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OVERACTIVE BLADDER (U LEE AND S ADELSTEIN, SECTION EDITORS)

Treatment of Overactive Bladder in the Frail Patient

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Abstract

Purpose of Review To understand how frailty interacts with overactive bladder. To explore how frailty should be considered when devising an individualized treatment plan for OAB patients.

Recent Findings Frailty can be assessed in the outpatient office without undue burden. The urology community is increasingly aware of the importance of evaluating a patient for frailty and including this assessment in treatment algorithms. Frailty should be considered when treating OAB patients, since frail OAB patients are more susceptible to the potential deleterious consequences of medical therapy, onabotulinumtoxinA therapy, and sacral neuromodulation.

Summary A patient's frailty status should be considered during counseling regarding OAB therapy. Additional studies are needed to examine the treatment effects and risks in the frail OAB population.

Keywords Overactive bladder · Frailty · Risk assessment · Cognitive impairment

Introduction

International Urogynecological Association (IUGA) and International Continence Society (ICS) define overactive bladder (OAB) as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of UTI or other obvious pathology." [1, 2] Recent population studies estimate that OAB affects 8.1–10.3% of women around the world [3, 4]. These prevalence rates are slightly lower, but comparable to those found by larger epidemiologic studies including the EPIC and National Overactive Bladder Evaluation (NOBLE) studies, which suggested around 10.8–16.0% of men and 12.8–16.9% of women suffer from OAB [5, 6].

It has been reported that patients with OAB have impaired physical, psychological, and economic functioning compared to patients without OAB. This includes metrics such as decreased participation in physical activity, increased weight gain, greater likelihood of a diagnosis of depression or anxiety, and higher rates of occupational absenteeism and unemployment [7–9]. Of similar concern is the high rate of healthcare utilization of patients with OAB. One study found that female patients with OAB had twice as many annual healthcare interactions than their non-OAB counterparts [10]. The financial implications of OAB to society are great, with a predicted cost of $82.6 billion in 2020 in the USA alone [11]. With greater than 1 in 10 people worldwide affected by OAB, the global burden of this pathology is significant.

In recent years, the concept of frailty has been introduced to the medical community as a term to better stratify patients and their risk of poor health outcomes. Frailty can be defined as a syndrome of cumulative physiological decline. It is associated with increased vulnerability to adverse outcomes as the result of a stressor, such as a surgical procedure or illness. Frailty is recognized as distinct and different from the chronological age of a patient, though age itself is a contributor to the lack of resilience seen in frail patients. As the population of elderly individuals rapidly rises in the USA, it is important to consider a patient's multifactorial frailty status when deciding on a treatment course in order to avoid unintended complications [12]. One study involving patients residing in nursing homes showed that even after minor urologic surgery, mortality and functional decline is significant, suggesting that management of urologic conditions in this population requires special

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consideration [13••]. Treatment algorithms exist and provide a framework for managing a patient's symptoms, though frailty status is often omitted, as is the case for the AUA guidelines for treating OAB [14]. As a vital glimpse into a patient's overall health status, frailty needs to be utilized as a contributing factor in developing an individualized treatment plan.

Interaction Between OAB and Frailty

OAB, much like frailty, is a multi-factorial syndrome. The complex interactions of a patient's age, race/ethnicity, BMI, smoking status, diabetes and presence of neurologic conditions (such as multiple sclerosis, Parkinson's disease, spinal cord injury, and cerebral vascular accident) may all contribute to the development of OAB symptoms, particularly in the aging population. Together, these patients form a multifaceted phenotype, making it important to identify and assess for OAB in the office setting. Evaluation of a patient with suspected OAB begins with the clinical history, which forms the cornerstone of the diagnosis [14]. A urinalysis should be evaluated to rule out a urinary tract infection (UTI) or other obvious pathology per the defining features of OAB. Additional information can be garnered from bladder diaries, validated questionnaires, such as the overactive bladder symptom score (OABSS), and urodynamics in neurogenic, refractory and non-index OAB patients [15].

In contrast, the assessment of patient frailty is remarkably less straightforward despite recommendations from both the American Geriatric Society and the American College of Surgeons that determining a patient's baseline frailty in the preoperative period is essential in elderly patients [16]. Long before the term frailty existed, the American Society of Anesthesiologists (ASA) created a system that aimed to categorize patients by their overall health status and potential fitness for anesthesia in order to predict postoperative complications [17]. The subjectivity of the ASA score has been criticized, though many studies have found that this classification system does a fair job of accurately predicting poor postoperative outcomes [18, 19].

Since the introduction of the term frailty, a number of independent grading systems have been developed to assess patient frailty, though many are time intensive and require special equipment to perform. While there is no widely recognized gold standard for frailty screening, the most frequently cited screening tool is the validated Fried Frailty Index (FFI) [20]. This index involves patient participation with grip strength and measurement of walking speed in addition to reported weight loss, exhaustion and decreased overall physical activity. As an abbreviated assessment of functional mobility, the Timed "Up and Go" Test (TUGT) involves the patient rising from a chair, walking 3 m, turning and returning to the chair to sit [21]. Longer time to completion is associated with frailty and increased risk for falls. The TUGT has been successfully incorporated into busy urology clinical practices, indicating its feasibility in evaluating perioperative frailty [22•]. The Canadian Study of Health and Aging (CSHA) developed a pictorial frailty tool called the Clinical Frailty Scale (CFS), which is both simple to use and predictive of future health challenges [23]. The 7-point, and later 9-point, iterations of the CFS require the provider to stratify patients based on their degree of fitness and vulnerability. As the CFS-9 does not require additional equipment and can be quickly administered, it has significant advantages over more cumbersome tests (including the FFI and TUGT) and has been found to be an excellent tool for evaluating frailty in patients with pelvic floor conditions, performing similarly to the FFI [24]. As providers who see a large volume of patients over the age of 65, urologists are significant stakeholders in identifying frailty indices that best serve their patient population.

Database studies have suggested that there is significant interplay between OAB and frailty [25••, 26]. Using TUGT and gait speed as primary indicators of frailty, it was noted that patients with OAB were more likely to have slower times than other similar non-OAB urologic patients [25••]. The exact pathophysiologic mechanism contributing to this relationship has yet to be elucidated but is likely multifactorial in nature. Identification of a patient as frail requires a shift from the provider's typical OAB management and treatment algorithm in favor of a more individualized plan, as certain strategies may be more optimally suited for a frail patient than a pre-frail or non-frail patient [27]. In developing a treatment plan for OAB in frail patients, the following points should be considered.

Considerations for First-Line OAB Therapy

In the frail patient, severity of OAB symptoms and impact on quality of life must be weighed against the risks of treatment, as the management of OAB is aimed at minimizing symptoms, rather than cure. The first-line treatment for OAB in the frail patient involves behavioral therapy and lifestyle modification. Timed voiding, pelvic floor muscle training, and fluid management are useful approaches. There are no risk factors for these therapies and, as such, emphasis should be placed on adhering to the behavioral changes. Increased physical activity, in the form of walking and simple strength exercises, in conjunction with behavioral modification can reduce incontinence episodes in frail patients, suggesting a role for exercise in managing OAB as well [28]. Consideration should be given to a patient's functional status prior to initiating these treatment strategies, since a recommendation such as voiding every 2–3 h on a schedule may be challenging for those with mobility limitations. It has been shown that nearly 1/3 of all falls in frail patients occur during a walk to or from the

bathroom, although these falls could occur both with timed voiding or bothersome OAB symptoms [29].

Fluid management, including alterations in the type of fluid and reduction in quantity, can also significantly ameliorate OAB symptoms. Education and counseling to avoid bladder irritants such as coffee and soda in favor of plain water can be helpful. Fluid restriction to reduce bladder volumes and urine output can be useful in minimizing the urgency and frequency experienced by patients. Frail patients should also be screened for dehydration. The current food pyramid designed specifically for older adults recommends 8 glasses of water a day to maintain adequate hydration [30]. One self-reported study found that among community-dwelling elderly, over 55% consumed more than 7 glasses of water a day, which has been suggested to be more than adequate and may even cause overhydration [31, 32]. Thus, with careful consideration of a frail patient's current fluid intake, fluid intake modification can be undertaken to improve OAB symptoms while not contributing to dehydration and dangerous electrolyte disturbances.

These first-line treatment strategies require patient cooperation, cognitive attentiveness and, in some cases, caretaker support in order to be successful. It is possible that physiologic changes associated with the aging bladder and brain preclude responsiveness to appropriate behavioral modification and bladder training, necessitating further treatment for OAB symptoms [33•].

Considerations for Second Line OAB Therapy

Pharmacologic interventions are considered to be second-line therapy for the frail patient with OAB and are a useful adjunct to behavioral and lifestyle modifications [34]. Providers should consider dose escalation and side effect profiles when selecting a medication for a frail OAB patient. The joint American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) guidelines recommend using extended release formulation or the lowest dose possible in the frail patient [14].

Anti-muscarinic medications are known to be effective for reducing the frequency and severity of OAB symptoms; however, they must be used cautiously in the frail patient. The effects of anti-muscarinic medications are mediated primarily through M3 receptors, which are responsible for detrusor activity. It has been shown that the aging bladder has reduced quantities of M3 receptors, which perhaps provides a rationale for lower prescribed doses of anti-muscarinic medications in the older patient population [35]. The side effect profile of anti-muscarinics depends largely on the medication's ability to cross the blood brain barrier. Those medications that cross easily may have more central nervous system (CNS) side effects such as headache, dizziness, drowsiness, and particularly concerning in the frail patient, cognitive impairment. The risk of cognitive decline in patients taking anti-muscarinic medications has been well documented and is thought to be cumulative, with the effects compounding over many years [36–38]. Male patients and those patients under the age of 75 appear to be more likely to experience cognitive impairment from anti-muscarinic medications [39••]. Although some studies suggest that there is no association between anti-muscarinic medications and the development of cognitive impairment [40], baseline cognitive impairment should be considered a contra-indication for starting anti-muscarinic therapy. Certain anti-muscarinic medications may be less likely to cause cognitive decline than others. The current literature indicates that darifenacin, trospium, and solifenacin may be relatively safer in the aging and frail, but it should be noted that many studies in this population are conducted on a short-term scale and may not represent long-term cognitive realities [41–45]. The American Geriatrics Society also strongly recommends against the use of all anti-muscarinics for the treatment of OAB in patients with baseline dementia or cognitive impairment [46]. Frail patients with baseline cognitive impairment or dementia, particularly those taking an acetylcholinesterase inhibitor concomitantly, may be at even higher risk of accelerated decline in cognition and functional capacity [47].

The β_3 adrenergic agonist, mirabegron, is a suitable alternative for the treatment of OAB, particularly due to its favorable side effect profile compared to anti-muscarinic medications. Stimulation of β_3 adrenergic receptors in the bladder allows for detrusor relaxation, increasing bladder capacity and reducing OAB symptoms [27]. Mirabegron has been shown to reduce episodes of voiding frequency, incontinence, and urgency [48]. It is generally well tolerated, with its most worrisome side effect being worsening hypertension, though UTI, diarrhea, and headache have also been reported in patients over 65 [49••]. The recent phase IV PILLAR study, which examined the safety and efficacy of mirabegron in patients older than 65 years of age, demonstrated significant improvements in OAB symptoms over a 3-month time period [49••]. Notably, there was no change in cognitive impairment, as measured by Montreal Cognitive Assessment (MoCA) scores, in patients receiving mirabegron compared to placebo. A retrospective study examining the risk of dementia in patients taking an anti-muscarinic medication compared to those taking a β_3 agonist found a significantly greater likelihood of dementia in those taking any anti-muscarinic [39••]. Although more longitudinal data is needed regarding the safety of mirabegron in frail and elderly patients, mirabegron appears to be a favorable choice in the frail patient with OAB.

Selection of a pharmaceutical agent for the management of OAB necessitates joint decision making with the patient and/or caregiver with careful discussion of the risks and side effect profiles in the context of the patient's current medication list.

Population studies estimate that 67% of patients over the age of 70 take more than 5 medications daily, a prescription burden that is referred to as polypharmacy [50]. Studies have found that frailty and polypharmacy are inextricably linked in what is likely a complex bidirectional relationship [50, 51]. The worrying effects of polypharmacy including adverse drug events and drug-drug interactions must be weighed against the potential benefit of a pharmacologic agent to treat OAB symptoms. The decision to start an OAB medication should be made through a shared decision pathway when possible.

Considerations for Third-Line OAB Therapy

When behavioral modifications and pharmacological therapies fail, there are a number of third line treatments available that range in their level of invasiveness. Peripheral tibial nerve stimulation (PTNS) is the least invasive third-line option, and it is not associated with detrimental side effects. While this treatment modality may be ideal for frail OAB patients, there are logistic limitations that must be considered when selecting the appropriate patient. The majority of PTNS studies have examined a 12-week induction treatment course with maintenance therapy performed on a monthly basis. In order to follow the prescribed course of therapy, a significant number of office visits are required. Frail patients may have logistical challenges that prevent them from being able to complete the entire regimen. If patients are able to complete multiple office visits, PTNS offers a minimal risk treatment option that is well suited for frail OAB patients.

Intradetrusor injection of onabotulinumtoxinA is an alternate effective treatment for patients intolerant of or unresponsive to anti-muscarinics or β_3 agonists. However, there are special considerations when counseling frail patients on the adverse effects associated with onabotulinumtoxinA therapy. Urinary retention is one such effect that can be particularly difficult to manage in frail patients. Liao et al. demonstrated that while onabotulinumtoxinA therapy resulted in improvement in UUI and quality of life scores, frail elderly patients were more likely to have elevated post void residual (PVR) volumes of greater than 150 mL. While it did not reach statistical significance, a higher percentage of frail elderly patients also experienced urinary retention [52]. Similarly, Kuo et al. found that patients older than 75 were more likely to experience urinary retention or have elevated PVR volumes [53]. Patients with significant medical comorbidities, such as chronic kidney disease, COPD, congestive heart failure, and diabetes, were also more likely to have elevated PVRs. Patients with urinary retention after treatment with onabotulinumtoxinA require clean intermittent catheterization (CIC) or an indwelling catheter if they are not able to catheterize themselves. Intermittent catheterization can be challenging in frail patients who may not have the manual dexterity to perform CIC. In addition to the increased risk of urinary retention, consideration must also be given to the need to stop anticoagulation therapy around the time of onabotulinumtoxinA injection. Even temporary cessation of anticoagulation therapy may not be possible in frail OAB patients with a significant thrombotic risk.

Sacral neuromodulation (SNM) is the final third-line option in treating OAB. One of the largest studies looking at the safety and efficacy of SNM in octagenarians found that there was no difference in success rate, revisions, or device explantation between octagenarians and non-octagenarians [54•]. While it has been shown to be an effective treatment modality, a patient's functional status should be considered before recommending SNM. Patients must have the manual dexterity as well as the cognitive ability to understand and operate the patient programming device. A number of perioperative considerations should also be emphasized when treating a frail OAB patient. During device implantation, patients are positioned prone and the procedure requires at least monitored anesthesia care with sedation. Frail patients may have medical comorbidities making broth prone positioning and anesthesia higher risk compared to the general population. Similar to onabotulinumtoxinA therapy, risk assessment should also consider the need to hold anticoagulation in the perioperative period surrounding device implantation. Finally, Greenberg et al. reported a revision rate of 19% and an explanation rate 28% [54•]. Each additional procedure exposes the frail OAB patient to perioperative risks.

Conclusion

OAB conservatively affects around 10% of the global population, contributing to significant morbidity and healthcare costs. In the context of the vulnerable frail patient, these negative health impacts are amplified. As the aging population of the world continues to grow, the prevalence of OAB and frailty will see a parallel rise. Frail patients are more likely to encounter issues with pharmaceutical interactions, experience functional challenges and suffer from adverse side effects in the treatment of OAB, necessitating more thoughtful attention to management in this setting. The heightened attention to patient frailty status in recent years has led to increased recognition that frailty needs to inform our treatment algorithms. Specific attention needs to be placed on the inclusion of frail patients in research studies surrounding OAB treatment options in order to optimize guidelines for this population, as this remains highly understudied. Further investigation aimed at determining how the OAB treatment algorithms should be adjusted in the context of frail patients could lead to significantly improved quality of life, patient satisfaction, and reduced healthcare spending.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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