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Overactive Bladder in the Elderly

A Guide to Pharmacological Management

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Contents

Abstract

Overactive bladder (OAB) is a common condition characterised by the symptoms of urinary frequency and urgency, with or without urge incontinence and nocturia. The prevalence of OAB increases markedly with age in both men and women. OAB can have a detrimental effect on physical functioning and psychological well-being, as well as significantly reducing quality of life.

Antimuscarinic therapy – with or without behavioural therapy – represents the most common treatment for patients with OAB. Several antimuscarinic agents are currently available for the treatment of OAB in adults, including oxybutynin, tolterodine, trospium chloride, darifenacin and solifenacin. The antimuscarinics all appear to exert their clinical effect through inhibition of the bladder muscarinic receptors, but they vary both in structure and in their functional profile. While efficacy has been demonstrated in adult populations (including patients >65 years of age), few studies have been reported specifically in a geriatric population, and antimuscarinics are often underutilised in the elderly despite the marked increase in the prevalence of OAB in this age group. One explanation for this apparent underuse of an effective treatment option may be concerns about the frequency of anticholinergic adverse events, such as dry mouth; the likelihood of detrimental CNS effects, including cognitive impairment and sleep disturbances; and the potential for harmful interactions with existing pharmacotherapy.

When selecting an antimuscarinic agent for the management of an elderly patient presenting with OAB, in addition to considering evidence of clinical efficacy and tolerability, issues of safety specific to an older population should be borne in mind. In particular, the likelihood of detrimental CNS effects should be

considered, including cognitive impairment and sleep disturbances, secondary to anticholinergic load. Oxybutynin and tolterodine have both been associated with cognitive adverse events and effects on sleep architecture and quality. In contrast, trospium chloride and darifenacin do not appear to be associated with cognitive adverse events and trospium chloride does not negatively affect sleep architecture or quality. Biotransformation by the cytochrome P450 (CYP450) system is an important step in the activation or elimination of a large number of drugs, including oxybutynin, tolterodine, darifenacin and solifenacin, raising the possibility of clinically relevant and potentially serious drug interactions. In elderly patients, such interactions are of particular relevance given the potential for declining activity of certain members of the CYP450 family combined with decreased hepatic blood flow, which can reduce first-pass metabolism and thus the bioavailability of drugs metabolised via this route. Of the antimuscarinic agents used to treat OAB, only trospium chloride is not extensively metabolised in the liver by the CYP450 system and is excreted largely as the active parent compound in the urine.

This paper provides an overview of the pathophysiology of OAB and reviews current approaches to achieving a differential diagnosis and selecting appropriate treatment for the older patient. The pharmacology and clinical effects of current medication for the treatment of OAB symptoms in patients defined by the OAB pharmacology literature as 'elderly' are also reviewed.

Over 33 million individuals in the US are currently thought to be living with overactive bladder (OAB).[1] The International Continence Society describes OAB as urgency (a sudden compelling desire to pass urine), with or without urge incontinence (involuntary leakage of urine associated with urgency), usually accompanied by frequency (the patient considers that he/she voids too often during the day) and nocturia (whereby the individual wakes at night one or more times to void).[2] This new definition represents a departure from prior versions that required complicated urodynamic testing before a diagnosis could be made. Recent data have suggested that urodynamic testing may be of little clinical utility in the management of OAB, as patients with the condition appear to respond equally well to antimuscarinic therapy regardless of whether their symptoms are urodynamically verified.[3] These updated definitions emphasise the subjective nature of the disorder and the importance of the patient's perception of the severity of their symptoms.

The prevalence of OAB, and incontinence in general, increases markedly with advancing age in both men and women.[1,4,5] Two surveys, a US-based national telephone survey of >5000 community-dwelling adults and a European survey involving 16 776 interviews with adults ≥40 years of age in six European countries, found an overall prevalence rate of around 16.5%. However, marked differences were found between men and women when the prevalence of OAB with and without urge incontinence was examined.[1,5] OAB with urge incontinence increased steadily with advancing age but was higher among women of all ages compared with men.[1,5] In the US study, a marked increase was observed among women >44 years of age and men >64 years of age (figure 1).[1] The frequency of OAB without an incontinence component was higher among men of all ages compared with women, reaching a peak of almost 22% in men >54 years of age.[1] In contrast, OAB without urge incontinence gradually increased in women <44 years of age and reached a plateau in women >44 years of age.[1]

The prevalence of OAB among older patients in residential care settings has not been systematically examined. However, all-cause urinary incontinence

is thought to affect between 30% and 50% of adults >65 years of age in residential care in the US.[6] As OAB is thought to be the most common bladder disorder causing urinary incontinence in elderly people,[7] the frequency of OAB among older persons in residential care is also likely to be relatively high. Recurrent urinary tract infections (UTIs) are also common in the elderly.[8] However, as a causative organism is often never detected and asymptomatic bacteriuria is also common in older persons, it is not clear that all such patients have an infective aetiology for their symptoms and they may, in fact, be experiencing OAB.

The impact of OAB on quality of life is known to be both significant and far-reaching.[1,9] For older patients, this additional burden may be particularly distressing, as they may already be coping with quality of life issues as a result of co-morbid medical conditions or other age-related health issues. OAB can also have a considerable impact on psychological health status; affected patients may experience depression, apathy, low self-esteem, guilt and shame.[10] Older patients may also be more prone to falls and fractures,[11] skin infections and UTIs as a result of their OAB, especially if they have an incontinence component. Indeed, the emergence of bladder symptoms is often the deciding factor in a move from community to residential-based care.[12]

As life expectancy increases, the prevalence of OAB is expected to rise. In today's society, people ≥65 years of age should not be considered geriatric. Patients 75–85 years of age currently represent a significant part of the population, and this will rapidly rise to include patients up to 95 years of age. Data relating to the prevalence and impact of OAB are sparse for patients >85 years of age.

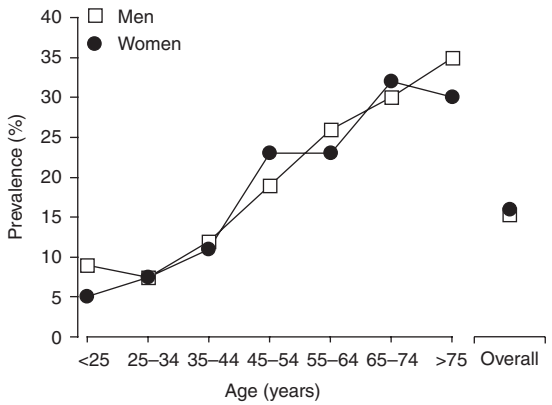

Fig. 1. Age-related prevalence of overactive bladder among an adult, noninstitutionalised, US population (reproduced from Stewart et al.[1] with permission).

The high prevalence rate combined with the significant health burden OAB can confer in older patients supports the need for robust interventions to manage and minimise the detrimental effects of this disorder. This paper provides an overview of the pathophysiology of OAB and reviews current diagnostic approaches and treatment strategies (particularly pharmacological interventions), with specific emphasis on those that apply to the older patient.

1. Pathophysiology of Overactive Bladder (OAB) in the Older Patient

The functioning of the urinary system is known to decline with advancing age, leading to reduced bladder capacity and decreased ability to postpone voiding.[13,14] However, despite the commonly held belief among the lay community, aging in itself is not a cause of OAB or incontinence, and such symptoms should not be regarded as inexorable or untreatable in older people. The precise cause of OAB in older patients is multifactorial and may involve abnormalities in the nervous supply, the urothelium, or the muscular structure of the urinary bladder itself, leading to an abnormal sense of urgency and/or involuntary bladder contractions.[15]

The urinary bladder is controlled through a complex interaction between the central and peripheral nervous systems, with local regulatory factors also playing a role.[16,17] The extensive afferent innervation of the urinary bladder, both within the detrusor muscle and directly below the urothelium, implicates these nerve fibres in a control mechanism involving sensory feedback (mechanical and chemical), as well as in the initiation of micturition (figure 2).[18] The symptoms of OAB may emerge as a result of changes in the structure or functionality of the nervous supply to the bladder or in the central control areas of the brain and CNS (neurogenic dysfunction). Abnormalities in the sensory feedback

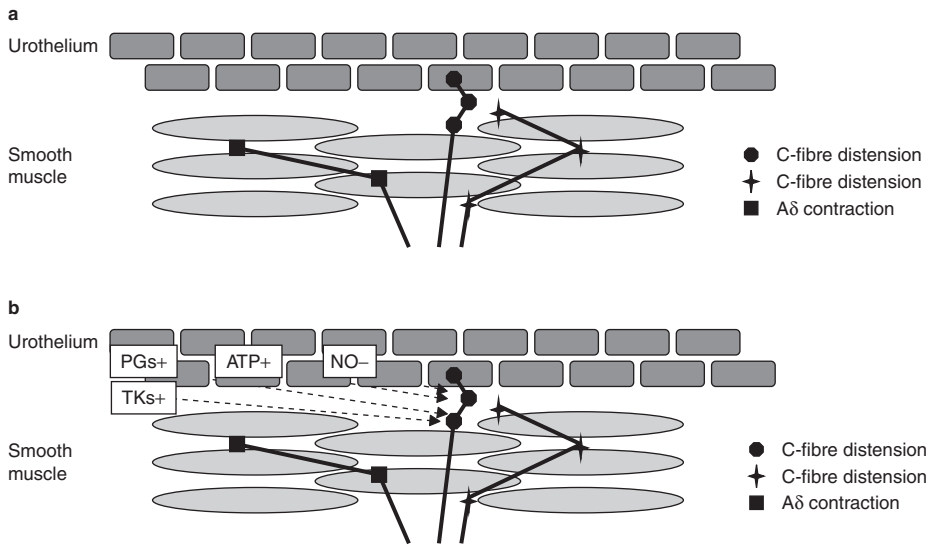

Fig. 2. Urothelial mechanoafferent transduction (**a**) and possible mediators/transmitter moieties (**b**) [reproduced from Andersson[18] with permission]. **ATP** = adenosine triphosphate; **NO** = nitric oxide; **PG** = prostaglandin; **TK** = tachykinin.

mechanisms may also contribute to the emergence of OAB symptoms. Muscarinic receptors – in particular M_3 receptors and, to some extent, M_2 receptors – mediate the initiation of micturition in response to acetylcholine. Upregulation of M_2 receptors occurs with aging and in certain pathological states, such as bladder outlet obstruction and neurological disease,[19] leading to frequent micturition.

Structural or functional changes within the bladder muscle layers (myogenic dysfunction), such as infiltration of smooth muscle by elastin and collagen, and patchy denervation, may also give rise to OAB symptoms.[20] Changes in the electrical coupling between muscle cells may lead to uncontrolled spread of the muscle contraction over the whole bladder, resulting in sensations of urgency and even incontinence.[20,21] Activation of stretch-sensitive neurons that mediate the sensation of urgency may also contribute to the symptoms of OAB as a result of localised spontaneous contractions of smooth muscle known as micromotions.[22]

2. Differential Diagnosis in the Older Patient with Bladder Symptoms

In addition to the multifactorial pathophysiology of OAB, the symptoms of urgency and frequency, with or without urge incontinence and nocturia, may arise from or be exacerbated by a variety of medical and environmental factors. When evaluating an older patient presenting with OAB-like symptoms, a urinalysis should be ordered, a full physical examination should be performed and the full medical history, including current drug regimen, should be reviewed (table I; figure 3).[23] A useful acronym for identifying acute and potentially treatable causes of urinary incontinence that may also have relevance for the evaluation of patients presenting with symptoms of OAB is DIAPPERS (table II).[24] Bladder symptoms may arise alongside a variety of medically recognised conditions and patient behaviours, for example peripheral oedema, poorly controlled diabetes mellitus, or elevated circulating atrial natriuretic peptide.[25] The drugs used to treat these medical conditions, for example, diuretics, and also certain environmental factors, for example, fluid intake and decreased mobility, may also give rise to or exacerbate bladder symptoms.[26]

In most cases, after a UTI and any other lower urinary tract pathology have been excluded, a diagnosis of OAB can be confidently applied.[2] However, urodynamic testing may be necessary in men in order to exclude bladder outlet obstruction associated with benign prostatic hyperplasia, or in women in whom detrusor hyperactivity and impaired detrusor contractile function are suspected. Urodynamic testing is also advised when empirical therapy has not been successful.

The degree of bother associated with urinary symptoms should be assessed before a management strategy is developed. In addition to direct questioning of the patient, a number of clinical tools are available to assess and track the severity of bladder symptoms, including bladder diaries, pad tests and symptom questionnaires. Bladder diaries in various forms are readily available on the Internet (figure 4). They are particularly useful for establishing the nature of the presenting symptoms or for monitoring improvement in symptoms, as they allow patients to record their experiences and track changes over time, given that significant symptom improvement may occur over weeks and months rather than days. Bladder diaries can be used to record micturition frequency, in addition to episodes of incontinence and urgency, and may help to identify activities that exacerbate bladder symptoms. Recording fluid intake is less reliable, but total fluid output can be measured and information on volume voided per micturition can facilitate a diagnosis of OAB and nocturia. Diaries can also be used to keep track of pelvic floor exercises. A number of symptom-based questionnaires are also available with varying degrees of specificity for the symptoms of OAB and more general bladder symptoms.[28,29]

3. Nonpharmacological Management of OAB in the Older Patient

A number of nonpharmacological options are available that may help to improve the symptoms of OAB, including behavioural modification (e.g. dietary change, fluid management, avoidance of caffeine and other bladder irritants, and pre-emptive or prompted voiding), bladder retraining (a programme

Table I. Evaluation process to achieve a differential diagnosis for overactive bladder in the older patient

Evaluation	Rationale
Urinalysis	To exclude urinary tract infection and screen for haematuria that may warrant further investigation
Medical history and current drug regimen	To identify any co-morbid medical conditions that may contribute to symptoms including: cardiac conditions (congestive heart failure, venous insufficiency); and endocrine disorders such as diabetes mellitus or estrogen deficiency in women Also to identify any current medication that may cause or exacerbate bladder symptoms such as diuretics, opioids, calcium channel antagonists, and cholinesterase inhibitors
Physical examination	A rectal examination should be carried out to exclude any gross pathology including prostatic enlargement in men and also faecal impaction/constipation in men and women Also consider the use of a symptom index for the assessment of benign prostatic hypertrophy in older men, as recommended by the American Urological Association[27] A pelvic examination should be conducted in women to exclude any gynaecological causes Overall physical status should be assessed, including mobility
Neurological assessment	To exclude or assess the potential impact of: damage to the CNS including stroke, spinal cord injury and multiple sclerosis; neurological disease such as Alzheimer's disease and Parkinson's disease; peripheral nerve damage such as that resulting from diabetic neuropathy; and cognitive impairment as a result of other causes such as dementia or delirium
Special assessments	Should be considered in certain patient groups including: cystoscopy in patients with gross haematuria or other risk factors for bladder cancer; measurement of residual post-void volume may be useful to exclude obstruction in older men or urinary retention in patients with diabetes mellitus, spinal cord injury or benign prostatic hyperplasia; and urodynamic testing in patients with nonspecific symptoms or those whose initial therapy has not been successful

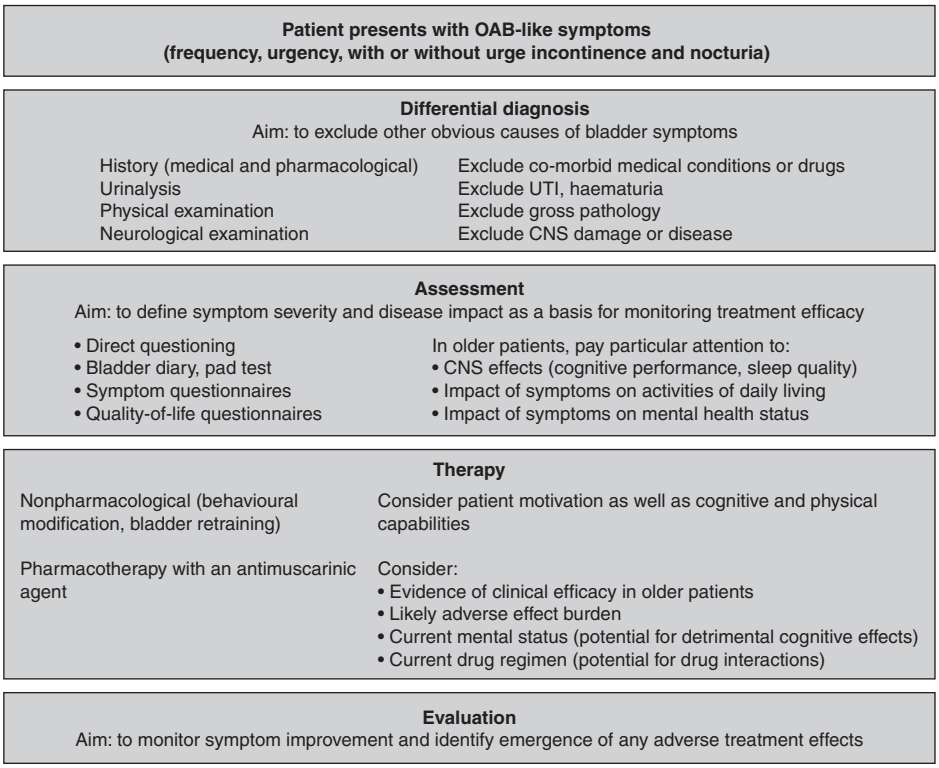

Fig. 3. Management algorithm for the older patient presenting with symptoms of overactive bladder (OAB). **UTI** = urinary tract infection.

of delaying voiding for increasing periods of time once urgency is experienced) and pelvic floor exercises to strengthen and tone the muscles that permit the patient to delay voiding. These approaches may offer comparable efficacy to antimuscarinic therapy in well motivated, cognitively intact patients[31] and may also provide additional benefits when combined with pharmacotherapy.[32] However, nonpharmacological management of OAB requires considerable motivation and commitment, and the usefulness of such approaches may be limited in older patients, particularly among the frail elderly or those living in assisted-care facilities.

4. Pharmacological Management of OAB in the Older Patient

The current standard of care for older patients with OAB is medication. Antimuscarinic agents are the most widely prescribed drug class for the management of OAB. Other pharmacological approaches may be used in specific situations, for example, α-adrenoceptor antagonists for men with benign prostatic hyperplasia, topical estrogen in women with vaginal atrophy, and desmopressin for nocturia, but these are not within the scope of this review.

The efficacy of antimuscarinics has been demonstrated in adult populations, including patients >65 years of age (table III), but few studies have been reported that specifically examine these agents in a geriatric population. Moreover, there is a widespread belief, although not reported in the literature, that antimuscarinics are often underutilised in the elderly despite the marked increase in the prevalence of OAB in this age group. This apparent underuse of an effective treatment option may result from concerns about the frequency of anticholinergic adverse events, such as dry mouth; the likelihood of detrimental CNS effects, including cognitive impairment and sleep disturbances; and the potential

Table II. Acronym for the evaluation of acute and potentially treatable causes of urinary incontinence in adults[24]

D	Delirium or confusion
I	Infection
A	Atrophic vaginitis or urethritis
P	Pharmaceutical agents (e.g. anticholinergic agents, diuretics, α-adrenoceptor agonists, calcium channel antagonists)
P	Psychological factors (e.g. depression, dementia)
E	Excess urine output (e.g. volume-expanded states, retention overflow)
R	Restricted mobility
S	Stool impaction

for harmful interactions with existing pharmacotherapy.

Until recently, the accepted belief has been that antimuscarinics exert their effects by directly inhibiting the muscarinic receptors within the bladder wall muscle that, when stimulated by acetylcholine released from activated cholinergic nerves, lead to bladder contraction and voiding.[48] However, recent reviews have suggested that antimuscarinics may actually work via afferent pathways, mitigating the sensation of urgency.[18]

The currently available antimuscarinics fall into two main structural classes: the tertiary amines oxybutynin, tolterodine, darifenacin and solifenacin and the quaternary amine trospium chloride (figure 5). The structural differences between the agents result in distinct pharmacological and biochemical properties, particularly in their metabolism and membrane penetration, which may be of particular relevance when selecting appropriate pharmacotherapy for the older patient (table IV).

Oxybutynin and tolterodine have proven effective in a range of patient populations and are available as both immediate-release and extended-release oral tablets.[49-51] Symptomatic improvement with the immediate-release formulation of oxybutynin has been reported in three studies in female patients >75 years of age, including a small group of frail elderly women.[33-35] No specific studies have been reported for the extended-release formulation in this patient group. Oxybutynin is also now available as a transdermal patch, which appears to be associated with a lower frequency of dry mouth than either the immediate-release or extended-release formulations in adults, but is associated with localised application

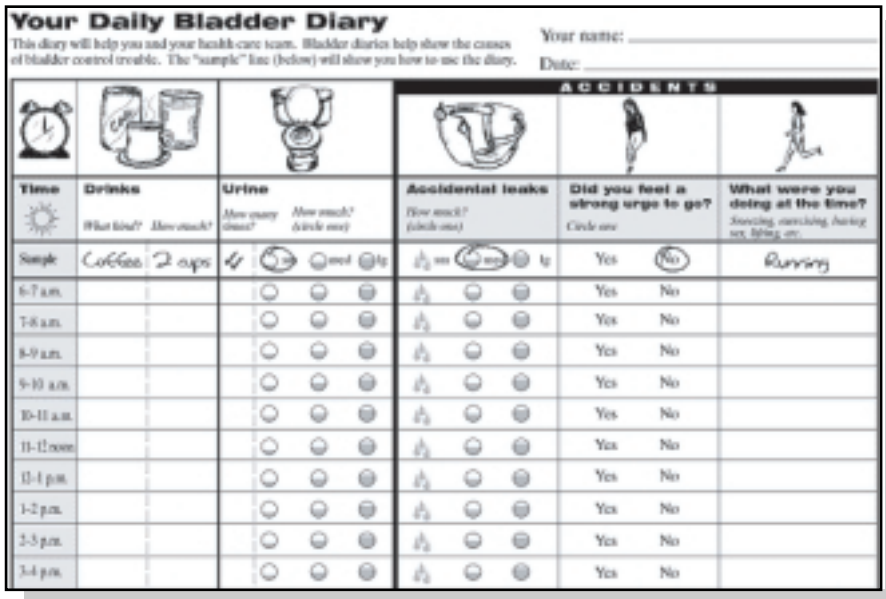

Fig. 4. Example of a bladder diary (reproduced from the National Kidney and Urologic Diseases Information Clearinghouse[30] with permission).

Table III. Current pharmacological options for the management of overactive bladder (OAB) in adults, with special reference to older patients

Agent	Dose	Patient group	Efficacy measures	Most frequent adverse events[a]	Reference
Oxybutynin	2.5mg bid	Frail elderly patients >70 years of age (n = 28)	Significant improvements vs placebo in daytime frequency and incontinence and subjective evaluation of symptoms	Dry mouth (93%), heartburn (57%), blurred vision (50%), constipation (50%), dry skin (50%)	33
	NS	Female patients ≥75 years of age (n = 98)	Improvements in both daily micturition frequency and urge incontinence episodes	NR	34
	2.5–5.0mg tid	Female patients >55 years of age (n = 35)	Significant improvements in bladder capacity, voiding frequency and incontinence episodes	NR	35
Oxybutynin extended-release	5–30mg qd	Adults ≥65 years of age (n = 159). Meta-analysis of data from three clinical trials	81% decrease in the number of urge urinary incontinence episodes, complete continence achieved in 40% of patients	NR	36
Oxybutynin transdermal patch	3.9 mg/day over 96 hours	Adults with urge and mixed urinary incontinence, mean age 59.4 years (n = 125)	Significant improvements vs placebo in urinary incontinence episodes per week, micturition frequency, and mean voided volume; quality of life also improved	Application-site erythema (5.6%), pruritus (16.8%), dry mouth (9.6%)	37
	3.9 mg/day over 96 hours	Adults with urge and mixed urinary incontinence, mean age 63.1 years (n = 121)	Significant improvements vs placebo in urinary incontinence episodes per day and mean voided volume; quality of life also improved	Application-site erythema (8.3%), pruritus (14.0%)	38
Tolterodine	2mg bid	Adults ≥50 years of age (n = 190)	Statistically significant decrease in mean number of voids per day and urge incontinence episodes per day, and increased mean voided volume vs placebo	Dry mouth (37%), headache (11%), dyspepsia (9%)	39
	1mg or 2mg bid	Adults ≥65 years of age (n = 134)	Significant decrease in micturition frequency and urge incontinence episodes per day, and increased mean voided volume vs placebo	Dry mouth (30% and 48%), headache (5% and 7%), diarrhoea (8% and 4%)	40

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Table III. Contd

Agent	Dose	Patient group	Efficacy measures	Most frequent adverse events[a]	Reference
Tolterodine extended-release	4mg qd	Adults aged ≥65 years (n = 214)	Statistically significant improvement vs placebo in number of incontinence episodes per week, mean voided volume and urgency symptoms	Dry mouth (24.3%), constipation (6.1%)	41
Darifenacin	7.5 mg/day or 15 mg/day	Adults aged ≥65 years (n = 207)	Statistically significant improvement vs placebo in number of incontinence episodes per week, number of micturitions per day, urgency episodes and bladder capacity	Dry mouth (20% and 31%), constipation (19% and 24%)	42
Solifenacin	5mg or 10mg qd	Adults (n = 547), of whom 189 were ≥65 years of age	Significant improvements vs placebo in mean number of urgency episodes per week, incontinence episodes, mean number of micturitions per day, and mean voided volume	Dry mouth (14% and 21.3%), constipation (7.2% and 7.8%), blurred vision (3.6% and 5.6%)	43
	5mg or 10mg qd	Adults, mean age 55.7 years (n = 576)	Significant improvements vs placebo in mean number of micturitions per day, incontinence episodes, nocturia, urgency episodes, and mean voided volume	Dry mouth (7.7% and 23.1%), constipation (3.7% and 9.1%), blurred vision (4.0% and 5.9%)	44
Trospium chloride	20mg bid	Adults, mean age 63 years (n = 262)	Significant improvements vs placebo in mean number of voids per day, number of urge incontinence episodes per day and urgency severity	Dry mouth (22%), constipation (9.5%), headache (6.5%)	45
	20mg bid	Adults, mean age 61.1 years (n = 329)	Significant improvements vs placebo in mean number of voids per day, number of urge incontinence episodes per day, mean voided volume and urgency severity	Dry mouth (19.8%), constipation (10.9%), headache (5.5%)	46
		European postmarketing surveillance data in >10 000 adults including 2870 adults >50 years of age	Marked decreases in micturition frequency, number of incontinence episodes and nocturia	NR	47

a Adverse events occurring at a frequency of ≥5% of the study group.

bid = twice daily; **n** = number of subjects receiving the specified antimuscarinic agent; **NR** = not reported; **NS** = not stated; **qd** = once daily; **tid** = three-times daily.

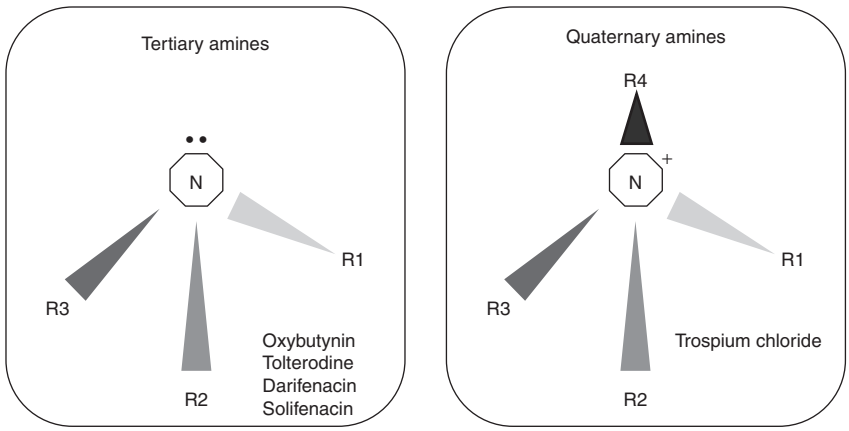

Fig. 5. Chemical structure of antimuscarinic amines used in the treatment of overactive bladder.

site reactions (26.4% of patients).[38] The efficacy of the immediate-release formulation of tolterodine at a dosage of 1mg or 2mg twice daily has been reported in two studies in patients ≥50 years of age.[39,40] The extended-release formulation of tolterodine – initiated and maintained at a dosage of 4 mg/day – has also proven efficacious, safe and well tolerated in patients ≥65 years of age.[41] In direct comparisons in adult populations, extended-release oxybutynin (10 mg/day) and long-acting tolterodine (4 mg/day) appear to have comparable efficacy and tolerability.[50]

Two new antimuscarinic agents, darifenacin and solifenacin, received approval from regulatory bodies and became available to physicians in 2005. In a pooled analysis of data from three large-scale multicentre trials, darifenacin significantly reduced weekly incontinence episodes among adult patients with OAB, conferring additional improvements in terms of frequency, urgency and urge severity.[52,53] While no specific clinical studies have been conducted in an older population, 30% of patients who took part in the three phase III fixed-dose, placebo-controlled studies were ≥65 years of age. No overall differences in safety or efficacy were observed between patients ≥65 years of age and those <65 years of age.[42,54] Phase III studies have also confirmed the efficacy of solifenacin in relieving the symptoms of OAB in adult patients, although there are as yet no reports of the efficacy and tolerability of this agent in studies conducted specifically in older patients.[43,55] The US prescribing information for solifenacin indicates that similar safety and efficacy were observed in both older patients (623 patients ≥65 years of age and 189 patients ≥75 years of age) and younger patients (1188 patients <65 years of age) treated with solfenacin.[56]

Trospium chloride, which is new to the US market but has a favourable clinical history in Europe, has also proven effective in the management of OAB in a variety of patients.[45,46] Although there have been no studies to date that have examined trospium chloride specifically in older patients, data are available from postmarketing surveillance studies in Europe involving over 10 000 adults with OAB and including 2870 adults >50 years of age.[47] Patients experienced marked improvements in micturition frequency, number of incontinence episodes and nocturia; furthermore, efficacy in patients >50 years of age was comparable to that in younger patients. In one study of 4022 adults, micturition frequency was reduced in 51% of patients and nocturia was eliminated in 41% of patients.[47,57] Quality of life improved significantly, with many patients able to resume their leisure activities without restriction. Two placebo-controlled studies conducted more recently in the US have further confirmed the efficacy of trospium chloride in the treatment of OAB.[45,46] Both studies demonstrated significant improvements with trospium chloride therapy in

Table IV. Key structural and pharmacokinetic differences between the antimuscarinics and potential differences in the tolerability profiles of these agents

Agent	Chemical structure	Metabolism/ excretion	Potential for drug interactions	Reported CNS effects	
				cognition	sleep
Oxybutynin	Tertiary amine	Hepatic	Potent inhibitor of CYP3A4	Yes	Yes
Tolterodine	Tertiary amine	Hepatic	Coadministration with CYP3A4 or 2D6 inhibitors or other drugs metabolised via these enzymes should be avoided	Minimal effects on quantitative EEG measures but case reports of night terrors, effects on memory and hallucinations	Yes
Darifenacin	Tertiary amine	Hepatic	Coadministration with CYP3A4 or 2D6 inhibitors or other drugs metabolised via these enzymes should be avoided	None reported to date	None reported to date
Solifenacin	Tertiary amine	Hepatic	Potent inhibitor of CYP3A4	None reported to date	None reported to date
Trospium chloride	Quaternary amine	Renal excretion 60–80% as the parent compound	May interfere with renally excreted cationic compounds	No Minimal effects on quantitative EEG measures	None reported to date

CYP = cytochrome P450; **EEG** = electroencephalogram.

micturition frequency, urge incontinence episodes and urgency severity, as well as marked improvements in quality of life across multiple domains. In head-to-head comparisons with oxybutynin and tolterodine, trospium chloride appears to provide comparable efficacy but with fewer adverse effects.[47] Dry mouth, while still the most frequently reported adverse event, appears to occur at a lower frequency with trospium chloride than with either oxybutynin[58] or tolterodine,[48] and in the European postmarketing surveillance studies, dry mouth was reported at a frequency of 4.1%.[48] The US package insert for trospium chloride indicates that of the 591 patients with OAB who received treatment with this agent in the two US-based, placebo-controlled, efficacy and safety studies, 249 (42%) were ≥65 years of age and 88 (15%) were ≥75 years of age. In these two studies, the incidence of commonly reported adverse events in patients treated with trospium chloride (including dry mouth, constipation, dyspepsia, UTI and urinary retention) was higher in patients ≥75 years of age compared with younger patients. This effect may be related to an enhanced sensitivity to anticholinergic agents in these patients, and thus, based on tolerability, the dosage of trospium chloride may be reduced to 20 mg/day in patients ≥75 years of age.

5. Relationship between the Structure and Function of Antimuscarinics: Implications for the Older Patient

Successful management of the older patient with OAB requires an appreciation of age-related changes that may affect the absorption, distribution, metabolism and elimination of antimuscarinic agents, as well as the potential for adverse effects and drug interactions. Structural differences between the currently available antimuscarinics appear to translate into important pharmacological and clinical differences of particular relevance to the older patient. These include differences in the nature and severity of adverse effects commonly associated with anticholinergic therapy, such as dry mouth, constipation and cognitive changes.

5.1 Lipophilicity and Hydrophilicity: CNS Effects

Older patients may be more sensitive to the cholinergic effects of antimuscarinic therapy as a result of reductions in metabolism and elimination as well as pharmacokinetic drug interactions. In addition, elderly patients often take prescribed and over-the-counter medications with direct anticholinergic properties. The cumulative effects of multiple anticholinergic agents may put patients at risk of cognitive adverse effects and delirium,[59,60] and for patients experiencing dementia, may exacerbate existing cognitive deficits. Thus the ability of antimuscarinic agents to cross the blood-brain barrier and their effects on the CNS are important considerations when selecting antimuscarinic medication for the older patient with OAB. Differences in the molecular characteristics of the available antimuscarinic agents affect the likelihood that these agents will cross the blood-brain barrier. In general, a large, polar molecule that is hydrophilic is less likely to cross the blood-brain barrier than a small, neutral, hydrophobic molecule.

Tolterodine and oxybutynin have both been associated with impaired cognitive functioning.[61] In a study of 12 elderly volunteers, short-term oxybutynin therapy resulted in significant cognitive impairment across multiple domains.[62] Hence, older patients receiving oxybutynin therapy should be carefully monitored for any deterioration in their cognitive functioning. There is some suggestion that tolterodine is less likely to be associated with cognitive impairment compared with oxybutynin as it is less lipophilic and, therefore, less likely to cross the blood-brain barrier.[49,63] However, there remain case studies in the literature showing an association between tolterodine therapy and night terrors, hallucinations and forgetfulness.[64-66]

Darifenacin is another tertiary amine capable of crossing the blood-brain barrier, but it did not appear to be associated with significant cognitive impairment in a placebo-controlled study of 129 elderly volunteers.[67] This apparent lack of CNS effect may be explained by the selectivity of this agent for M_3 receptors and its lower affinity for M_1 receptors. No studies examining the specific effects of solifenacin on cognitive functioning in older patients have been reported to date.

As a quaternary amine, trospium chloride is hydrophilic and lipophobic and has the theoretical advantage compared with tertiary amines that it is unlikely to cross the blood-brain barrier.[68,69] This may lead to a number of clinical characteristics of particular importance when managing the older patient, including a lack of associated cognitive dysfunction. While there have been no studies that have directly examined whether trospium chloride causes cognitive adverse effects, the theory is supported by experimental studies, clinical studies, the lack of incidence of cognitive adverse events in monitoring reports and physician experience.[70-73]

Two studies have confirmed the lack of effect of trospium chloride on cerebral functioning in healthy adult volunteers.[70,71] Both studies included oxybutynin as a comparator and one study also included tolterodine. Oxybutynin administration resulted in marked changes in electroencephalographic activity in both studies, whereas trospium chloride and tolterodine appeared to be associated with minimal effects. The clinical relevance of these results is not clear; however, they may provide an additional indicator of blood-brain barrier transfer of these compounds.

Differences have also been observed between oxybutynin, tolterodine, and trospium chloride in terms of the effects of these agents on sleep architecture and quality.[72] Diefenbach et al.[72] recruited 24 healthy adults aged ≥50 years and conducted polysomnographic recordings and cognitive testing following single doses of oxybutynin, tolterodine, trospium chloride or placebo. Oxybutynin and tolterodine administration resulted in statistically significant reductions in rapid eye movement (REM) sleep and a slight increase in REM latency. These changes were not observed following trospium chloride administration. Further investigation is warranted in order to establish whether these statistical differences are clinically relevant. While no changes in cognitive functioning were observed following single-dose administration in this study, the

potential for such effects remains a possibility during oxybutynin or tolterodine therapy, especially in older patients whose sleep architecture may already be disturbed as a result of co-morbid medical conditions. A placebo-controlled study of trospium chloride therapy in 658 adult patients with OAB also found no effect of this agent on daytime sleepiness and no increase in CNS effects such as somnolence.[73]

Increased permeability of the blood-brain barrier to certain substances has been documented in elderly people in a number of studies;[74,75] however, in the absence of significant neurological disease, this increased permeability does not appear to result in the indiscriminate transfer of molecules into the cerebrospinal fluid.[75,76] How the increased permeability of the blood-brain barrier affects transfer of anticholinergic agents into the cerebrospinal fluid is not known.

5.2 Biotransformation and Excretion: Potential for Drug Interactions

Biotransformation by the cytochrome P450 (CYP450) system is an important step in the activation or elimination of a large number of drugs, including oxybutynin, tolterodine, darifenacin and solifenacin. Co-administration of drugs (a common practice among the elderly) that are metabolised via the same pathways raises the possibility of clinically relevant and potentially serious drug interactions. In older patients, metabolism via the CYP450 system is of particular relevance given the potential for declining activity of certain members of the CYP450 family combined with decreased hepatic blood flow, which can reduce first-pass metabolism and thus bioavailability of drugs metabolised via this route.

Oxybutynin is metabolised via the CYP450 isozyme 3A subfamily and is a potent inhibitor of both the CYP3A4 and CYP2D6 isozymes, whereas tolterodine undergoes polymorphic metabolism in the liver via both the CYP2D6 and CYP3A4 pathways.[77] Darifenacin is also extensively metabolised in the liver by CYP3A4 and CYP2D6 and may act as an inhibitor of CYP2D6 substrates.[54] The primary pathway for elimination of solifenacin is hepatic metabolism via CYP3A4; however, alternative metabolic pathways exist.[56] The prescribing information for each of these agents recommends caution when co-prescribing them with inducers or inhibitors of the same isozyme. The clinical relevance of many of the drug interactions documented in the prescribing information is not known. However, ketoconazole, a potent CYP3A4 inhibitor, results in clinically relevant interactions when co-prescribed with tolterodine, solifenacin, darifenacin or oxybutynin.[54,56,77-79]

Unlike the other antimuscarinic agents described in the previous paragraph, trospium chloride is not metabolised by the CYP450 system in the liver, which minimises the likelihood of any potentially harmful drug interactions with this agent. Sixty to 80% of the absorbed dose of trospium chloride is excreted largely unchanged through the kidneys, and the active compound may in fact accumulate in the bladder.[80] Given the recent shift in understanding of the pathophysiology of OAB to implicate the afferent nerves of the bladder and urothelium, this accumulation may be clinically beneficial.[18,80] Accumulation in the bladder may contribute to the pharmacological activity of the drug and could account for its rapid onset of action (statistically significant differences in most outcomes observed after 1 week of treatment)[45] and relatively greater effect on the bladder compared with the salivary glands, as shown by the comparatively low incidence of 'cholinergic adverse effects' such as dry mouth.[47]

6. Managing the Older Patient with OAB: Clinical Guidance

Antimuscarinic therapy, with or without behavioural therapy, currently represents the standard of care for patients with OAB. However, when selecting an antimuscarinic agent for the management of an older patient presenting with OAB, consideration should be given to: evidence of clinical efficacy, specifically that in the older population; the frequency of anticholinergic adverse events, such as dry mouth; the likelihood of detrimental CNS effects, including cognitive impairment and

sleep disturbances; and the potential for interaction with existing pharmacotherapy. Figure 3 illustrates a management algorithm suitable for the older patient with OAB.

Nonpharmacological therapies, such as behavioural modification, may offer some symptomatic benefit and should be implemented in all patients with OAB. Patients or their healthcare providers should also be encouraged to implement behavioural changes (such as fluid management and alterations in diet) and bladder retraining, which may prove useful in mobile, motivated older patients.

Several antimuscarinic agents are currently available for the treatment of OAB in adults, including oxybutynin, tolterodine, trospium chloride, darifenacin and solifenacin. Antimuscarinics appear to exert their clinical effect either through inhibition of the bladder muscarinic receptors or modulation of afferent impulses by way of the urothelium. Variations in both their structure and their functional profile may account for differences in clinical outcomes. Dry mouth is the most frequently reported adverse event with antimuscarinic therapy, and extended-release formulations of oxybutynin and tolterodine have reduced the frequency of this event to levels comparable with those observed for trospium chloride, darifenacin and solifenacin. Oxybutynin and tolterodine have both been associated with significant negative cognitive effects, in addition to affecting sleep architecture and quality. In contrast, trospium chloride does not appear to be associated with cognitive adverse events or to negatively affect sleep architecture or quality, possibly because of its hydrophilic, lipophobic chemical structure and consequent inability to cross the blood-brain barrier. It is anticipated that both darifenacin and solifenacin, as tertiary amines, will be able to cross the blood-brain barrier; however, darifenacin is not associated with cognitive adverse events, which may be reflect the selectivity of this agent for the M_3 receptor. Data are awaited on the cognitive effects of solifenacin. Oxybutynin, tolterodine, darifenacin, and solifenacin are all metabolised hepatically via the CYP450 system and may interact with other drugs metabolised via this route. Trospium chloride is not extensively metabolised by the liver and is excreted largely unchanged through the kidneys.

7. Conclusion

Effective strategies are available for the management of OAB with or without an incontinence component in older patients. Patients can expect both symptomatic and quality of life improvements but prescribing needs to be selective.

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