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Review Article

Practical points in the medical treatment of overactive bladder and nocturia in the elderly

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ABSTRACT

The prevalence of overactive bladder (OAB) increases with age. Degeneration of the central nervous system in the elderly has been proposed as one of the pathogenic factors of OAB. Antimuscarinic therapy is effective in the treatment of OAB; however, intolerable systemic adverse events and cognitive dysfunction during treatment with nonselective antimuscarinic agents is of growing concern in elderly patients. The newly developed beta-3 adrenoceptor agonist mirabegron does not adversely affect flow rate and detrusor pressure, and its therapeutic efficacy and tolerability are similar in patients aged > 65 years and > 75 years, suggesting it might be the therapeutic choice in older patients with OAB. Nocturia can cause sleep deprivation at night and increase daytime sleepiness and loss of energy in the elderly. Desmopressin add-on therapy is effective in improving nocturia and storage symptoms. However, elderly patients with a baseline serum sodium level below the normal range are at high risk of developing significant hyponatremia.

1. Prevalence of overactive bladder in the elderly

Overactive bladder (OAB) is a clinical diagnosis with the core symptom of urgency, accompanied by frequency and nocturia, with or without urgency urinary incontinence [1]. The strongest predictor of OAB-associated bother is urinary urgency [2]. OAB symptoms can be bothersome and can negatively affect health-related quality of life (HR-QoL) [3,4]. Because the prevalence of OAB increases with age, identifying and treating OAB in the elderly is important [5,6]. Several medical comorbidities may have associations with urinary storage symptoms [7]. The risk of nocturnal polyuria also increases in patients aged ≥ 65 years [8].

In one study, patients with congestive heart failure had more storage urinary symptoms suggestive of OAB than age-matched controls [9]. Another study demonstrated that patients with congestive heart failure had high OAB symptom scores and storage International Prostate Symptom Scores (IPSSs) suggestive of OAB and/or storage lower urinary tract symptoms (LUTSs) [10,11].

Diabetes mellitus (DM) is a chronic metabolic condition and causes numerous complications. Clinicians have become concerned about OAB and its component symptoms [12,13]. Patients with type 2 DM present with more OAB symptoms such as urgency and nocturia than controls. The effects of diabetes due to poor blood sugar control as measured by glycated hemoglobin could play a crucial role in the development of OAB symptoms [14]. In a recent study, Wen et al [15] found that DM patients with a body mass index > 25 and obesity were more likely to have OAB than those without these conditions. Chapple et al [16] reported that 21.4% of 3962 diabetic women had OAB. Some patients have both detrusor overactivity (DO) and inadequate contractility, resulting in urgency urinary incontinence and a large postvoid residual volume (PVR) [17]. Different urodynamic findings of low detrusor contractility with or without increased isovolumetric contractions have also been found in women with idiopathic underactive bladder [18].

2. Pathophysiology of OAB in the elderly

OAB is common in both sexes and increases in prevalence with aging. Animal and human studies have revealed that increased release of acetylcholine from nonneuronal and neuronal sources during bladder filling causes OAB and DO, and this afferent activity can be inhibited by antimuscarinics [19]. In addition, increased

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purinergic receptor sensitivity and raised P2X3 receptor expression in the urothelium of aged bladders might alter the afferent pathway, resulting in OAB in the older population [20]. Chronic ischemia and inflammation in the aged bladder might also contribute to bladder dysfunction in the elderly [21]. In patients with DM, the PVR is significantly increased, which might increase the bother of voiding dysfunction in addition to OAB in the elderly [22].

3. Neurological disease in OAB elderly patients

The incidence of OAB increases with aging; thus, degeneration of the central nervous system (CNS) in the elderly is proposed as one of the pathogenic factors of OAB [23]. In patients with CNS disorders such as cerebrovascular accident and Parkinson's disease (PD), white matter disease causing dementia increases significantly with age and can also cause OAB and urinary incontinence [24]. A random-effect meta-analysis found that the prevalence of urinary incontinence was 50.9% in patients with multiple sclerosis, 52.3% in those with spinal cord injury, 33.1% in those with PD, and 23.6% in stroke patients [25].

In patients older than 60 years with irritative urinary symptoms, brain magnetic resonance image showed subclinical high-intensity ischemic changes in the basal ganglia in 82.6% of elderly OAB patients [26]. OAB is common in elderly people with CNS lesions. In a community health survey, 31% of patients with CNS disease reported OAB symptoms, and the overall prevalence of neurogenic OAB was 0.6%. Patients with neurogenic OAB have a poorer HR-QoL compared with patients with general OAB [27].

Anticholinergic treatment of OAB in patients with CNS lesions could cause CNS adverse events (AEs) and impaired bladder emptying. Although antimuscarinic treatment has a high success rate, cognitive dysfunction during treatment with nonselective antimuscarinic agents for OAB is of growing concern [28]. In the past decade, intravesical injection of onabotulinumtoxinA (BoNT-A) has emerged as an effective treatment for OAB among patients refractory to or intolerant of antimuscarinic agents [29]. BoNT-A significantly improves OAB symptoms and urodynamic parameters in neurogenic DO and OAB. However, increased PVR and risk of urinary tract infection after BoNT-A treatment remain concerns among frail elderly patients [30]. If patients wish to be completely dry and avoid an indwelling catheter, clean intermittent catheterization to periodically empty the patient's bladder should be taught to the caregiver. All OAB patients with cerebrovascular accident, PD, or dementia should be informed of possible AEs and bladder management strategy prior to institution of BoNT-A treatment.

4. Antimuscarinic therapy and response in the elderly with or without benign prostatic hyperplasia

First-line treatment for OAB should start with lifestyle modification, followed by the second-line pharmacotherapy [31]. The most commonly used antimuscarinic agents for OAB are oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine, and trospium. These antimuscarinics have proven effective in decreasing urgency, urgency incontinence, and nocturia episodes [32].

Multiple studies have suggested that antimuscarinic therapy alone or in combination with alpha1-receptor antagonists improves OAB symptoms in men with and without bladder outlet obstruction (BOO) [33–35]. Therefore, a deeper understanding of the pathophysiology of OAB that underlies male LUTS, and examination of the relationship between symptoms and urodynamic findings are needed in the diagnosis and treatment of male LUTS associated with OAB [36].

Antimuscarinics were previously considered contraindicated in patients with benign prostatic hyperplasia (BPH) or BOO [37]. Because the symptoms of BPH and OAB overlap, antimuscarinics with or without α blockers appear to be an effective and safe alternative for male storage symptoms in men with BPH and without an elevated PVR volume [35,37–39]. However, antimuscarinics are usually reserved as second-line medication in men with OAB because of fears of precipitating urinary retention.

There is still controversy about which BPH patients are suitable for first-line antimuscarinic monotherapy. Current guidelines suggest that antimuscarinic monotherapy can be used for men without BOO, whereas combination therapy is usually suggested for men with concomitant BOO and OAB [40,41]. However, determining the presence and the degree of BOO is occasionally difficult without a pressure flow study. Uroflowmetry and PVR measurement are commonly used parameters, but there is still no definite cutoff value indicating which patients are suitable for antimuscarinic monotherapy.

We reported that using IPSS subscores that measure and calculate the IPSS voiding-to-storage subscore ratio is a simple and useful method to differentiate failure to voiding and failure to storage lower urinary tract dysfunction [42]. Our previous results showed that first-line antimuscarinic monotherapy is safe and effective for men with enlarged prostates and predominant storage symptoms. A small total prostatic volume, high maximum flow rate, and high IPSS-S subscore are predictors of successful first-line antimuscarinic monotherapy [43].

5. AEs with antimuscarinic treatment are common in the elderly

Antimuscarinic therapy with or without lifestyle modification is the most common treatment for patients with OAB. However, several drug-related AEs, such as dry mouth, cognitive impairment, constipation and sleep disturbance, can develop, especially in older patients [44]. In a survey of OAB treatment results in Japan, only 32.3% of patients were satisfied with their treatment, and 33.1% were dissatisfied. Among the AEs, constipation negatively influenced patient satisfaction more than dry mouth did [45]. AEs from antimuscarinic therapy were reported in 46.8% of patients in a recent long-term study of combined solifenacin and tamsulosin treatment for men with both storage and voiding LUTSs [46]. These AEs might result in discontinuation or inadequate dose treatment of elderly OAB patients. Clinicians should use caution in prescribing antimuscarinics in frail elderly patients. The potential adverse CNS events of each anticholinergic agent must be weighed against the severity of OAB symptoms [47].

Many anticholinergics can cross the blood–brain barrier and cause CNS effects such as cognitive impairment [48]. Cognitive impairment is a serious concern in antimuscarinic therapy for elderly patients with OAB. Oxybutynin is often recommended in guidelines, but it is associated with a high incidence of cognitive impairment, and is therefore not recommended for use in frail older OAB patients [49].

A study of persistence with solifenacin add-on therapy after tamsulosin monotherapy in men with BPH and residual OAB revealed that only 25% of men remained on solifenacin therapy after 1 year. The reasons for discontinuation were AEs in 35%, lack of efficacy in 33%, and improvement in symptoms in 16% [50]. A systemic review of persistence and adherence to treatment of OAB with anticholinergic therapy revealed that 43–83% of patients discontinued medication within the first 30 days and rates continued to rise over time [51]. The persistence rate for antimuscarinics depends on the drug used. In a UK survey, patients aged 60 years and older were more likely to persist with prescribed oral antimuscarinic drugs (solifenacin) than younger patients [52]. The proportion of patients who were adherent during antimuscarinic treatment was 60.4% [53].

Among antimuscarinic agents, high dose oxybutynin and propiverine had the least favorable relationship between efficacy and AEs [54]. Oxybutynin was associated with significant decreases in the cognitive functions of power and continuity of attention [55]. Flexible dosing with fesoterodine by escalating from low to high doses significantly improved OAB symptoms and AEs in vulnerable community-dwelling individuals who are older than 75 years, similar to younger populations [56]. The adherence rate of antimuscarinic therapy might be drug-specific. In elderly patients, it is better to start with a low dose of appropriate antimuscarinics and gradually escalate to a tolerable and effective dose.

6. Can a second antimuscarinic be used for refractory OAB symptoms in the elderly?

If a patient experiences inadequate symptom control and/or unacceptable AEs with one antimuscarinic, then a dose modification or a different antimuscarinic medication may be tried [57]. One study proved that additive treatment with extended-release (ER) tolterodine is a beneficial and safe therapeutic option in older men with BPH/BOO and storage symptoms treated with alpha blockers and/or 5-alpha-reductase inhibitors [58]. Several recent trials also proved that adding antimuscarinics to an alpha blocker provided efficacy in improvement of residual OAB symptoms in men with LUTSs [33–35,59].

In elderly women with severe OAB, a combination of two very high-dose antimuscarinics (40 mg solifenacin + 60 mg trospium) was effective in reducing OAB recurrence in maintenance therapy for 7 months [60]. A recent clinical trial showed that combination therapy with mirabegron (25 mg or 50 mg) and different doses of solifenacin significantly increased the maximal voided volume and reduced frequency and urgency episodes compared with solifenacin monotherapy [61].

Combined antimuscarinic and alpha blocker treatment is generally more effective than monotherapy or placebo. Studies have proved that combination therapy with tolterodine-ER and tamsulosin is significantly more effective than placebo or tamsulosin monotherapy in the treatment of men with OAB and BPH [62,63]. In elderly men with BPH and OAB, a combination of an alpha blocker and antimuscarinic was safe and effective in improving LUTSs in the short term without increasing PVR and urinary retention [64].

7. Mirabegron is safe in elderly OAB patients without increasing the risks of a large PVR or acute urinary retention

Mirabegron, a β_3-adrenoceptor agonist, is the first of this class of drugs for the treatment of OAB [65]. Mirabegron has demonstrated significant dose-dependent improvements in key OAB symptoms. A dose ranging study showed that 50 mg mirabegron once daily is most promising for clinical OAB [66]. OAB patients who are either antimuscarinic treatment naïve or have received prior antimuscarinic treatment could benefit from mirabegron treatment in reducing the frequency of micturition and incontinence episodes [67]. Pooled safety data indicated that mirabegron is a valuable treatment option for patients with OAB as the incidence of dry mouth, the chief cause of discontinuation of antimuscarinic agents, was lower than with tolterodine ER (4 mg) [68].

Recent Phase III trials have confirmed the efficacy and safety of mirabegron in treatment of OAB [69–73]. A urodynamic study in men with OAB and BOO revealed that mirabegron did not adversely affect the maximum flow rate (Q_{max}) and detrusor pressure at Q_{max} after 12 weeks of treatment [74]. The incidence of bothersome antimuscarinic AEs such as dry mouth with mirabegron was at placebo level, and of a lower magnitude (6-fold less) than tolterodine [68,75]. The therapeutic efficacy and tolerability of mirabegron showed no significant difference between patients aged > 65 years and > 75 years, supporting that mirabegron might be the therapeutic choice in elderly OAB patients [75]. The evidence suggests that mirabegron might provide a safe way to get rid of diapers in elderly OAB patients without increasing the risks of a large PVR or acute urinary retention. Reported AEs with mirabegron are rare [69–73]. However, hypertension and tachycardia in elderly OAB patients who have cardiovascular disease still require careful monitoring after long-term treatment.

8. Nocturnal polyuria remains an important cause of OAB in the elderly

Nocturia is defined as wakening from sleep one or more times to void. Nocturia is the most common core LUTS in the elderly, and is reported in 29.9% of men with LUTS [76]. The prevalence of nocturia is high in both sexes and increases with age [77]. Nocturia may be caused by nocturnal polyuria and reduced bladder capacity, alone or in combination, and polyuria [78]. Urodynamic study of patients with nocturia revealed DO incontinence in 26% of women and DO in 64% of men. Nocturnal polyuria was noted in 55% of patients with nocturia [78]. Nocturia may cause sleep deprivation at night and increase daytime sleepiness and loss of energy, which may have a great impact on HR-QoL in the elderly [79].

Aging is an important risk factor for nocturia. The nocturnal polyuria index increases significantly with age. Reduced bladder capacity and increased nocturnal urine output are important in the pathogenesis of nocturia in the elderly [80]. Nocturnal polyuria in the elderly is known to be caused by an age-related change in the circadian rhythm of arginine vasopressin secretion [81]. Nocturia in older men with LUTSs might also result from DO due to BOO and increased bladder oversensitivity. Nocturia and frequency are noted to correlate inversely with the maximum cystometric bladder capacity [82,83]. Nocturia and enuresis are also important symptoms of a sleep disorder. The nocturnal polyuria of sleep apnea is an evoked response to conditions of negative intrathoracic pressure owing to inspiratory effort posed against a closed airway [84]. Nocturia is frequently seen in obese elderly men. Nocturnal polyuria with abnormal circadian rhythm of plasma arginine vasopressin has also been noted in poststroke patients [85]. Desmopressin significantly increases the osmolality of nighttime urine in elderly patients with nocturnal polyuria [86]. A double-blind, placebo-controlled study in men with nocturia revealed 34% of the desmopressin group had fewer than half the number of nocturnal voids compared with baseline [87]. The duration of the first sleep period also increased in the desmopressin group, which significantly improved the quality of sleep versus placebo [88]. Desmopressin add-on therapy is also effective in improving nocturia and storage symptoms in men receiving an alpha blocker for LUTSs [89].

Although desmopressin is effective in decreasing nocturnal voids in elderly patients, the safety in patients older than 65 years is a great concern. Hyponatremia might develop in the patients taking vasopressin [87,90]. Elderly patients (> 65 years) with a baseline serum sodium level below the normal range are at high risk (75%) of developing significant hyponatremia [91]. Long-term desmopressin treatment gradually decreased the serum Na concentration and induced significant hyponatremia in patients who did not have initial hyponatremia. After discontinuing desmopressin, the serum sodium returned to the normal level. In addition, desmopressin treatment for 1 year in elderly patients did not affect the baseline endogenous antidiureic hormone level [92]. Therefore, assessment of the serum sodium level is necessary at least every 6 months in elderly patients receiving long-term vasopressin treatment.

9. Conclusions

Elderly patients might have medical and neurological diseases that increase their vulnerability in the management of urination. Although antimuscarinic therapy may improve OAB symptoms, AEs are common in the elderly. A new class of drug for OAB, the beta-3 adrenoceptor agonist mirabegron, may provide a safe treatment for elderly OAB patients without increasing the risks of a large PVR. Clinicians should be aware of the balance between therapeutic efficacy and safety in the treatment of OAB in the elderly.

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