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CURRENT OPINION

Overactive Bladder in Frail Older Adults

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Abstract
Overactive bladder (OAB) and frailty are multidimensional syndromes, and the prevalence of both increases with age. Little evidence exists for a direct association between OAB and frailty, but urinary urgency may well be a precursor of frailty in older people. Frail older adults are no less deserving of treatment than fit older adults, and lifestyle, behavioral, and pharmacological interventions remain the primary options for treatment, with some evidence for efficacy. Data on onabotulinumtoxinA therapy or percutaneous tibial nerve stimulation in frail older adults are sparse. Frail older adults are often excluded from drug trials, but evidence is accumulating that antimuscarinics and, to a lesser extent, beta-adrenergic agonists are safe, well-tolerated, and effective in older adults. Cognitive impairment associated with frailty should not be used as justification for avoiding the use of antimuscarinics. More studies are required to better understand the association between OAB and frailty, as both are associated with poor outcomes and may be amenable to intervention. Drug trials for OAB treatments should be encouraged to include frail older adults, as this population is highly affected yet often excluded.

Key Points

In frail older adults, lifestyle, behavioral, and pharmacological interventions remain the main options for treatment of overactive bladder (OAB).

There is evidence to support that medications such as antimuscarinics and beta-adrenergic agonists are safe, well-tolerated, and effective in medically complex or vulnerable older adults.

Data on more invasive therapies for OAB in frail older adults are generally lacking.

1 Introduction

Overactive bladder (OAB) is a clinically diagnosed symptom complex defined by the International Continence Society as consisting of urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with or without urgency urinary incontinence (UI), in the absence of urinary tract infection or other obvious urological disease. OAB is now subdivided into OAB-dry (without urgency UI) and OAB-wet (with urgency UI) [1]. Urgency UI affects approximately 40% of the OAB population overall, with rates increasing in association with age. In a cross-sectional multinational survey, the overall prevalence of OAB was 11.8%, reaching a peak in later life with little difference between men and women [2]. UI has consistently been associated with shame [3], poor quality of life [4, 5], poor self-rated health [6], social isolation, depression [7], decline in function and instrumental activities of daily living (IADLs) [8], falls and fractures [9], onerous out-of-pocket expenses [10], and, in older adults, institutionalization [11, 12]. The degree of impact of OAB appears to be related to both the presence of urgency UI and the overall severity of the condition.

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2 Frailty and Overactive Bladder (OAB)

OAB and urgency UI have been posited as an early marker of frailty, being a result of a common pathway to the geriatric syndromes, defined as multifactorial health conditions that render older people more vulnerable to stressors [13, 14]. Frailty in older people has garnered increasing interest from the research community over the past few years, as its presence can predict poorer outcomes from hospital treatment and longer lengths of stay than in non-frail older adults [15, 16]. Although frailty lacks a single standard definition, it too is a multidimensional syndrome comprising loss of reserve (energy, physical ability, cognition, health) leading to a state of vulnerability in the face of stressors [16]. Frailty has been described using a phenotypic model or as a result of accumulated deficits [16, 17]. Both models have advantages and disadvantages. For example, the phenotypic model does not include cognitive impairment [17] or social factors. Many validated tools are available to aid in the assessment of frailty, for example the Clinical Frailty Scale [16] and the Edmonton Frail Scale [18].

Several studies have suggested that the relationship between UI and frailty is not unidirectional. Incident UI in those aged > 65 years has been associated with a twofold increased risk of impairment in ADLs, IADLs (e.g., transportation, finances, shopping, laundry, housekeeping), and poor performance on three physical measures, suggesting that incident UI may be an early marker of the onset of frailty [19]. In a Taiwanese study of UI and its association with frailty among 440 men aged ≥ 80 years using the Clinical Frailty Scale, the prevalence of UI was 19.1%. Frailty was more common among subjects with UI than among those without (60.7 vs. 32.3%). Men with UI also had more comorbidity and poorer physical function and were more likely to have depressive symptoms, impaired cognitive function, poorer nutritional status, more polypharmacy, and fecal incontinence than men who were not frail [20]. In a population-based study of older Mexican Americans, incident but not prevalent UI was independently associated with functional decline in ADLs, IADLs, and physical performance [21]. Another population-based study found an association between UI and IADL decline but not ADL decline, nursing home admission, or death, after adjustment for age and comorbidity [22]. A Brazilian study showed that older people who presented with either "slowness" or "exhaustion" had a risk of UI almost five times greater than those without [23]. However, a similar cross-sectional study of 521 Brazilian older adults assessed the association between frailty and geriatric syndromes and demonstrated no association between UI and frailty [24]. Although one early study suggested that older people with UI had a higher mortality risk, subsequent studies that more fully adjusted for comorbidity and functional status did not find any association [22, 25–27].

Published evidence for an association between frailty and OAB is sparse. A study of 175,632 nursing home residents found that, although subjects were not strictly frail, those with lower urinary tract symptoms (LUTS; UI or OAB) exhibited a higher burden of cognitive and mobility impairment and higher numbers of comorbidities than those without [28], a finding replicated in community-dwelling older people [29]. Frailty, as determined by an increased time to complete a Timed Up and Go Test (TUGT) is associated with OAB, independent of age [30]. An association was reported between mortality and UI, although this disappeared when controlled for frailty, indicating that the UI was not independently associated with mortality but through its association with frailty [31]. More studies on the link between OAB and frailty are needed to determine its directionality and whether intervention on either side of the association can address either OAB or frailty and have any effect upon meaningful outcomes.

3 Stigma

Both UI and LUTS, such as frequency and urgency, are stigmatized [32], which leads to underdiagnosis and undertreatment. The significant stigma associated with UI is especially relevant in frail older adults, as this may exacerbate the well-described delays in healthcare seeking [33–35]. Frailty itself may also be a stigmatizing condition, but—as yet—the significance and impact of this is unclear. UI may exacerbate the frailty state and is associated with reduced physical activity, increased sedentary behavior, and reduced social activity, all leading to functional decline, social isolation, and loneliness, which act as risk factors for cognitive decline and dementia [36]. The association between depression and LUTS in non-frail adults is well supported [37–40]. A Japanese cross-sectional study of men and women aged > 70 years showed that the risk of having OAB was significantly higher in those with depressive symptoms than in those without depressive symptoms [41].

4 Pathophysiology

Urinary urgency, defined as a sudden desire to void that is difficult to defer [42], is a pathological entity and the suggested driver of other OAB-related symptoms [43]. Micturition is under conscious control, mediated by multiple areas of the brain, including prefrontal and frontal cortices, the limbic system, and hindbrain [44]. Functional positron emission tomography scanning demonstrates that the

periaqueductal gray matter, pons, and the ventral and dorsal portions of the pontine tegmentum are all active during bladder filling [45]. Functional magnetic resonance imaging (MRI) studies in older people have suggested that failure of activation in areas of the brain relating to continence, such as the orbitofrontal regions and the insula, impair the ability to suppress urgency [46]. The pontine micturition center (PMC) may be permanently in an "on" state, where suppression maintains the bladder in storage mode and the conscious decision to void leads the PMC to be unsuppressed, allowing the bladder to enter voiding mode [44].

The accumulation of white matter hyperintensities (WMH) within the brain is associated with aging [47, 48]. These are more common in those with vascular risk factors [49]. Irrespective of their underlying cause, good evidence indicates that the presence and amount of WMH correlates with geriatric syndromes [50], including falls [51, 52], cognitive impairment [51, 53], and UI [54–56]. The association between WMH and frailty is less clear, and results from the few completed studies are conflicting [57–62]. However, evidence does exist for an association between WMH and individual components of the frailty syndrome, including impaired executive function, slow gait speed [63], reduced physical function [64], and falls [65]. Additionally, an association has been reported between the severity of LUTS and the degree of WMH on MRI [66]. Urinary urgency then may reflect cerebral impairment as much as lower urinary tract dysfunction and may also be a presage of incipient frailty.

5 Management

In contrast with the treatment of young fit patients with a single disease entity usually included in clinical trials, a different approach is needed in multimorbid frail older adults. Comorbid disease, cognitive impairment, mobility restriction, functional impairment, living situation (i.e., in institutions), dependency on caregivers, polypharmacy, and remaining life expectancy must be taken into account [67]. Discussion regarding the patient's and caregiver's expectations of treatment is extremely important in formulating a management plan, as counseling about realistic expectations of treatment improves treatment adherence. Similarly, it is important to consider the patient (and caregiver) burden of any management plan, particularly when the patient may have several chronic diseases.

5.1 Conservative Management

The usual first-line lifestyle interventions for OAB include modifying fluid intake, avoiding caffeine, weight loss, smoking cessation, management of constipation, and physical exercise [68–71]. However, none of these interventions have been thoroughly evaluated in frail older adults. Additionally, the consequences of dehydration may outweigh the advantages of fluid restriction, as inadequate fluid intake is common and has detrimental effects in long-term care residents and frail older hospitalized patients [72, 73]. Dehydration may actually increase the risk of UI and its severity in frail older adults with OAB because of its significant association with two known risk factors for UI: constipation and delirium [74, 75].

Behavioral interventions may be especially beneficial for frail older adults because they have few, if any, side effects. These interventions come in two major types: voiding programs, including strategies to suppress urgency and delay voiding, and pelvic floor muscle training [67]. Additionally, functional training with exercise targeted at improving mobility and toileting skills is an effective intervention for frail older adults, especially those in long-term care settings, who are at risk for functional decline and UI because of difficulty reaching the toilet in a timely manner [75]. While prompted voiding and timed voiding can be helpful interventions in UI, patients with OAB should be discouraged from visiting the toilet in anticipation of a future need to void and should try to delay urination for as long as possible [70].

Lifestyle and behavioral interventions in themselves may be sufficient to improve symptoms and the quality of life of frail older adults. However, while conservative therapies are low risk, they may be rendered less effective by severe OAB symptoms or by cognitive or functional impairment, which are often part of the frailty syndrome. In these cases, either containment (if the predominant distressing symptom is urgency incontinence) or pharmacological measures are indicated. Containment for UI is discussed in more depth elsewhere [76–78], but healthcare practitioners may find the Continence Product Advisor website useful in choosing specific products for specific populations (https://www.continenceproductadvisor.org/).

5.2 Pharmacological Management

Pharmacological agents used in OAB include bladder antimuscarinics (darifenacin, fesoterodine, imidafenacin, oxybutynin, propiverine, solifenacin, trospium, and tolterodine). In OAB, these medications block the muscarinic receptors on the detrusor muscle and urothelium, which are stimulated by acetylcholine. During the storage phase, these medications decrease urgency and increase bladder capacity [79]. Given that this receptor is widespread throughout the body, these medications are all associated with well-known anticholinergic side effects, including dry mouth, constipation, and blurred vision, among others. Although detrusor muscle contractions are part of the normal physiology of voiding, use of bladder antimuscarinics at usual therapeutic doses

is seldom associated with either impaired voiding or acute urinary retention requiring catheterization [80].

Recently, epidemiological studies have associated high anticholinergic burden with an increased likelihood of incident dementia diagnosis. Although the strength of this association is relatively weak and data on OAB drugs largely lacking, these trials have resulted in concern about the cognitive impact of anticholinergic medications for OAB. Guidelines suggest that older adults may be at higher risk of cognitive impairment as a result of exposure to anticholinergics, but no data exist to support this assertion. For example, a study of the use of delayed-release oxybutynin in nursing home residents, a group likely to have a large frailty component, found no evidence for cognitive decline or incident delirium over 1 year [81]. However, immediate-release oxybutynin is associated with a high incidence of adverse drug events and, in higher doses, causes cognitive impairment in cognitively intact older people [82]. The newer-generation anticholinergics appear safe in short-term detailed trials of cognition in cognitively intact older people [83]. Data also support the cognitive safety of solifenacin in older people with mild cognitive impairment [84]. Observational studies of older people, using Folstein's Mini Mental State Examination (MMSE) scores, showed no decline over a year's exposure to propiverine, imidafenacin, and solifenacin [85–87]. Although there are no data from trials in frail older people, the older patients with OAB in the vulnerable elders study [88] verged upon frail, were medically complex, and scored ≥ 3 on the validated Vulnerable Elders Survey [89], indicating a high risk of functional deterioration or hospitalization. This 12-week randomized controlled trial (RCT) showed that fesoterodine was effective, safe, and well-tolerated in these medically complex older people. There was no change in MMSE scores over the duration of the study. Similar to other trials of fesoterodine in older people, the majority chose to increase their dose of fesoterodine from 4 to 8 mg without an increase in withdrawals [90]. Over 50% of the fesoterodine-treated patients achieved continence at the end of the study.

Despite the limitations of evidence, national and international guidelines [91, 92] recommend using antimuscarinic drugs with caution in older people and avoiding the use of immediate-release oxybutynin. At its extreme, it has been suggested that all antimuscarinics for OAB should be avoided [93]. Despite the weight of evidence for efficacy in older people, a recent systematic review of antimuscarinics and beta-adrenergic agonists for OAB in patients aged > 65 years rated only three RCTs as "strong" in quality [94]. Evidence from large-scale trials is particularly lacking in frail older adults, although a trial including adults defined as frail by an increased TUGT compared with non-frail older adults achieved improved OAB symptoms at 3 months using antimuscarinics, mirabegron, onabotulinum toxin, or sacral neurostimulation as deemed necessary by the treating physician. There was no significant difference in treatment outcomes or side effects between frail and non-frail subjects [95].

Evidence regarding the concomitant use of bladder antimuscarinics and cholinesterase inhibitors is conflicting. Early evidence suggested, intuitively, that worse cognitive outcomes were associated with prescribing these two classes of drugs with opposing mechanisms [96, 97], but more recent evidence suggests this is not the case [98] and it appears possible to achieve good continence outcomes without cognitive decline.

Latterly, the beta-adrenergic receptor agonist mirabegron, and more recently vibegron, have been available as an alternative to antimuscarinics. These medications are specific for beta-3-adrenoceptors present in the detrusor and urothelium. The proposed mechanism of action is relaxation of the detrusor in the storage phase, although it is likely that these drugs also modulate the afferent sensory output from the bladder and reduce the sensation of urgency. The potentially favorable side effect and tolerability profile seen with mirabegron when compared with antimuscarinics is thought to be largely because of the absence of troublesome antimuscarinic side effects and the drug's low propensity to cross the blood–brain barrier [99]. However, the use of these medications may be limited in the multimorbid older adult given their contraindications in uncontrolled hypertension and the potential for drug–drug interactions [100–102]. The commonly held beliefs regarding hypertension and adverse cardiac events are unsupported by available trial data [103].

No specific data exist on the use of beta-adrenoceptor agonists in frail older adults. A placebo-controlled RCT of flexibly dosed mirabegron in community-dwelling patients aged > 65 years with OAB-wet has shown efficacy, with 38% of drug-treated patients achieving continence at 12 weeks [104]. There was no change in Montreal Cognitive Assessment scores between groups over the 12 weeks of the study [105].

5.3 Advanced Therapies

If conservative and pharmacotherapeutic attempts to manage UI fail, there is some evidence for the efficacy of intradetrusor injection of onabotulinumtoxinA for urgency UI caused by detrusor overactivity or OAB, although this seems less effective in frail than in non-frail older men, with a higher likelihood of developing complications, including urinary retention [106]. No data exist for percutaneous tibial nerve stimulation in frail older adults, although some data are available for older adults. In theory, there are few reasons, other than the practical logistical difficulties of delivering the typically 12 weeks of therapy, why this should not be offered to frail older adults. No long-term data are available

[107, 108]. Sacral nerve stimulation is safe and effective therapy that is supported by long-term studies [109], but again no data exist for frail older adults, and these modalities are unlikely to be offered to frail older people.

6 Conclusion

Although few data are available from high-quality clinical trials of OAB treatment in frail older people, some evidence is accumulating from trials of drug treatment. There has been little development in the data on conservative treatments over the last 3 decades, and limitations of evidence still exist. Overall, should evidence indicate that an intervention is effective in older people, there is probably no reason it will not work in frail older adults.

Declarations

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