REVIEW ARTICLE

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Antimuscarinic Treatment in Overactive Bladder

Special Considerations in Elderly Patients

Adrian S. Wagg

Division of Geriatric Medicine, Department of Medicine, University of Alberta, Edmonton, AB, Canada

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Abstract

Overactive bladder is a common condition that increases in prevalence in association with age. Antimuscarinic therapy remains the mainstay of pharmacological treatment for the condition, and there is an increasing body of evidence that supports the use of these drugs. Despite this, and because of concerns about associated adverse effects, older people are less likely to receive active treatment for their condition. This review considers some of the factors that need to be taken into account when using these medications.

1. Introduction

Overactive bladder (OAB) is defined by the International Continence Society (ICS) as urinary urgency, usually accompanied by frequency and nocturia with or without urgency urinary incontinence (UI), in the absence of urinary tract infection (UTI) or other obvious pathology.[1] These symptoms can have a considerable negative impact on a subject's quality of life, typically resulting in embarrassment, loss of dignity and a withdrawal from social activities and interactions,[2] perhaps increasing the likelihood of social isolation, a significant factor associated with functional decline in the elderly.[3] Population-based surveys have shown that OAB is a common disorder across adult life, but its prevalence increases in association with age. For example, in a cross-sectional survey of 19 165 adults in Canada, Germany, Italy, Sweden and the UK (the EPIC study), the overall prevalence of OAB was 11.8%.[4] The overall rates were similar between men and

women, and increased with age; urgency was reported in 19.1% of men and 18.3% of women aged 60 years or over. In a population-based survey of 5204 adults in the US (the NOBLE study), the overall prevalence of OAB was 16% in men and 16.9% in women; the prevalence was age-related.[5] Apart from the impact attributable to its lower urinary tract symptoms, OAB is associated with a number of health-related problems in older people. Published data show an increased risk of falls and fractures, sleep disturbance, depression, UTI and institutionalization associated with UI.[6,7] With population aging and its associated increased life expectancy, there appears to be an increased expectation of retaining a good quality of life. People also appear to be more demanding of healthcare services, and this means that, as the absolute number of people with OAB in the population rises, the demand for adequate treatment of the condition will also increase. This review discusses issues in older people that may need to be taken into account when treating OAB with antimuscarinic agents.

2. Antimuscarinic Therapy

The main pharmacological treatment for OAB is the use of antimuscarinic agents. The pathophysiology of OAB is not completely understood, but it is likely that antimuscarinic drugs act by inhibiting the M_2 and M_3 subtypes of muscarinic receptors in the urinary bladder, perhaps leading to a decrease in detrusor contractions and an alteration of sensory function in the storage phase of micturition. M_3 receptors are found in many other tissues – the smooth muscle of the bowel, salivary glands, the ciliary muscle of the eye, and the brain, which means that the use of antimuscarinic agents can give rise to anticholinergic-type adverse events such as dry mouth, constipation and blurred vision.[8] These adverse effects are usually mild to moderate in severity and data suggest that these are generally tolerated by older patients if they are obtaining effective relief of symptoms. There is accumulating evidence that, perhaps because of the increased severity of UI in older people,[9] or because they are less successful with behavioural or lifestyle measures, older people are not only more likely to request drug therapy to control their OAB symptoms if it is withdrawn[10] but are also more likely to need higher doses of drug to achieve a benefit, particularly in the oldest old (>75 years of age).[11,12] The limited available human data appear to show that muscarinic (M_3/M_2) receptor expression appears to decline in association with increasing age;[13] this suggests that the increased doses taken may not related to physiological change at the level of the bladder, as less antimuscarinic, rather than more, should be required to achieve complete blockade. Additionally, evidence suggests that perhaps despite a higher rate of adverse events, the elderly are more adherent to therapy than younger people.[14]

Data on the efficacy of antimuscarinic agents in cognitively intact, community-dwelling older people exist from *post hoc* pooled analyses from clinical trials and increasingly from trials specifically designed to assess the efficacy of newer antimuscarinic agents in the older population. There is still, however, a dearth of data about the use of such agents in older, frailer populations.

3. Cognition and Delirium

Aging has been described in terms of a progressive cholinergic deficiency.[15] Animal studies have indicated that M_1 receptors in the neocortex, hippocampus and neostriatum of the forebrain play an important role in memory and cognition; however, levels of M_3 receptors are low in the forebrain, and the functional role of M_4 and M_5 receptors remains unclear.[16] The cholinergic system plays an important role in human cognition and also in the pathology of Alzheimer's dementia, where blockade of muscarinic receptor subtypes can increase amyloidogenic processing of amyloid precursor protein and promote tau phosphorylation.[17] Anticholinergic treatment in older people is an identified risk factor for impaired cognition,[18] and a high anticholinergic load is associated with an increased likelihood of scoring poorly on the Mini-Mental State Examination (MMSE).[19] Epidemiological studies suggest that continued anticholinergic treatment over 4 years, compared with non-use of anticholinergic

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drugs, is associated not only with impaired cognition and verbal fluency in women and impaired visual memory and executive function in men, but also with a risk of incident dementia.[20] Another recent retrospective analysis of anticholinergic drug therapy in older adults revealed a positive association between drug usage and morbidity and mortality.[21]

Medications with anticholinergic properties are commonly taken by older people, and an estimated 20–50% of people with dementia in the US take at least one medication with anticholinergic activities.[19,22] As far as bladder medication goes, oxybutynin has been associated with impaired cognition in cognitively intact older adults[23] and this drug is specifically mentioned as unsuitable for the elderly in the revised Beers' criteria.[24] Although drugs with anticholinergic properties have been associated with an incidence of delirium in older people[25] and increased hospital admissions in those with coronary vascular disease,[26] there are equally reports which show no association.[27]

Antimuscarinics for the bladder have been associated with delirium in older people, most often in those at risk of cognitive decline[28,29] but also in those with no pre-existing cognitive impairment.[30] Such reactions are uncommon, are likely to be idiosyncratic and are reversible. There is little evidence of widespread cognitive dysfunction occurring in daily clinical practice related to the use of antimuscarinics for OAB.[31] However, although there are no long-term data on the risks associated with antimuscarinics for the bladder, how safe are these products likely to be for older people, who may be at greater cognitive risk?

Mechanisms that determine the degree of cognitive risk with individual antimuscarinic drugs are not fully understood, but probably include differences in receptor binding profiles and the extent to which they cross the blood brain barrier, including such factors as lipophilicity, degree of ionization and size. Antimuscarinics with greater selectivity for the M_3 receptor rather than the M_1 receptor should theoretically be associated with less potential to cause cognitive impairment. Data do exist on the short-term cognitive safety of bladder antimuscarinics in cognitively intact older people. Generally these have shown no effect on cognition as assessed by a battery of neuropsychological tests assessing speed of working memory, speed of memory, power of working memory, attention, name-face recall and continuity of attention.[32-36] Studies on trospium chloride have also assessed cerebrospinal fluid penetration, the effect on EEG activity and on simulated driving ability.[37-40] Oxybutynin, in its extended-release forms, which are often used as an active control, often at doses higher than those typically used in clinical practice, has shown variable effects on memory in these groups.

The problem in older people may be 3-fold; firstly, approximately 18% of people may either not be cognitively intact or be at risk of cognitive impairment;[41] secondly they may suffer from diseases associated with an increased risk of cognitive impairment;[42-46] and thirdly, older people often take other agents with anticholinergic properties.[21,47-49] Attention needs to be paid to coexisting medication when prescribing an antimuscarinic agent for older people; if other drugs with antimuscarinic properties are being taken, these should be withdrawn if possible. A recent review by Gerretsen and Pollock[50] gives a comprehensive overview of this topic. If withdrawal cannot be achieved, a careful and early review of cognitive adverse effects, if possible with the assistance of a family member or carer, should be conducted to assess any negative impact so it can be managed accordingly.

4. Cardiovascular Factors

There is a well established association between resting pulse rate and cardiac mortality.[51,52] Resting heart rate also appears to predict subsequent development of coronary artery disease and heart failure in older adults.[53] Antimuscarinics, acting upon cardiac M_2 receptors, modulate pacemaker activity, atrioventricular node function and ventricular contraction. The parasympathetic nervous system also controls vagal tone, which decreases in association with aging. Antimuscarinics may also lead to a reduction in heart rate variability and alter the recovery of heart rate after

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exercise, two factors also associated with an increased risk of cardiac-related death.[54]

In a retrospective analysis of bladder antimuscarinic prescriptions from a US insurance database, Andersson et al.[55] found that people with OAB were more likely to have co-existent cardiovascular disease than those without. Of subjects with OAB, 39.1% had resting heart rates over 80 bpm, suggesting that they might be at risk of adverse events should the antimuscarinic raise their resting heart rate. However, there is currently no evidence suggesting that a pharmacologically raised heart rate, versus a native resting heart rate, is associated with a poor outcome. In clinical trials, antimuscarinics for the bladder for the most part have shown no clinically significant increases in resting heart rate (>5 bpm), with the exception of a few trials: two trials of tolterodine, one in healthy volunteers, who, at the 4 mg dose, just reached a statistically significant difference versus placebo, and another versus darifenacin and placebo, in which a greater proportion of the tolterodine-treated subjects had increases in resting heart rate >5 bpm; a comparison of propiverine versus oxybutynin and placebo, in which propiverine doses of 20 and 45 mg were associated with statistically significant rises in resting heart rate; and a single trial of trospium, which examined the drug's effect on EEG variables and found that trospium was associated with a rise of 9 bpm when given intravenously but no significant rise was associated with oral administration.[56-62] The elderly in particular may also be more susceptible to these effects than younger adults. An analysis from a US FDA dataset comparing those who took an inhaled antimuscarinic to those on an oral agent found that those who received an inhaled agent were, with the exception of stroke and hypertension, at higher risk of developing cardiovascular adverse effects.[63] A 12-week, post-marketing observational study of solifenacin use examined cardiovascular adverse effects in 4450 patients with OAB under the care of office-based urologists and concluded that only in those with pre-existing cardiac morbidity and those over the age of 80 years was there an increase in the incidence of cardiac adverse effects.[58] Overall, antimuscarinics for the bladder appear to be generally safe from a cardiac point of view;[64] however, there are few data from studies that specifically evaluated cardiac safety in older people or in those with pre-existing cardiac disease. Once again, only a general note of caution can be given when dealing with older, frailer people.

5. Common Adverse Effects

The use of antimuscarinics for OAB is limited chiefly by their tolerability. Studies show that this limited tolerability is one of the main reasons why patients stop their medications. While this is not an issue that specifically affects the elderly, dry mouth, constipation and dyspepsia are common symptoms in older people that may be made worse by these medications.

5.1 Dry Mouth

Xerostomia is common in older people.[65] A study of 175 acutely hospitalized community-dwelling older people (mean age [SD] 82 [5.7] years) and 252 outpatients (mean age [SD] 77 [5.7] years) found that 63% of the hospitalized elderly and 57% of outpatients complained of dry mouth. Dry mouth was more common amongst those on multiple medications.[66] In general, older people, women and those taking multiple medications are more likely to report the symptom. Antimuscarinics clearly may exacerbate this condition, leading to concerns about deteriorating dental health, and a 2011 warning to the FDA from the American Dental Association.[67] Meta-analyses of bladder antimuscarinics show minor variations in the incidence of dry mouth from clinical trials, with oxybutynin associated with the highest prevalence.[68] A recent subcut analysis of a randomized controlled trial of solifenacin 5 mg/day versus oxybutynin 5 mg three times daily examined the tolerability of both drugs in subjects under and over the age of 65 years; the study found that dry mouth was no more common amongst those over the age of 65 years than amongst younger subjects but was more common and more severe with oxybutynin.[69] In a pooled analysis of data from registration trials, it was

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found that, in subjects over 75 years of age treated with 8 mg or 4 mg of fesoterodine, dry mouth was more common in the older aged sample.[11]

5.2 Constipation

Constipation is also a troublesome problem for many people, but it often afflicts the elderly. Estimates of the prevalence of constipation in a recent study in the US that used Rome III criteria[70] found the prevalence of chronic constipation in a sample of 2000 men and women over the age of 40 years to be 26.3% in men and 15.3% in women. Men and women with OAB were significantly more likely to report faecal incontinence than those without OAB.[71] In self-reports by older people, prevalence estimates range between 26% and 34% for women and 16% and 26% of men for the age groups >65 years and >85 years.[72-74] Most OAB trials use self-report to ascertain rates of occurrence, and variably report prevalence at baseline. A recent meta-analysis of constipation rates associated with the use of OAB drugs included 37 studies in 19 434 subjects (12 368 treated with drugs) and found an overall odds ratio (OR) of 2.18 (95% CI 1.82, 2.6) for constipation associated with treatment; ORs ranged between 3.02 (95% CI 2.37, 3.84) for solifenacin and 1.36 (95% CI 1.01, 1.85) for tolterodine.[75] Constipation is usually manageable with proprietary laxatives such as polyethylene glycol, but if severe, it may need either antimuscarinic dose reduction or cessation.

6. Polypharmacy, Medications and Incontinence

Older people consume a high proportion of prescribed medications. Those over 65 years of age comprise between 12–16% of the population in the US, UK and Canada but consume 32%, 50% and 45% of prescribed medications, respectively.[76-81] Aside from the question of concomitant medications with antimuscarinic properties, discussed above (section 3), there are a number of factors that need to be taken into account when prescribing antimuscarinic agents for incontinence. Firstly, the pharmacokinetics of antimuscarinic therapy may be altered in older people. Gastric emptying is often reduced, which theoretically leads to reduced absorption of drugs; there are, however, few data to suggest that this is a material or clinically significant concern in the elderly. Reduced gastric motility caused by the action of antimuscarinic therapy may, however, lead to reduced absorption of other medications, particularly extended-release compounds.

The common decrease in serum albumin in older people leads to increased plasma levels of free drug. This is known to affect tolterodine and may be partially responsible for the increased incidence of adverse effects in some older people. Older people also have a reduced hepatic mass and hepatic blood flow compared with younger people, leading to reduced clearance of drugs. This will potentially affect levels of oxybutynin, tolterodine, darifenacin and solifenacin. These four drugs and fesoterodine are dependent on the cytochrome P450 (CYP) system for their metabolism; in the case of fesoterodine, this is only true for excretion; its conversion to its active metabolite, 5-hydroxymethyl tolterodine, being accomplished by non-specific esterases throughout the body. Drug-drug interactions involving potent CYP3A4 inhibitors (azole antifungals, macrolide antibiotics, cyclosporin, vinblastine) are important when considering therapy with oxybutynin, solifenacin, darifenacin and tolterodine.[82] There is one case report of an interaction between tolterodine and warfarin in two older patients,[83] which has not been seen in healthy volunteers. Naturopathic/herbal and traditional Chinese medical preparations should also be considered for potential interactions, especially in areas where these agents are used frequently. Some medications may predispose an older person to incontinence. Wherever possible, they should be reviewed and, if possible, any offending drugs, should be removed or altered. Although the list of medications that theoretically may worsen incontinence is long (table I), there is little published evidence of the associations between these medications and incontinence. However, evidence does exist for diuretics, prostaglandin inhibitors, α-blockers, selective serotonin reuptake inhibitors, cholinesterase inhibitors (CEIs) and systemic hormone replacement therapy.[85-92]

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Table I. Medications potentially interfering with successful maintenance of continence in older people (this table was published in *Brocklehurst's Textbook of Geriatric Medicine and Gerontology*,[84] p 929, copyright Elsevier 2010; reproduced with permission)

Medication	Effects on continence
α-Adrenergic antagonists	Decrease smooth muscle tone in the urethra and may precipitate stress urinary incontinence in women
Angiotensin converting enzyme (ACE) inhibitors	Cause cough that can exacerbate stress urinary incontinence
Agents with antimuscarinic properties	May cause ineffective voiding and constipation that can contribute to incontinence; may cause cognitive impairment and reduce effective toileting ability
Calcium channel blockers	May cause constipation (verapamil) that can contribute to incontinence; may cause dependent oedema (amlodipine, nifedipine), which can contribute to nocturnal polyuria
Cholinesterase inhibitors	Increase bladder contractile function and may precipitate urgency incontinence
Diuretics	Cause diuresis and precipitate incontinence
Lithium	Polyuria due to diabetes insipidus-like state
Opioid analgesics	May cause constipation, confusion and immobility – all of which can contribute to incontinence
Psychotropic drugs; sedatives, hypnotics, antipsychotics; histamine H_1 receptor antagonists	May cause confusion and impaired mobility and precipitate incontinence; most have anticholinergic effects
Selective serotonin reuptake inhibitors	Increase cholinergic transmission and may lead to urgency urinary incontinence
Gabapentin, glitazones, non-steroidal anti-inflammatory agents	Can cause oedema, which can lead to polyuria while supine and exacerbate nocturia and night-time incontinence

7. Cholinesterase Inhibitors

Dementia is common and underdiagnosed in older people. The main drug class used for therapy for Alzheimer's disease, the CEIs, appears to be associated with an increased risk of urinary urgency and urgency incontinence. There is evidence CEIs can cause or worsen UI, originating from a case report[91] and followed by a case series of 216 consecutive patients with probable Alzheimer's disease from a memory clinic in Scotland.[93] In the latter, CEI treatment was associated with a 7% risk of new incontinence; the highest risk was seen in those with the most behavioural problems; there was a lower risk in those who appeared to respond positively to treatment with drug.

Further evidence for an interaction between antimuscarinics and CEIs comes from a database study of nursing home residents in one US state.[94] Residents with dementia newly treated with CEIs were more likely to then be prescribed a bladder antimuscarinic than those residents with dementia not given a CEI, an example of a geriatric 'prescribing cascade.'[95] Concomitant use of antimuscarinics (extended-release oxybutynin and tolterodine) and CEIs in nursing home residents was associated with a decline in activities of daily living function in the most functionally able residents, but there was no worsening of cognition, probably because the cognitive measure (Minimum Data Set – Cognition Scale [MDS-COGS]) was inadequately sensitive. More importantly, there was no case of delirium observed.[96] A study in which the primary objective was to assess the cognitive impact of trospium chloride in older people with dementia treated with galantamine over a 6-month period was recently conducted.[97] The study hypothesized that galantamine in combination would not result in any adverse outcome such as that reported by Sink et al.[96] A total of 46 subjects with UI and dementia were enrolled; 10 withdrew from the study. No effect on cognition or activities of daily living was detected over the duration of the study. A within-group analysis demonstrated an improvement in nocturia and a reduction in pad use in this combination group.[97] A small study reported some positive effects of treating UI with propiverine in subjects with probable Alzheimer's disease taking CEIs.[98] Although intuitively illogical, given the opposing pharmacological actions, there seems to be no

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reason not to use bladder antimuscarinics for older people with dementia. The current weight of evidence appears to be that a positive outcome in terms of bladder control can be achieved without significant detriment to either cognition or activities of daily living. There is, as yet, no data on quality of life for this frail older group. When treating patients in this population, an early review of the effect of the drug on continence and cognitive status should be performed to ensure safe, effective prescribing.

8. Conclusions

Antimuscarinic therapy is effective for the treatment of OAB in older people. With adequate surveillance and appropriate regard for coexisting medications and medical conditions in older people, these drugs can be used safely and effectively. Prescribers should be mindful of other anticholinergics that the patient may be taking when prescribing an antimuscarinic; exposure to these medications in the long-term may be associated with poorer outcomes, and therefore, limitation of the total anticholinergic load would seem clinically sensible. Antimuscarinics should be started at the lowest dose available for reasons of tolerability rather than efficacy, and clinicians should be prepared to increase the dose of the medication in a similar fashion to younger people, given the data on disease severity and the lesser impact of behavioural therapies in this older age group.

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Correspondence: Dr *Adrian S. Wagg*, Professor of Healthy Ageing, 1-116 Clinical Sciences Building, 11350 – 83 Avenue, Edmonton T6G, Canada.
E-mail: Adrian.wagg@ualberta.ca

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