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REVIEW ARTICLE

Treatment of Overactive Bladder in the Elderly Female: The Case for Trospium, Oxybutynin, Fesoterodine and Darifenacin

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Abstract Overactive bladder (OAB) is a common constellation of lower urinary tract storage symptoms that causes a significant impact on a person's quality of life. The elderly may be disproportionally impacted by these symptoms due to concomitant poor mobility, comorbid conditions such as diabetes and heart failure, and polypharmacy. While behavioral modification and pelvic floor muscle training should be considered first-line treatment options, pharmacotherapy remains the backbone of the therapeutic regimen. Trospium, oxybutynin, fesoterodine, and darifenacin all have unique properties that may confer certain advantages in the elderly population. The hydrophilicity and quaternary amine structure of trospium may limit its ability to cross the blood–brain barrier and thus minimize impact on cognition in the elderly. In its oral form, oxybutynin may have the most significant effect on cognition; however, the transdermal preparations may be favorable in the elderly population due to the ability to avoid first-pass metabolism and its limited antimuscarinic adverse effects. Fesoterodine may be the most extensively studied OAB medication in the elderly population. Darifenacin has a strong affinity for the M3 receptor in the bladder, while having a weak affinity for the M1 receptor commonly found in the brain. It must be noted that all muscarinic receptor antagonists are associated with common adverse effects to some degree, and frequent re-evaluation of the elderly patient is necessary to confirm the proper benefit-to-risk profile.

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Key Points

Comorbidities and polypharmacy may significantly impact pre-existing symptoms of overactive bladder in the elderly.

Some antimuscarinics may impact cognition in the elderly, and their use should be closely monitored.

1 Introduction

As defined by the International Continence Society, overactive bladder (OAB) is "urgency, with or without urgency incontinence (UUI), usually with frequency and nocturia where there is no infection or other obvious pathology" [1]. While OAB can affect men and women of all ages, it is especially prevalent in the elderly. The NOBLE (National Overactive Bladder Evaluation) program sampled over 5200 US adults via phone interview and found that the prevalence of OAB in women increases with age, with a substantial increase in those aged ≥44 years [2]. OAB prevalence was 2 % in women aged 18–24 years, increasing to 19.1 % in those aged 65–74 years [2]. The alarming growth rate of the aging population in the USA is another factor to consider. In the 2010 census, there were more people aged ≥65 years than ever before [3]. This total of 40.3 million represented a 5.3 million increase from the 2000 census, with all 50 states experiencing an increase in those individuals aged ≥85 years during that decade. Likewise, the population of elderly adults aged ≥65 years

increased at a more rapid rate than did the total population (15.1 vs. 9.7 %) [3].

The economic burden of OAB is staggering. With regards to total national cost, those with OAB spent approximately $US65.9 billion in 2007 alone, with projected increases to $US76.2 billion and $US82.6 billion in 2015 and 2020, respectively [4]. Total national costs were highest in the 45–54/55–64 age groups because they were the largest respective groups, and in the ≥75 age group because they incurred a higher average cost. On an individual level, per capita cost increased as the participants aged. Although there were no significant increases between the ages of 25 and 64 years, there was a slight increase in per capita costs in those aged 65–74 and a significant increase in those aged ≥75 years. Furthermore, in those aged ≥65 years, per capita costs were slightly higher in women than in men [4, 5].

Finally, those with OAB experience a diminished quality of life (QoL), and physicians may not always be aware of this. One study revealed that, in 25–37 % of patients evaluated for urinary symptoms, physicians underestimated the extent to which these patients were affected by their complaints [6]. Results from the EPIC study showed that, across both sexes, continent and incontinent individuals with OAB reported diminished health-related QoL, decreased work productivity, decreased sexual activity, and higher rates of depression [7, 8]. Furthermore, 15.4 % of those with OAB symptoms experienced decreased enjoyment of sexual activity as opposed to 2.8 % in those without OAB symptoms [7]. Sleep disturbances, falls, and fractures have also been shown to be increased in those with OAB [9].

It is clear that OAB and its associated symptoms have significant physical, emotional, and financial effects, underscoring the importance of effectively treating this population. Furthermore, as the elderly have a greater prevalence of OAB, it is imperative to understand the ways in which the elderly differ from younger individuals in their responses to therapeutic interventions. While behavioral therapy and pelvic floor exercises are first-line treatments, pharmacotherapy remains the backbone of treating OAB across all age groups. The purpose of this article is to examine the efficacy and tolerability of trospium, oxybutynin, fesoterodine, and darifenacin in the treatment of OAB in the older individual.

2 Pathophysiology of Overactive Bladder (OAB)

The pathophysiology of urinary storage is a complex interplay of the sympathetic, parasympathetic, and somatic nervous systems. Urinary storage is mediated primarily by the sympathetic nervous system. As the bladder begins to fill and tension in the bladder wall increases, afferent nerves from the urinary bladder activate spinal reflex pathways governed by the pontine micturition center in the brainstem [10]. This will lead to increased sympathetic outflow from the thoracolumbar spinal cord, in turn causing relaxation of the detrusor and contraction of the smooth sphincter via the hypogastric nerve. Additionally, the somatic nervous system, through the pudendal nerve leads to striated urethral sphincter contraction to facilitate urinary storage. On the other hand, the parasympathetic nervous system, which is responsible for bladder contraction and bladder outlet relaxation, is mostly quiescent throughout the process of bladder filling.

The storage symptoms of OAB have traditionally been associated with detrusor overactivity (DO), which involves involuntary contractions of the detrusor muscle during the storage phase [11]. This phenomenon is likely multifactorial and may have an idiopathic, myogenic, neurogenic, or mixed etiology, although the mechanism by which DO arises is not completely understood [11, 12]. Andersson suggests that increased release of acetylcholine from the urothelium during bladder filling leads to heightened detrusor sensitivity to these neurotransmitters [13]. This leads to an increase in the involuntary contractions within the detrusor, along with a resultant surge in afferent signaling, thus worsening the symptoms of urgency. Although muscarinic receptors have been found in both, the urothelium houses approximately twice as many receptors as the detrusor [14]. Thus, it is now postulated that the muscarinic receptor antagonists (antimuscarinics) act on the urothelial muscarinic receptors during bladder filling. Additionally, contractility of detrusor muscle fibers within the bladder does not appear to be affected by the antimuscarinic action of these medications [15].

At present, five muscarinic receptor subtypes have been described (M1–M5). These receptors each have unique properties and are found in various locations throughout the body. In the urinary bladder, muscarinic receptors exist in the detrusor smooth muscle, urothelium, as well as parasympathetic and sympathetic nerve endings. Although M3 receptors are known to regulate contraction of the bladder, there is a nearly fourfold increase in the number of M2 receptors (associated with afferent transmission) within the bladder [16, 17]. Additionally, anticholinergic agents antagonize the effect of acetylcholine on M1 receptors in the brain [18]. Differences in ability to penetrate the central nervous system (CNS), and in affinity for the M1 receptor, may partially explain the differences in CNS effects associated with the anticholinergic OAB agents. For example, agents such as oxybutynin and tolterodine that have a low M3:M1 binding affinity ratio have a greater theoretical risk of CNS adverse events (AEs), while more M3-selective drugs such as darifenacin have a lower risk of CNS AEs [19, 20].

Passive or active transport across the blood-brain barrier (BBB) should be mentioned, as the elderly are especially prone to increased BBB permeability owing to concomitant comorbidities such as type 2 diabetes mellitus (DM) [20]. Small, neutrally charged, and lipophilic molecules typically cross the BBB by passive diffusion. Additionally, active efflux mechanisms transport molecules across the BBB. A molecule that has passively crossed the BBB can be rapidly transported out of the brain if that molecule is a substrate for efflux-based transport systems, such as the permeability-glycoprotein (P-gp) system [20]. Animal studies have shown that trospium is a substrate for P-gp and is actively transported out of the brain by P-gp [20, 21]. Conversely, brain concentrations of oxybutynin were similar in mice that had P-gp and those that were P-gp deficient [22]. Further animal studies confirmed that brain penetration is low for anticholinergics that are P-gp substrates (5-hydroxymethyl tolterodine [5-HMT], darifenacin, and trospium), and significant for those that are not (oxybutynin, solifenacin, and tolterodine) [23].

3 Anatomic and Physiological Changes in the Elderly

The elderly population may undergo anatomic and physiologic changes that predispose them to DO and OAB. On the cellular level, detrusor biopsies in geriatric patients with DO showed a 'dysjunction pattern,' consisting of widened intercellular spaces, scarce intermediate muscle cell junctions, abundant distinctive protrusion junctions, and ultraclose cell abutments [24]. These changes in the aging detrusor are postulated to lead to decreased bladder compliance, resulting in reduced bladder capacity and increased afferent signaling at a lower urinary volume. Additionally, the ability to efficiently sense bladder filling and delay micturition declines with age [25, 26]. Interestingly, the aforementioned changes do not appear to be related to reduced function in the muscarinic receptors in the urinary bladder, as studies have shown that those individuals aged ≥65 years have similar response rates to antimuscarinic therapy as the younger population [27, 28]. This underscores that, despite the obvious anatomical and physiological changes in the elderly, the centerpiece of OAB treatment for all age groups remains antimuscarinic therapy.

4 Non-Urologic Contributors/Comorbidities in the Elderly

The elderly often have comorbid conditions that may significantly affect the symptoms of OAB. Impaired mobility increases the likelihood of urgency progressing to incontinence, with one study showing that women aged 60–84 with decreased mobility are 2.5 times more likely to have UUI than those with unimpaired mobility [29]. The assessment of functional status when treating the elderly becomes critical, because even a normal desire to micturate may be affected by an inability to efficiently ambulate to the bathroom and transfer to the commode. Other common comorbid conditions found with increasing prevalence in the elderly population include DM and congestive heart failure (CHF). DM is associated with polyuria, which stems from glucosuria and the subsequent osmotic diuresis. Likewise, uncontrolled or poorly controlled DM may lead to neuropathic symptoms such as DO [30]. The presentation of patients with CHF in a fluid-overloaded state, or those receiving diuretics, may mimic OAB or exacerbate pre-existing OAB. Furthermore, neurologic diseases such as cerebrovascular accidents, delirium, dementia, sleep disorders, and Parkinson's disease can all affect OAB in the elderly [31].

Polypharmacy in the elderly often exacerbates OAB symptoms. Medications with antimuscarinic side effects are potentially worrisome, especially antipsychotics and tricyclic antidepressants. These anticholinergic effects can potentially manifest in impaired detrusor contractility and urinary retention [31]. Antihypertensive medications such as calcium channel blockers and alpha-adrenergic agonists can be associated with defective detrusor contractility and contraction of the bladder neck, respectively, leading to urinary retention. Benzodiazepine use can cause disorientation and decreased awareness in the elderly, leading to secondary incontinence [32].

Finally, the use of cholinesterase inhibitors such as donepezil and rivastigmine in the treatment of Alzheimer's disease with anticholinergic medications for OAB may reduce the effectiveness of both drugs [33]. Some studies estimate that up to one-third of individuals with dementia use anticholinergics and cholinesterase inhibitors concurrently, and the combination has been shown to increase the rates of functional decline versus cholinesterase inhibitors alone [34]. Sink et al. [35] evaluated changes in cognitive function and activities of daily living (ADL) in >3500 nursing home residents receiving a cholinesterase inhibitor. Of these, 10.6 % were prescribed concomitant oxybutynin and tolterodine. In residents in the top quartile of ADL function, ADL function declined an average of 1.08 points per quarter when not receiving anticholinergics compared with 1.62 points per quarter when receiving dual therapy. This represented a statistically significant 50 % greater rate in quarterly decline in ADL function. These few examples underscore the importance of taking careful consideration of each patient's medical history and concomitant medication use.

5 Anticholinergic Load

While many symptoms are attributed to individual medications, anticholinergic load generated by the sum of the anticholinergic medications may beget cumulative or synergistic effects [36]. In addition to the traditional anticholinergics, many other common medications may have anticholinergic properties. These include warfarin, ranitidine, digoxin, codeine, and diazepam [37]. The anticholinergic cognitive burden (ACB) assigns a score to each medication with anticholinergic activity, with scores of 1 representing mild activity and 2–3 representing severe anticholinergic activity [38]. Darifenacin, oxybutynin, and tolterodine all have a score of 3. The authors found that the odds ratio (OR) for having a diagnosis of mild cognitive impairment was 2.73 (95 % confidence interval [CI] 1.25–5.87) among older adults exposed to at least three possible anticholinergics for at least 90 days. A list of medications and their accompanying scores are presented in the paper by Cai et al. [38].

Additionally, Rudolph et al. [39] developed the Anticholinergic Risk Scale (ARS). Much like the ACB, the ARS ranks the identified medications on a scale of 0–3 according to the anticholinergic potential (0, limited or none; 1, moderate; 2, strong; 3, very strong). As expected, higher ARS scores were associated with increased risk of anticholinergic AEs in their cohort of 132 geriatric patients. Additionally, in a 2-year longitudinal study of >13,000 participants aged ≥65 years in the Medical Research Council Cognitive Function and Ageing Study, 47 and 4 % of the population used a medication with possible and definite anticholinergic properties at baseline, respectively [40]. After adjusting for criteria such as age, number of comorbid health conditions, and cognitive performance at baseline, use of medications with definite anticholinergic effects was associated with a 0.33-point decline in Mini-Mental State Examination (MMSE) score than not taking anticholinergics. Two-year mortality was greater for those taking definite (OR 1.68) and possible (OR 1.56) anticholinergics.

6 Pharmacologic Treatment with Muscarinic Receptor Antagonists

The most recent American Urological Association/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (AUA/SUFU) guideline on OAB treatment lists behavioral therapies such as bladder training, bladder control strategies, pelvic floor muscle training, and fluid management as first-line therapy for all OAB patients (standard) [41]. Oral antimuscarinic medications, along with β3-adrenoceptor agonists, were classified as second-line therapy (standard), and could be combined with behavioral therapy. Antimuscarinics are presently considered to be the mainstay of pharmacologic therapy for OAB symptoms. All of the available drugs in this class (oxybutynin, tolterodine, solifenacin, darifenacin, trospium, and fesoterodine) are available in single-dose, extended-release (ER) daily oral formulations; however, some may be available in immediate-release (IR) oral or transdermal preparations. Each has unique pharmacologic properties and rates of metabolism. For this review, we focus on four medications: trospium, oxybutynin, fesoterodine, and darifenacin.

7 The Case for Trospium

The IR formulation of trospium chloride was US FDA approved in 2004 and the ER formulation in 2007. While other antimuscarinics are tertiary amines, trospium has a quaternary amine structure, making it potentially beneficial for use in the elderly population. First, its hydrophilicity makes it the least likely drug in its class to passively cross the BBB and contribute to cognitive AEs. Second, the bulk of trospium is excreted unchanged in the urine, and this lack of reactivity allows for fewer drug–drug interactions, particularly useful in the elderly due to frequent polypharmacy. This route of elimination also suggests the possibility of local effects of trospium on the urothelium, previously found to be the site of the majority of muscarinic receptors.

7.1 Trospium Immediate Release (IR)

Trospium IR is dosed at 20 mg, two to three times daily; however, 20 mg at nighttime may be sufficient in some patients aged >75 years. A meta-analysis of two European clinical trials revealed that patients receiving trospium IR twice daily showed a significant increase in maximum cystometric bladder capacity (MCC) and in urinary volume at first unstable detrusor contraction compared with those receiving placebo [42]. Additionally, patients in the treatment group were significantly more likely to report ‘marked improvement’ in their symptoms than those receiving placebo [42]. After its FDA approval, two additional multicenter phase III trials demonstrated that those treated with trospium IR experienced a decrease in the number of daily toilet voids, average urgency severity, urge frequency, and UUI episodes [43, 44].

While dry mouth is the most commonly reported AE [45], an alteration in sleep architecture is another important variable to consider when administering antimuscarinics to older adults. One placebo-controlled study of 658 patients revealed that trospium IR did not increase daytime

sleepiness across all age groups, as measured by the Stanford Sleepiness Scale [46]. An additional study recruited 24 adults aged ≥50 years to undergo polysomnographic recordings and cognitive testing after being administered single doses of oxybutynin, tolterodine, trospium, or placebo [47]. While oxybutynin and tolterodine therapy produced diminished rapid eye movement (REM) sleep and slightly increased REM latency, trospium resulted in no observable changes in sleep architecture.

7.2 Trospium Extended Release (ER)

Trospium ER (60 mg) is dosed once daily. The ER formulation has a relatively lower maximum concentration (C_{max}), lower median time to C_{max}, and a longer $t_{½}$ than trospium IR [48]. These data are particularly relevant in the treatment of OAB in the older population, who undergo age-related physiologic and pharmacokinetic changes that could influence dosing and the accumulation of certain drugs in the bloodstream. In pooled data from two randomized, phase III trials that included 1165 patients, those receiving trospium ER had fewer daily voids and fewer daily UUI episodes than those receiving placebo [49, 50]. The same study showed that CNS AEs were less prominent in those receiving trospium ER (dizziness in 0.2 %, headache in 1.4 %) than in those receiving placebo (dizziness in 1.0 %, headache in 2.4 %). Of note, a subgroup analysis of pooled data from the aforementioned phase III randomized controlled trials (RCTs) was completed for 143 subjects aged ≥75 years [51]. After 12 weeks, trospium ER therapy in this population resulted in greater improvements in voiding diary parameters, OAB Patient Global Assessment, and QoL. Additionally, efficacy and tolerability were maintained in those receiving open-label trospium ER for 1 year. After 48 weeks, those in the placebo-to-trospium group experienced a mean change of −3.21 in the number of daily voids, while those in the trospium-to-trospium group experienced a mean change of −3.35 daily toilet voids [51].

Treatment-emergent AEs (TEAEs) experienced by those in the placebo and trospium ER groups, respectively, were as follows: dry mouth (3.7 vs. 10.7 %), constipation (1.5 vs. 8.5 %), and dry eyes (0.2 vs. 1.6 %) [52]. Staskin et al. [53] further validated the reduced incidence of CNS AEs with trospium ER therapy. Twelve cognitively-intact adults aged ≥65–75 years took trospium ER once daily for 10 days to reach a steady-state level in the plasma. On day 10, cerebrospinal fluid (CSF) and plasma samples measured trospium levels. The results revealed undetectable CSF levels (<40 pg/mL) of trospium on day 10, concurrent with measurable peak plasma values (C_{max} = 925 pg/mL). Memory testing performed on day 0 and day 10 showed no significant drug effect. Despite these findings, elderly patients with pre-existing dementia should be treated with caution.

As polypharmacy increases with age, it is vital to know whether trospium is safe to take with multiple other medications. In a post hoc analysis, Sand et al. [54] analyzed 1135 patients who were receiving concomitant medications alongside trospium ER. The likelihood of experiencing a TEAE was influenced by concomitant medication use, but not by the use of trospium ER. Randomization into the trospium ER or placebo group had no impact on the odds of experiencing a TEAE. Rather, those receiving seven or more concomitant medications had an OR of 3.39 (95 % CI 2.4–4.8, $p < 0.0001$) for experiencing any TEAE, when compared with those receiving 1–2 concomitant medications. Furthermore, since trospium is principally excreted through the kidneys, elderly patients with impaired renal function must be carefully monitored for AEs and may require dose adjustments.

There is currently a lack of studies that directly test the efficacy and tolerability of trospium IR versus trospium ER in the elderly. One systematic review reported that trospium IR and ER are equally effective in improving the key outcome parameters related to OAB [55]. The results of this review also demonstrated that trospium ER was associated with a lower rate of dry mouth, while having comparable efficacy and tolerability to other antimuscarinic drugs. It must be noted that what limited data we have regarding trospium in the elderly is based on ad hoc analyses rather than prospective studies.

8 The Case for Oxybutynin

Oxybutynin is a well-studied antimuscarinic agent that is available in several preparations. A proportion of the parent drug is metabolized into *N*-desethyloxybutynin (*N*-DEO), a downstream active metabolite of this agent. *N*-DEO exerts its effects on the bladder and, to a lesser extent, numerous other end organs, which result in the AEs associated with this drug [56]. Hence, high ratios of *N*-DEO to oxybutynin are thought to be associated with an increased incidence of anticholinergic side effects.

8.1 Oxybutynin IR

Oral oxybutynin IR undergoes the first-pass effect in the liver, resulting in a meager bioavailability of 6 % [57]. However, the *N*-DEO to oxybutynin ratio in the IR formulation is 5.5–1 [57], higher than that found in any of the other preparations, potentially providing an explanation for both its efficacy and its tolerability.

A meta-analysis of 76 trials and 36,662 patients concluded that, compared with placebo, oxybutynin IR 15 mg daily resulted in a significant reduction in micturitions/24 h, while oxybutynin IR 10 mg daily resulted in

significant reductions in micturitions and urgency episodes/24 h [58]. Daily doses of oxybutynin IR (20, 15, and 10 mg) ranked first, second, and fourth, respectively, in having the worst AE profiles leading to decreased tolerability. In another meta-analysis, patients receiving oxybutynin IR 7.5–15 mg daily were at significantly higher risk for withdrawal from trial due to any cause when compared with placebo [59]. Interestingly, this was not the case for any other active treatment included in the study.

The efficacy of oxybutynin IR in elderly women has likewise been well established. When comparing elderly and younger populations on oxybutynin 2.5–3 mg three times daily, no statistically significant difference was found in the mean peak drug level measured in the blood [60]. One randomized, double-blind, placebo-controlled, parallel-group trial studied 57 elderly adults with DO associated with frequency or incontinence [61]. Those receiving oxybutynin had significantly reduced daytime frequency, as well as increased subjective benefit. The most commonly reported AEs were dry mouth (93 %), heartburn (57 %), blurred vision (50 %), constipation (50 %), and dry skin (50 %) [61]. In another randomized, double-blind, placebo-controlled trial, 105 elderly women with UUI were randomized to biofeedback-assisted behavioral training, oxybutynin, or placebo [62]. Significant improvements in voiding frequency and UUI episodes were noted in both the behavioral training and the oxybutynin groups. When cystometry was repeated after completion of treatment, those treated with oxybutynin also experienced a 68.9 mL increase in bladder capacity, 69.9 mL increase in strong desire to void, and 44.4 mL increase in first desire to void (all $p < 0.001$) [62].

CNS AEs are the most serious concern when treating elderly patients with oxybutynin IR. The rates of somnolence (14.9 %) and dizziness (16.6 %) reported in the oxybutynin IR trials are noteworthy, as are post-market reports of agitation, hallucinations, and memory impairment [63]. Although direct data via quantitative EEG to account for these CNS impairments are currently lacking, their incidence must not be overlooked when treating the elderly. In a double-blind, placebo-controlled cross-over study of 12 volunteers with an mean age of 69 years, Katz et al. [64] demonstrated that oxybutynin IR (5 and 10 mg) caused significant cognitive decrements on 7 of 15 cognitive measures. Owing to these concerns, the UK National Institute for Health and Care Excellence (NICE) stated that oxybutynin IR should not be offered to frail older women, such as those with multiple comorbidities, functional impairments such as walking or dressing difficulties, and any degree of cognitive impairment [65]. The NICE Guideline Development Group likewise recommends that the use of other existing medications affecting the total anticholinergic load should always be taken into account.

8.2 Oxybutynin ER

The *N*-DEO to oxybutynin ratio in once-daily oxybutynin ER is roughly 4.3–1, lower than in oxybutynin IR [66]. This particular medication is synthesized in a way that allows osmotic pressure to release oxybutynin in a controlled fashion over the course of 24 h [66]. The efficacy of oxybutynin ER appears to be comparable to that of the IR formulation at similar dosages [67]; however, the patients receiving oxybutynin ER experienced only 57 % of the total AEs experienced by those in the IR group. One meta-analysis of multiple RCTs found that the AE profile of oxybutynin ER was more favorable than that of oxybutynin IR [68]. Oxybutynin IR was significantly more likely to cause moderate-to-severe or severe dry mouth (OR 1.49) or any AE (OR 1.9).

Oxybutynin ER has been shown to maintain efficacy in the older OAB population. A meta-analysis of data from three clinical trials involving 159 adults aged >65 years showed that oxybutynin ER at various doses (5–30 mg) resulted in an 81 % decrease in the number of daily UUI episodes [69]. Another open-label study recruited 240 patients (46 % aged ≥65 years) to be treated with daily oxybutynin ER 15 mg for 4 weeks [70]. Significant reductions in incontinence, nocturia, and night-time incontinence were noted, with no difference between patients aged <65 and ≥65 years. Dry mouth was the most frequently reported AE, affecting 24.8 % of patients aged <65 years and 36.0 % of patients ≥65 ($p = 0.0584$) [70].

Although effective, the use of oxybutynin ER continues to cause concern regarding cognitive decline in elderly adults. In a multicenter, double-blind, double-dummy, parallel-group, 3-week study, Kay et al. [71] randomly assigned 150 adults aged ≥60 years to oxybutynin, darifenacin, or placebo. The oxybutynin group was treated with oxybutynin ER 10 mg daily during week 1, with 15 mg daily during week 2, and with 20 mg daily during week 3, while patients in the darifenacin group were treated with 7.5 mg during weeks 1 and 2 and 15 mg during week 3. Results showed no significant difference between the darifenacin and placebo group in cognitive function and memory; however, those treated with oxybutynin ER performed significantly worse on the Name-Face Association Test (NFAT) at week 3 than patients receiving placebo or darifenacin [71].

8.3 Transdermal Oxybutynin Patch

In an effort to overcome the significant decrease in bioavailability of oral oxybutynin from the first-pass effect and attain more stable plasma drug levels, an oxybutynin transdermal delivery system (OXY-TDS patch) was

devised [72]. Each patch contains 36 mg of oxybutynin, delivering approximately 3.9 mg/day through skin with average permeability [58]. The *N*-DEO to oxybutynin ration in OXY-TDS is significantly lower than either of the oral forms of oxybutynin, at 1.3:1, owing to its avoidance of first-pass metabolism [73].

The efficacy of OXY-TDS is well-established. In a meta-analysis of relevant RCTs, OXY-TDS was associated with significant decreases in the mean number of incontinence episodes/day and the mean number of micturitions/day while resulting in an increase in the voided volume/micturition compared with placebo [59]. Moreover, OXY-TDS has been shown to have comparable efficacy to oral antimuscarinic therapy. When compared with placebo, OXY-TDS and daily tolterodine 4 mg both significantly reduced the number of daily incontinence episodes and increased mean voided volume [74]. Those treated with OXY-TDS were less likely to experience dry mouth than those taking tolterodine (4.1 vs. 7.3 %); however, application site reactions, ranging from pruritus to dermatitis and irritation, were reported by 14 % of subjects in the OXY-TDS group [74, 75]. Those treated with OXY-TDS have also reported subjective benefit, an important factor when considering patient adherence [74, 75]. Although the amount of direct data regarding the use of OXY-TDS in the elderly is limited, the decreased incidence of anticholinergic side effects suggests a possible advantage of this formulation in this population. Likewise, OXY-TDS may be a good option for those elderly who do not want to take an oral medication on a daily basis.

8.4 Topical Oxybutynin Gel

Oxybutynin chloride topical gel (OTG) has the lowest *N*-DEO to oxybutynin ratio (0.8:1) of all the oxybutynin preparations and may cut down on the application-site reactions caused by OXY-TDS [76, 77]. It is available in small packets containing 1 g of OTG that can be applied to the abdomen, upper arms/shoulders, or thighs daily. The efficacy of OTG was demonstrated in a randomized, parallel group, double-blind, placebo-controlled trial [78]. Patients were recruited from 76 US clinics and randomized to 1 gram of OTG or placebo for 12 weeks. Of the 789 patients, 704 were women (89.2 %), with a mean age of 59. Those treated with OTG had greater reductions in UUI episodes and mean urinary frequency and a significant increase in voided volume [78]. Although dry mouth (6.9 vs. 2.8 %) and application-site reactions (5.4 vs. 1.0 %) were more likely in the OTG group, they were infrequent overall [78]. Application-site reactions were less common than in studies of OXY-TDS, and no serious AEs were reported.

There do not appear to be any overall differences in the pharmacokinetics, safety, or effectiveness when comparing older and younger populations in the OTG trials [63]. One randomized, double-blind, placebo- and active-controlled study assessed the cognitive and psychomotor function in 152 older healthy adults aged 60–79 treated with either OTG plus oral placebo, oxybutynin IR 5 mg three times/-day plus placebo gel, or double placebo [79]. Although no significant differences were observed between the groups regarding psychomotor function or the delayed recall NFAT, a significant decline was noted in the oxybutynin IR group for the Misplaced Objects Test. Additionally, almost twice as many individuals receiving oxybutynin IR exhibited a significant decrease in the Total Recall score for the Hopkins Verbal Learning Test-Revised compared with the OTG or double placebo group. Thus, OTG appears to be an effective and safe choice for the elderly population, with fewer anticholinergic or cognitive side effects than the oral preparations and potentially fewer application-site reactions than OXY-TDS. As for trospium, it must be noted that the limited data we have regarding oxybutynin in any formulation in the elderly population is based on ad hoc analyses rather than prospective studies.

9 The Case for Fesoterodine

Fesoterodine is a nonspecific, competitive muscarinic receptor antagonist that, by itself, is not a potent antimuscarinic agent. After oral administration, fesoterodine is rapidly and extensively hydrolyzed by nonspecific esterases to its active metabolite 5-HMT, a non-selective blocker of muscarinic receptors [80]. 5-HMT is responsible for the antimuscarinic activity of fesoterodine. Hydrolysis of fesoterodine is rapid and extensive, and no parent compound is detectable in plasma after oral administration [81]. This ER medication is available in both 4- and 8-mg doses.

In two 12-week, multicenter, randomized, double-blind, placebo-controlled studies of fesoterodine in patients with OAB, both doses of fesoterodine significantly improved the mean number of micturitions and UUI episodes/24 h compared with placebo [82, 83]. Likewise, results for most secondary endpoints, including mean voided volume, number of continent days, and number of urgency episodes were also significantly improved versus placebo. The most frequently reported AEs (≥4 %) after fesoterodine administration in the two phase III trials were dry mouth (placebo 7 %, fesoterodine 4 mg 19 %, fesoterodine 8 mg 35 %) and constipation (placebo 2 %, fesoterodine 4 mg 4 %, fesoterodine 8 mg 6 %) [82, 83]. Less than 1 % of all patients discontinued fesoterodine due to dry mouth.

Fesoterodine has been extensively studied in the elderly population. The SOFIA (Study of Fesoterodine in an Aging Population) study was a 12-week randomized, placebo-controlled trial of the drug in patients aged ≥65 years with

a 12-week open-label phase [84]. Participants receiving fesoterodine started on 4 mg and could increase to 8 mg at week 4 or 8 and de-escalate to 4 mg at week 8. At week 12, the fesoterodine group had statistically greater improvement than the placebo group in urgency episodes, micturitions, nocturnal micturitions, pad use, and OAB Questionnaire scores. Rates of dry mouth and constipation were 34 and 9 % with fesoterodine and 5 and 3 % with placebo, respectively. There was no change in MMSE scores. Of the original 794 entered into the double-blind phase, 654 entered the 12-week open-label phase [85]. AEs were reported by 30.7 and 48.1 % of patients who had received double-blind fesoterodine and placebo, respectively; however, only 1.9 and 9.4 % discontinued due to AEs, respectively. Patients who received double-blind fesoterodine maintained their efficacy response, while those initially receiving double-blind placebo had similar outcomes after the 12-week open-label phase. Dubeau et al. [86] also evaluated the impact of fesoterodine in a 12-week, randomized, double-blind, flexible dose, placebo-controlled trial in medically complex, vulnerable elderly subjects. Subjects had scores of ≥3 on the Vulnerable Elders Survey, a measure of physical impairment and its impact on daily activities. After 562 patients were randomized, the fesoterodine group had significantly greater improvements in UUI episodes/24 h and most other diary variables and QoL measures at 12 weeks. The diary dry rate was also significantly higher. AEs were generally similar to those of younger populations.

10 The Case for Darifenacin

A unique feature of darifenacin is its strong predilection for the M3 receptor, the most common muscarinic receptor in the bladder, and a weak predilection for the M1 receptor most commonly found in brain tissue [87]. In theory, this should result in increased efficacy with limited CNS AEs, a desirable quality when prescribing antimuscarinic treatment in the elderly population. Darifenacin is dosed once daily and is available in 7.5- and 15-mg doses [88].

In a pooled analysis of three phase III trials encompassing 1059 adults (85 % women), patients were randomized to 12 weeks of daily darifenacin 7.5 or 15 mg or placebo [89]. Compared with placebo, both dosages of darifenacin were associated with significant decreases in the frequency and severity of urgency, voiding frequency, number of significant leaks, number of weekly incontinence episodes, and an increase in bladder capacity [89]. Dry mouth and constipation were the most commonly reported AEs, but withdrawal rates for both darifenacin 7.5 and 15 mg were low (0.6 and 2.1 %, respectively). Furthermore, darifenacin appears to have a durable effect in the older population. In a 12-week double-blind RCT, 400 patients aged >65 years were randomized to darifenacin (7.5 mg daily for 2 weeks, then optional titration to 15 mg daily) or placebo (with sham titration) [90]. Compared with placebo, the darifenacin group experienced significant reductions in mean UUI episodes, micturition frequency, and improvement in QoL [90].

The impact of darifenacin on the CNS remains in question. Kay and Ebinger [91] reviewed five randomized, double-blind, multiple-dose studies regarding cognitive function and antimuscarinic treatment. No cognitive impairment was noted in the three studies involving darifenacin [71, 92, 93]. One of the studies was a double-blind, 3-period crossover study that recruited 129 volunteers (all aged >65 years) with mild or no pre-existing cognitive impairment [93]. The volunteers received three of five treatments, including daily controlled-release darifenacin (3.75, 7.5, or 15 mg), darifenacin IR (5 mg three times daily) or matching placebo for 14 days, with each treatment followed by a 7-day washout period. No significant differences between darifenacin and placebo were noted in the primary endpoints, including memory scanning sensitivity, speed of choice reaction time, or word recognition sensitivity [93]. Thus, the M3-selectivity of darifenacin may be of potential benefit in the elderly population.

Previously, agents with high M3-selectivity were thought to be associated with more constipation. A post hoc analysis of pooled data from the phase III trials revealed that constipation occurred in 14.8 % of the patients receiving darifenacin 7.5 mg and 21.3 % of those receiving 15 mg compared with 6.2 % of those receiving placebo [94]. However, discontinuation rates due to constipation were quite low (0.6, 1.2, and 0.3 % in the darifenacin 7.5, 15 mg, and placebo groups, respectively) [94]. Concomitant laxative use was also infrequently required (3.3, 6.6, and 1.5 % in the darifenacin 7.5, 15 mg, and placebo groups, respectively). Results concerning patient-reported perception of treatment and bowel habit questionnaires suggested little, if any, difference in those treated with darifenacin [94].

The increased selectivity of darifenacin for the M3 receptor may also have some benefit in those with cardiovascular comorbidities. One randomized, placebo-controlled, double-blind, crossover study in 162 healthy participants aged >50 years showed no significant impact on heart rate in those treated with darifenacin versus placebo [95]. Tolterodine, a less-selective antimuscarinic agent, was associated with a significantly higher proportion of participants experiencing an increased mean heart rate of >5 beats per minute (BPM) over 24 h compared with those receiving darifenacin or placebo. Additionally, the sustained safety and tolerability of darifenacin in the elderly population has been validated in a 2-year, open-label extension study of patients aged ≥65 years [96].

11 Conclusions

While all elderly should be started on behavioral therapy and offered pelvic floor muscle training, the treatment algorithm will likely take the practitioner in the direction of pharmacotherapy. Owing to the unique comorbidities and the increased likelihood of polypharmacy with elderly patients, the choice of antimuscarinic becomes a watershed decision. While all of the mentioned drugs have a beneficial impact on OAB symptoms and have some potential for typical antimuscarinic AEs (e.g. dry mouth, dry eyes, constipation), some of the medicines, such as OTG, trospium, and darifenacin, may have a lesser impact on cognition. It is important to remember that the mere reporting of symptoms like somnolence and dizziness may not adequately reflect the impact of anticholinergic use on CNS AEs. The evaluation of CNS side effects must be based on computer-assisted psychiatric tests, as patient-reported symptoms, as well as those detected by the physician, may not be sensitive enough to detect deterioration of short-term memory from medication use. Specifically, transdermal preparations that minimize first-pass metabolism may be associated with a lower incidence of antimuscarinic AEs. The choice of pharmaceutical intervention should not be approached at random, and the specific pharmacodynamics and pharmacokinetics should be taken into account. Finally, close monitoring for efficacy and AEs should be undertaken for the entire duration of treatment.

Compliance with Ethical Standards

Conflict of interest S. Clint McFerren and Alex Gomelsky declare that they have no conflict of interest.

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