permeability, and reductions in muscarinic receptor density. The available evidence suggests that the use of drugs with a low affinity toward M1 receptors minimizes cognitive adverse events.[28,31]

A study by Fox et al included patients of a prospective community-based epidemiological study of random samples of people aged 65 years and older. They collected sociodemographic data, cognitive measures (including the Mini-Mental State Examination [MMSE]), medication, and activities of daily living of each participant, hypothesizing that the use of medications with possible and definite anticholinergic activity could increase the risk of cognitive impairment and death in older people. The study showed a dose-response relationship between greater total Anticholinergic Cognitive Burden (ACB) score, MMSE decline and death at 2 years, even after adjusting for age, sex, baseline MMSE score, education, social class, the number of non-anticholinergic medications, and the number of health conditions.[32]

The Aging Brain Care (ABC) is a team-based medical home dementia care model that supports and supplements the work of the primary care team and helps primary care providers achieve the recommended standard of care.[33]

They have developed the ABC Anticholinergic Cognitive Burden Scale in order to help physicians to identify those medications taken by the patients which can impair their cognition and state the severity of their anticholinergic effect.[34] These drugs with documented anticholinergic activity were identified through a systematic review of the literature before they were included in the scale. These tools can be found at http://www.agingbraincare.org.

Cardiovascular side effects. M2 receptors located in the heart modulate the pacemaker activity and atrioventricular conduction. Their blockage increases the heart rate.[35] However, several studies have shown a positive relationship between resting heart rate and all-cause and CVS mortality, pointing that even small increases in hearth rate sustained for prolonged periods and increase mortality risk,[36] particularly in patients with CVS disease. The prolongation of QT interval and development of serious tachyarrhythmias such as polymorphic ventricular tachycardia (*torsade de pointes*) have also been reported.[37] Some antimuscarinics (tolterodine, fesoterodine, propiverine, trospium) have been demonstrated in randomized controlled trials to increase heart rate,[38,39] but its clinical relevance is not yet determined. Does this suggest that we may be exposing patients to hidden cardiac risk due to the intake of antimuscarinic drugs prescribed for a "benign" disease such as OAB? Although CVS safety of antimuscarinics seems to be high, studies specifically evaluating CVS side effects of antimuscarinics, especially in the long term, are lacking. Antimuscarinics such as darifenacin, solifenacin, and oxybutynin with the highest selectivity for M3 receptors over M2 do not appear to affect heart rate.[39,40]

Oxybutynin. Oxybutynin is a relatively nonselective muscarinic receptor antagonist which has been used for ~30 years for the management of OAB. But in in vitro binding analyses, however, oxybutynin shows a three-, sixfold higher affinity for M3 than for M1 receptors.[41] It is available in three formulations: immediate release (IR, taken twice daily), extended release (ER, taken once daily), and transdermal (applied once every three days), allowing the treatment to be tailored to the patient's needs.[27] Oxybutynin ER is better tolerated than oxybutynin IR, having lower incidence and severity of dry mouth. Oxybutynin ER has the widest US Food and Drug Administration-approved dosing range (5–30 mg), which may facilitate the achievement of the optimum balance between efficacy and tolerability. The recommended starting dose is 5 or 10 mg/day.

Oxybutynin is also available in a transdermal formulation,[42] which may be considered for patients who are unlikely to adhere to oral therapy or who dislike multiple-dose daily regimens. Because transdermal oxybutynin does not undergo the first-pass metabolism in the liver, much lower concentrations of *N*-desethyloxybutynin (the responsible active metabolite for the anticholinergic side effects) are observed. In clinical studies, transdermal oxybutynin has been associated with a relatively low risk of side effects, the most frequent being application-site reactions that can be minimized by the application of local topical corticosteroid or antihistamine.

Lower cognitive AEs due to the transdermal application of oxybutynin have also been reported. Kay et al[43] showed, in a randomized, double-blind, placebo- and active-controlled study on 152 patients, that the transdermal application of oxybutynin chloride leads to no clinically significant cognitive or recent memory-related impairment compared with placebo and has fewer side effects (whereas there was a decline from baseline in one memory test [misplaced objects test] in the control group). It should also be mentioned that this trial was carried out only for seven days and that the study population includes not only the elderly patients with the age ranged 60–79 years but also the patients with the mean age of 68 years who meet the definition of elderly patients which is used in our review.

For the orally administered, oxybutynin IR, there is evidence that it can cause/worsen cognitive dysfunction in elderly patients.[44–46] At the NICE CG 171, it is stated that oxybutynin IR should not be prescribed to frail older women.[15] It has also been hypothesized that more rapid functional deterioration might result from the combined use of cholinesterase inhibitors with antimuscarinic agents in elderly patients with cognitive dysfunction.[47]

Trospium chloride. Trospium chloride, a quaternary ammonium compound, has the efficacy equivalent to twice-daily oxybutynin IR and a lower incidence of dry mouth.[48] Trospium is not metabolized by the cytochrome P450 (CYP) system and has a low propensity to cross the BBB.[49] Thus, despite a limited dose range and twice-daily dosing, this agent may be theoretically considered favorable in patients who are elderly and receiving multiple concomitant medications, although no evidence is available as to the comparative efficacy and side effect profiles of trospium in different age groups. Sand et al[50] reported a post hoc subgroup analysis of pooled data including 143 patients ≥75 years from two randomized clinical trials, concluding good efficacy and tolerability.

Tolterodine. Tolterodine was the first antimuscarinic drug specifically developed for OAB, and both the parent drug and its metabolite 5-hydroxymethyl tolterodine (5-HMT) are equally active. The formation of this metabolite is mediated by the CYP isoenzyme CYP2D6, which leads to a interpersonal variation of the plasma concentration (130-fold) based on the patient's CYP2D6 genotype (ranging from extensive to poor metabolizer).[51]

In a randomized, double-blind trial performed by Malone-Lee et al,[52] tolterodine and oxybutynin were equally effective for improving baseline urinary symptoms in OAB patients aged ≥50 years; patients taking tolterodine showed significantly lower rates of adverse events compared with those taking oxybutynin (22/190 patients on the tolterodine group and 28/188 on the oxybutynin group withdrew the study), and also they required fewer dose reduction. Mean ages in the tolterodine and oxybutynin groups were 65.4 years (range 49–87) and 64.8 years (range 50–90), respectively.

Fesoterodine. Fesoterodine, the isobutyric acid ester of 5-HMT, acts as a prodrug which undergoes hydrolysis by ubiquitous esterases to its active metabolite without the involvement of CYP2D6,[53] but 5-HMT is metabolized in the liver by isoenzymes CYP2D6 and CYP3A4 to nonactive metabolites. No dosing adjustment is recommended in subjects with mild or moderate renal impairment,[54] nor in patients with moderate hepatic impairment (hepatic cirrhosis Child–Pugh class B).[55] Concerning drug interactions, no dose adjustment is necessary in the presence of CYP3A4 inducers,[56] and it did not affect the pharmacokinetics or anticoagulant activity of warfarin in healthy adults.[57]

Chapple et al performed a systematic review of clinical efficacy and safety of fesoterodine.[17] They included articles reporting results in elderly patients with OAB, the most relevant study being the Study of Fesoterodine In an Aged population (SOFIA) trial. They also highlighted a study by Kay et al investigating the influence of fesoterodine on cognition.

The SOFIA trial, funded by Pfizer, had a 12-week, randomized, double-blind, placebo-controlled phase, followed by a 12-week, open-label phase in elderly (aged ≥ 65 years) patients (47% men) with OAB symptoms for ≥3 months, including ≥8 micturitions/24 hours and ≥3 urgency episodes/24 hours, and an MMSE score of ≥20.[58] During the double-blind treatment, patients received fesoterodine 4 mg or placebo once daily, with stratification according to age (≤75 or >75 years) and dosing time (morning or evening), and they had the option to increase the dosage to fesoterodine 8 mg. At week 12, fesoterodine significantly improved urgency episodes/24 hours and health-related QoL (HRQoL) versus placebo regardless of age group or dosing time. The most common adverse events reported were dry mouth (fesoterodine, 34%; placebo, 5%) and constipation (fesoterodine, 9%; placebo, 3%). No change in mean MMSE score was observed from baseline to week 12 in either the treatment group. During the open-label treatment with fesoterodine, improvements in OAB symptoms and HRQoL were maintained for patients who received double-blind fesoterodine, whereas patients treated with double-blind placebo followed by open-label fesoterodine achieved similar improvements in efficacy end points at week 24. Flexible-dose fesoterodine was generally well tolerated in both elderly and very elderly (aged > 75 years) patients with OAB symptoms.[58]

A double-blind, four-way crossover study performed by Kay et al assessed the effects of fesoterodine on cognitive function in 20 healthy older adults aged 65–85 years with an MMSE score of ≥26 at baseline.[59] Each subject received the following dosage: fesoterodine 4 mg for six days with placebo on day 6; fesoterodine 4 mg for three days followed by fesoterodine 8 mg for three days with placebo on day 6; placebo for six days; and placebo for six days with alprazolam 1 mg on day 6, with a three-to-six-day washout period between treatments. The changes from baseline to day 6 in computer-based cognitive test battery (CogState) and Rey Auditory Verbal Learning Test scores were not significantly different between fesoterodine 4 or 8 mg and placebo. There was a significant decline in cognitive function with alprazolam 1 mg versus placebo. The most common adverse events for fesoterodine were dry mouth (4 mg, 10%; 8 mg, 32%) and dizziness (4 mg, 10%), and sedation (53%) for alprazolam 1 mg.

A systematic review of drugs in regular use by elderly patients, which aimed to classify appropriate and inappropriate drugs based on efficacy, safety, and tolerability following the FORTA (Fit fOR The Aged) classification[60] found fesoterodine is beneficial in older persons or frail elderly people (FORTA B: drugs with proven or obvious efficacy in older people, but limited extent of effect or safety concerns), having beneficial outcomes in HRQoL and few cognitive adverse events.[61]

Solifenacin. Solifenacin succinate is a once-daily oral antimuscarinic with moderate selectivity for the M3 receptors.[62] In doses of 5 or 10 mg/day, it has demonstrated statistically significant reductions in urgency and urgency incontinence episodes, as well as in number of micturitions/24 hours and the mean volume/micturition.[63,64] In these trials, solifenacin also allowed restoration of continence in ~50% of previously urgency incontinent patients.

Solifenacin is extensively metabolized in the liver by the way of CYP3A4 and is partly excreted by the kidneys. Reducing doses to 5 mg/day is recommended if renal function is impaired (CrCl < 30 mL/min) and also in moderate hepatic function impairment (Child–Pugh B), being contraindicated in patients with severe hepatic failure (Child–Pugh C).[65]

In 2006, Adrian Wagg et al published a retrospective analysis of pooled data from four studies, to analyze the efficacy and tolerability of solifenacin succinate specifically in the older population (aged ≥ 65 years).[66] They found 1,045 subjects in four double-blind, placebo-controlled studies of 12 weeks with solifenacin 5 and 10 mg;[64] 509 of the subjects who completed two of these double-blind studies accepted to enroll on a 40-week, open-label, flexible-dose extension trial.[67] Their statistical analysis shows that solifenacin 5 and 10 mg significantly improves all symptoms of OAB in the elderly population (urgency episodes per day, incontinence episodes per day, micturitions per day, and also volume voided/micturition) with an acceptable profile of secondary effects that furthermore are dose related. Most AEs were mild to moderate and did not result in discontinuation of treatment. It seems to be reasonable to begin with 5 mg/24 hours and then evaluate efficacy and tolerability, especially in older population. The same authors developed a randomized, double-blind, placebo-controlled, triple crossover study—the SENIOR study—to assess the cognitive effects of solifenacin and oxybutynin in subjects older than 75 years with mild cognitive impairment.[45] They evaluate extensively short-term cognitive effects of once-daily solifenacin 5 mg and twice-daily oxybutynin 5 mg. Subjects were randomized in six groups, with different sequences to receive solifenacin, oxybutynin, and placebo.

All subjects received each treatment during 21 days, followed by 21 days of washout. Cognitive function was assessed at baseline and at the end of each period using a standardized tool (cognitive drug research) to evaluate five cognitive domains: power of attention, continuity of attention, quality of working memory, quality of episodic working memory, and speed of memory. Solifenacin showed no effect on these five cognitive domains in elderly subjects with baseline mild cognitive impairment, whereas oxybutynin was associated with a statistically significant decrease in both power and continuity of attention at 1–2 hours after administration.

Darifenacin. Chapple et al designed a preplanned study of efficacy, tolerability, and safety of darifenacin compared with placebo in patients aged ≥65 years which failed to reach the statistical significance on its primary outcome (UUI episodes), but they did note that the proportion of people who derived benefit from active treatment was greater than those who received placebo treatment.[68] The cognitive safety of darifenacin has also been extensively tested in a series of chronic dosing studies in cognitively intact older people.[69] The NICE CG 171 recommends to use the daily preparation of darifenacin as a first option in women with OAB, although they do not make any special remark on patients older than 65 years.[15]

An international consensus following the FORTA classification labeled darifenacin as being associated with CVS notes of caution, significant anticholinergic reactions, with frequent constipation in elderly patients, and mental deterioration not unequivocally shown, but used as argument of caution.[61]

Imidafenacin. This antimuscarinic drug is commercially available only in Japan since 2007 and is administered 0.1–0.2 mg once daily. Its short half-life is supposed to minimize the development of adverse reactions. Some authors report an improvement in nocturia and a reduction in nocturnal urine production, leading to a higher sleep quality and lower daytime sleepiness in patients older than 50 years and up to 90 years.[70,71] It has also been used in combination therapy with α-blockers in patients with benign prostatic hyperplasia (BPH) and urgency/urge urinary incontinence.[72] De novo or worsening of cognitive impairment has been described in elderly patients when taking imidafenacin, although it is reversible.[73]

An experimental study by Yamamoto[74] was designed to assess the quantitative relationship between the central mAChR occupancy and cognitive impairment by oxybutynin and imidafenacin in *Macaca mulatta* monkeys using *N*-[11C] methyl-3-piperidyl benzilate and the Titration version of delayed matching to sample (T–DMS) task. They found that monkeys that were given oxybutynin at therapeutic doses developed cognitive impairment, and the occupation of the central mAChR was demonstrated. In contrast, although the oral administration of imidafenacin at therapeutic doses occupied the central mAChR to some extent, it did not induce cognitive impairment at all, suggesting that there is a threshold above which this side effect appears.

Central muscarinic receptors are involved in higher cognitive processes such as learning and memory. It is generally accepted that M1 receptors play an important functional role in this regard.

β3-Adrenoceptor Agonist: Mirabegron

Mirabegron is the first β3-adrenoceptor agonist approved for the treatment of OAB in Europe, the USA, Canada, Australia, and Japan. It is the first drug in this class, acting through stimulation of β3-adrenoceptors located in the human detrusor muscle, leading to an active relaxation during the filling phase. Clinical effects are reductions in urinary frequency, urgency episodes per day, and incontinence episodes per day, as well as mean voided volume/micturition, number of nocturia/episodes, and patient-reported outcomes compared to placebo.[75,76]

Mirabegron's efficacy and tolerability specifically in older population (≥65 and ≥75 years) was analyzed by extracting data from three 12-week, randomized, Phase III trials and from a one-year safety trial in this subgroup of patients.[77] With regard to efficacy, mirabegron at doses of 25 and 50 mg/day reduced the mean number of incontinence episodes and the mean micturition frequency. In one of these 12-week studies as well as in the one-year trial, an active control drug (tolterodine ER 4 mg/day) was included, showing less effect than either dose of mirabegron in the subgroup of patients older than 65 and 75 years. A slight decrease in the efficacy of tolterodine with advancing age was also observed in a previous study.[78] Patients who reported zero incontinence episodes reached 43.4% with mirabegron 50 mg. Dry mouth and constipation, AEs of particular interest in the older population typically associated with antimuscarinics, are found similar to placebo in these studies (four- to sixfold higher incidence with tolterodine than with mirabegron 25 or 50 mg) Hypertension, headache, urinary tract infection, and nasopharyngitis occurred with an incidence of ≥3% in the one-year study. Small increases were also observed in pulse rate (~1 bpm from baseline) and systolic and diastolic blood pressure. These were, however, lower than observed with tolterodine. Serious AEs leading to the discontinuation of therapy were higher with tolterodine than with mirabegron or placebo (hypertension, constipation, dry mouth). The authors concluded that mirabegron was effective and safe in the older population, suggesting that it could be a more suitable first-line option than antimuscarinics for OAB in community-dwelling older patients.[77] But it is important to emphasize that these conclusions are derived from a single study. CVS and cognitive side effects, which are of major concern in older people, have not been extensively studied.[61]

Recently (July 2015), the European Medicines Agency recommended some variations to the terms of the marketing authorization and the summary of product characteristics based upon post-commercialization reports. Several cases of hypertensive crisis have been reported, such as cerebrovascular

and cardiac events that were associated with hypertension. They, therefore, recommend not to use mirabegron in patients with systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg.[79] Several cases of urinary retention with a plausible temporary relationship have also been reported with a frequency between 1/1,000 and 10,000 (classified as "rare" AE). Other secondary effects such as insomnia have also been reported, although at this time its frequency has not been determined.[80]

Other Drugs and Combination Therapies for OAB

In addition to antimuscarinics and the β3-adrenoceptor agonist mirabegron, there are further substances or combinations of common urological drugs that are assumed to influence OAB symptoms. We focus, in particular, on two monotherapies and two promising combinations of substances which are widely used in elderly urological patients. Unfortunately, the literature of in vivo studies or reviews about the specific action, the efficiency, or the AEs of drugs in addition to antimuscarinics or mirabegron regarding the OAB symptoms, in general, in elderly male population, in particular, is very poor. This lack of reliable data led us to consider the following selection of drugs/combinations.

Monotherapies: α-blockers and phosphodiesterase-5 inhibitors. In 2013, Kim et al investigated the suppressive effects of tamsulosin and sildenafil on the afferent pathways of micturition in female rats, which were divided into four groups: one tamsulosin-receiving group, one sildenafil-receiving group, one vehicle group, and one control group. Cystometric parameters as well as the expression of c-Fos and nerve growth factor in different micturition-related brain regions and the spinal cord as an indicator for neuronal activity in the central micturition regions and bladder overactivity were measured. The cystometric findings were significantly reduced basal pressure, duration of bladder contractions, and intercontraction intervals in the tamsulosin and sildenafil groups, with a stronger effect for tamsulosin. They also found a significant decrease in the neuronal activity in all investigated regions of the tamsulosin and sildenafil groups. They concluded that tamsulosin and sildenafil may have a positive effect in improving OAB symptoms due to an inhibition of afferent pathways of micturition, while there was shown a stronger effect for tamsulosin as for sildenafil.[81] But further studies are needed to corroborate these findings.

Another in vivo analysis of the functional responses of phosphodiesterase (PDE) isoenzyme inhibitors in isolated normal human detrusor cells with carbachol-induced tension was performed by Ückert et al in 2001. They showed that the PDE-5 inhibitor morpholinosulfonylpyrazolopyrimidine was most efficient in the reversion of tissue tension induced by carbachol among all tested substances.[82] It was, therefore, assumed that PDE inhibitors could play a role in UUI treatment.

A randomized, double-blind, placebo-controlled study on PDE-1 inhibitor vinpocetine in urgency and urge incontinence patients nonresponding to standard pharmacological therapy was also undertaken by Ückert et al in 2001. The study population includes both genders and a wide range of age distribution (18–85 years) with no statement of the mean patient age. Vinpocetine versus placebo was given for a four-week period; male patients taking vinpocetine showed a statistically significant decrease in the micturition frequency, while the other clinical outcome parameters such as bladder volume at first sensation, bladder volume at voiding desire, maximum detrusor pressure, and voided volume did not show a significant superiority to placebo.[83]

Another randomized, placebo-controlled study was carried out by Gacci et al in 2012 to assess the safety and efficacy of a 12-week vardenafil plus tamsulosin versus tamsulosin alone treatment of lower urinary tract symptoms secondary to BPH. The Over Active Bladder Questionnaire (OABq) was used to record any changes regarding urgency and urge incontinence. Even though the age distribution of the 60 randomized males ranged from 40 to 80 years, the mean was 68.4 and 65.8 years in the tamsulosin plus placebo and tamsulosin plus vardenafil group, respectively. Consequently, the majority of the observed patients will be elderly according to our underlying definition. The study revealed that there was a significant improvement according to the OABq in both groups after the 12-week testing period. The substantial increase in the improvement of the OABq in the vardenafil group was not shown in the between-group ANOVA analysis, so it cannot be clearly deduced whether the benefit results only from tamsulosin. The treatment was revealed to be save, and the main AE was headache that was noticeably higher in the vardenafil group (11/30 versus 2/30).[84]

Combination therapy: solifenacin and mirabegron. In 2014, Abrams et al released a 12-week randomized, double-blind, parallel-group, placebo- and monotherapy-controlled trial in 20 European countries, where the combination of solifenacin and mirabegron was compared with solifenacin monotherapy in 1,306 male and female patients ≥18 years with OAB symptoms. They demonstrated that in comparison with the monotherapy the combination of solifenacin and mirabegron leads to a significant improvement in the OAB symptoms such as mean volume voided per micturition, micturition frequency, and urgency without showing considerable additional harms.[85]

Due to the relative low mean age of the randomized groups (mean age within the groups 53.4–56.5 years), this study does not comply with our definition of elderly patients. But given the promising results, we think this approach is worth mentioning, even though we recognize a strong need for further studies to establish efficacy in elderly patients.

Combination therapy: solifenacin and tamsulosin. In 2013, Van Kerrebroeck et al published the results of a double-blind, 12-week study comparing a combination of solifenacin and tamsulosin with tamsulosin monotherapy and with placebo in 1,334 men (mean age > 65 years) with storage

and voiding symptoms. Significant reductions in the Total Urgency and Frequency Score were observed in the combination group compared with placebo and tamsulosin monotherapy. Furthermore, the combination therapy revealed to be well tolerated with a low incidence of acute urinary retention (AUR; seven cases of drug-related AUR in total) and improved QoL measures.[86] Studies reporting a longer follow-up are still needed to confirm the benefit in relieving OAB symptoms by the combination of solifenacin and tamsulosin and the good tolerance of this association.

In summary, there is evidence that OAB symptoms are reduced by α-blockers and PDE inhibitors as monotherapy or the combined therapy of the antimuscarinic solifenacin with mirabegron as well as solifenacin with tamsulosin. There is a need for further studies with long-term follow-up to systematically evaluate the therapeutic and the AEs of these medications and combinations, particularly in consideration of the growing population of elderly patients.

Botulinum Toxin

Onabotulinum toxin A (OnabotA; BOTOX®) 100 U dissolved in 10 mL of saline and injected in 20 points of the bladder wall above the trigone (0.5 mL per injection site) is licensed in Europe to treat OAB with persistent or refractory UUI in adults.[10] It is also a valid treatment option in select elderly patients with refractory detrusor overactivity,[87] since its tolerability is excellent and side effects are minimal. Common adverse events are urinary tract infections and transient PVR urine increase that may need clean intermittent catheterization.[10]

It is well known that the efficacy of OnabotA lasts for nine months on average, and repeated injections are required also in the elderly population. The continued efficacy of repeat injections is the rule, but discontinuation rate may be high.[10]

Neuromodulation

Posterior tibial nerve stimulation. Percutaneous tibial nerve stimulation (PTNS) is a technique of neuromodulation of the lower urinary tract performed through the stimulation of the posterior tibial nerve (L4-S3) over the medial malleolus, just 3–5 cm above the ankle. It has been proposed as a treatment option for OAB, non-obstructive urinary retention, and chronic pelvic pain/painful bladder syndrome. Although there are no specific data in older population, two recent systematic reviews have shown success rates between 37% and 100% in nonresponders to first-line therapy of OAB, with no major complications reported.[88,89] Only temporal effects such as mild–moderate pain in the site of the puncture, bleeding at insertion site, leg cramp, or numbness/pain at the sole of the foot have been reported in about 8.5% of treated patients. Establishing whether these promising results can be expected in the older population is a matter of study. Certainly, its favorable complication profile, combined with its nonpharmacological and almost noninvasive nature, makes PTNS a very attractive option for the treatment of OAB in elderly patients.

Sacral roots neuromodulation. Sacral neuromodulation (SNM) is considered a third-line treatment for refractory OAB, urge incontinence, and non-obstructive urinary retention.

Although SNM is not contraindicated in older individuals, it is typically used in younger patients due to some concerns about cost-effectiveness, life expectancy, and the report of some authors who achieved inferior outcomes in patients older than 55 years old.[90] We have to take into account the costs of the device, the expected results, and the performance status in elderly patients before performing the implantation.[91] On the one hand, Amundsen and Webster found 48% of responders with 2/12 patients remaining completely dry.[92] On the other hand, White et al performed a prospective longitudinal study in which they tested 17/19 elderly patients undergoing definitive implant and 11/17 patients with functional implanted devices at a mean follow-up of 49.16 months and achieved better results.[91] With a mean follow-up of 48 months, their results in older patients (≥70 years) were comparable with younger patients treated during the same period (2001–2008), therefore they concluded that sacral nerve stimulation was safe and effective in older population. Probably in the elderly, SNM is a viable option when there is an acceptable life expectancy, the patient is community dwelling and mobile, and also he/she is able to accurately report his/her symptoms.[93]

Conclusions

OAB in elderly and frail elderly patients is a challenging disorder, since antimuscarinics may have different pharmacokinetic properties in this age group and are frequently associated with other drugs with anticholinergic activity. A greater permeability of the BBB and a lower threshold in these patients are possibly the most important factors leading to adverse events.

In addition to the well-established therapies, there are some promising newer substances, application forms, or drug combinations which have been shown to be beneficial for (elderly) OAB patients. Recently developed antimuscarinics and β3-agonists have a more bladder-selective action and can reduce adverse events such as cognitive deterioration, constipation, and cardiac events.

More studies specifically addressed to patients older than 65 years old are still needed to give more accurate recommendations in elderly patients.

Author Contributions

Wrote the first draft of the manuscript: BPF, DHH. Contributed to the writing of the manuscript: SCM. Agree with the review and conclusions: DMCD, TCM. Made critical revisions and approved final version: DMCD. All authors reviewed and approved of the final manuscript.

Current available medical treatments for OAB in elderly patients	
Antimuscarinics	
Oxybutynin	Not recommended in frail elderly women,[15] cognitive adverse events also reported with the transdermal application[43]
Trospium chloride	Low propensity to cross the normal BBB.[49] Good efficacy and tolerability[50]
Tolterodine	Lower rates of adverse events than oxybutynin[52]
Fesoterodine	Unique drug having studies specifically designed for elderly patients.[58] Proven efficacy in older people, but limited extent of effect or safety concerns[61]
Solifenacin	Good symptoms' relief and good safety profile.[66] Patients with mild cognitive impairment do not worsen[45]
Darifenacin	Has not shown statistically significant improvements in elderly patients[68]
Imidafenacin	Commercially available only in Japan. De novo or worsening of cognitive impairment (reversible) has been reported[73]
β3-adrenoceptor agonist	
Mirabegron	Avoids cholinergic side effects. Good tolerability and efficacy.[76,77] Do not use if systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg[79]
Other treatments	
α-blockers and PDE-5 inhibitors	Studies not specifically addressed on elderly patients nor on OAB symptoms. Significant symptoms' relief[84]
Combination therapy	
Solifenacin + mirabegron	Significant improvement in mean volume voided per micturition, frequency, and urgency[85]
Solifenacin + tamsulosin	Good results in patients with voiding and storage symptoms[86]

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