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INVITED REVIEW

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Third-line therapy for overactive bladder in the elderly: Nuances and considerations

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Abstract

Introduction: Overactive bladder (OAB) disproportionally affects older adults in both incidence and severity. OAB pharmacotherapy is often problematic in the elderly due to polypharmacy, adverse side effect profiles and contraindications in the setting of multiple comorbidities, and concerns regarding the risk of incident dementia with anticholinergic use. The burden of OAB in older patients coupled with concerns surrounding pharmacotherapy options should motivate optimization of nonpharmacologic therapies in this population. At the same time, several aspects of aging may impact treatment efficacy and decision-making. This narrative review critically summarizes current evidence regarding third-line OAB therapy use in the elderly and discusses nuances and treatment considerations specific to the population.

Methods: We performed an extensive, nonsystematic evidence assessment of available literature via PubMed on onabotulinumtoxinA (BTX-A), sacral neuromodulation, and percutaneous tibial nerve stimulation (PTNS) for OAB, with a focus on study in elderly and frail populations.

Results: While limited, available studies show all three third-line therapies are efficacious in older populations and there is no data to support one option over another. BTX-A likely has a higher risk of urinary tract infection and retention in older compared to younger populations, especially in the frail elderly. PTNS incurs the lowest risk, although adherence is poor, largely due to logistical burdens.

Conclusion: Advanced age and frailty should not preclude third-line therapy for refractory OAB, as available data support their efficacy and safety in these populations. Ultimately, treatment choices should be individualized and involve shared decision-making.

KEYWORDS

elderly, neuromodulation, onabotulinumtoxinA, overactive bladder

1 | INTRODUCTION

Overactive bladder (OAB) is a symptom complex including urinary urgency, frequency, and/or nocturia, with or without urinary incontinence.[1] While common in the general population, OAB disproportionally impacts older adults in both prevalence and severity.[2,3] Population-based studies estimate over a third of older adults suffer from OAB.[4] The condition is also associated with significant psychosocial and health-related quality-of-life costs in the elderly, causing increased social isolation, anxiety, depression, and fall risk.[4,5] Its economic burden is substantial as well: a 2010 analysis estimated a national cost of $83 billion by 2020, over half of which arises from costs associated with patients over age 65.[6]

Current updated 2019 guidelines from the American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction on the diagnosis and management of OAB provide a treatment algorithm based on progression from least to most invasive options.[7] Behavioral therapies and lifestyle modifications represent the foundation, with pharmacotherapy as second-line therapy, and procedural interventions as third-line options.

Pharmacotherapy for OAB, which includes anticholinergic and/or beta-3 agonist medications, is often problematic in elderly patients. Anticholinergics have well-known side effects of constipation, dry mouth, blurred vision, core temperature dysregulation, and cognitive impairment.[7] Of particular concern in the elderly, recent studies have suggested a strong association between anticholinergic use and risk of incident dementia.[8,9] Additionally, elderly patients are more likely to have contraindications to OAB pharmacotherapy use due to higher comorbidity indices and polypharmacy.

The greater severity and burden of OAB symptoms in older patients coupled with concerns surrounding the adverse effects of anticholinergic OAB medications should motivate us to optimize nonpharmacologic therapies in older patients. At the same time, multiple aspects of aging may impact treatment efficacy and decision-making. This narrative review will summarize the current evidence regarding third-line therapy use in the elderly and discuss nuances and treatment considerations specific to the elderly OAB population.

2 | GERIATRIC CONSIDERATIONS IN OAB PATIENTS

Traditionally, age 60–65 is considered "older" or "elderly," although aging is not a linear chronologic process.[10] Rather, aging is a multidimensional process leading to increased susceptibility to and incidence of disease, debility, and mortality. Aging introduces multiple, overlapping complexities to OAB treatment in older patients. Herein we briefly discuss several of these considerations.

2.1 | Physiologic considerations of aging

- *Aging bladder*—Older bladders have increased collagen and fibrosis with reduced innervation and sensation of bladder filling.[11,12] Urodynamic studies in older patients demonstrate reduced bladder capacity and compliance, higher urgency at lower volumes, and lower maximum flow rate.[12] Some of these changes are favored to be related to age-related endothelial dysfunction, atherosclerosis, and oxidative stress.[13]
- *Aging brain*—Functional magnetic resonance imaging (MRI) studies in women suggest that the aging brain has a reduced ability to process afferent information of bladder filling as well as reduced suprapontine inhibition of voiding reflexes, which likely predispose to OAB.[14] Furthermore, cerebral white matter lesions, which result from small vessel disease, increase with age and have been associated with urgency urinary incontinence (UUI).[15]

2.2 | Frailty

Frailty is a graded state of risk for adverse health outcomes resulting from age-related deficit accumulation.[16] Frail elderly has been defined as age ≥65 years with at least three of the following criteria: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity.[17] Studies have identified associations between frailty and OAB, urinary incontinence, recurrent urinary tract infections (UTIs), and falls related to toileting.[11,18,19] Higher incidence of OAB in older patients may be due to a higher incidence of frailty rather than age itself. A prospective observational study of patients ≥65 years presenting to a urologic practice found frailty (defined by slow Timed Get Up and Go Test) predicted OAB diagnosis (odds ratio [OR] 3.0), while age was not a significant predictor.[20] There is also a well-established association between frailty and increased risk of postoperative complications and morbidity across specialties.

Current OAB treatment algorithms do not consider pathophysiology underlying OAB symptoms or patient-specific factors like advanced age or frailty. Ongoing observational deep phenotyping work being done by the Lower Urinary Tract Disease Network II may aid in developing clinically meaningful subtypes that can direct

therapy. However, for now, when considering third-line OAB therapy in older patients, we are limited to interpreting available clinical research data. Below we discuss current evidence and considerations for third-line therapies in older OAB populations.

3 | ONABOTULINUMTOXINA

Onabotulinumtoxina (BTX-A) is a neurotoxin derived from *Clostridium botulinum*. Its mechanism of action in treating OAB and UUI involves inducing flaccid paralysis via blockade of the acetylcholine release at the synaptic junction. Additionally, there may be a supplementary role in modulating sensory signaling via blockade of bladder afferent nerve firing.[21]

3.1 | Safety and efficacy data in elderly patients

The original trials for BTX-A that led to Food and Drug Administration (FDA) approval included healthy elderly patients, but analyses did not stratify outcomes based on age. Furthermore, a recent systematic review of BTX-A in elderly patients failed to identify any randomized controlled trials that stratified analyses by age, underlining the limited available data focused on BTX-A use in the elderly patient population.[22] However, two secondary analyses of the ROSETTA trial, a randomized active-control trial comparing 200 units of BTX-A to sacral neuromodulation (SNM) in women with idiopathic UUI, have assessed the role of age on BTX-A safety and efficacy. The first, a 2017 analysis for predictors of treatment success in the trial found that greater age and functional comorbidity index were associated with a reduced likelihood of ≥50% improvement in UUI episodes after BTX-A (OR 0.44 per decade and OR 0.85 per 1 point of functional comorbidity index).[23] The study also identified lower OAB treatment satisfaction scores with BTX-A with higher age (coef. −6.53 per decade).

Another secondary ROSETTA analysis compared patients ≥65 years ($n = 191$, mean 73 years) against younger patients ($n = 173$, mean 54 years).[24] While authors found no difference in mean daily UUI episodes following BTX-A, there was a 3.3x higher rate of complete response to BTX-A and larger reductions in Overactive Bladder Quality of Life Short-form Questionnaire (OAB-q SF) scores (−7.5) in the younger group. They also reported no difference in catheterization rates based on age but higher UTI rates in women ≥65 years (OR 1.9). An important limitation of these secondary ROSETTA analyses is that the 200-unit dose of BTX-A used in the trial is twice the FDA-approved dose for idiopathic OAB.

Several small, nonrandomized controlled studies have assessed BTX-A's safety and efficacy in older and frail patient populations. A 2010 randomized trial of varying BTX-A doses (100, 150, or 200 units) in 217 patients with refractory idiopathic detrusor overactivity, of which 45% were ≥75 years old, found no difference in success rates or adverse events at 3 months based on age.[25] Conversely, a prospective 2017 Polish study assessing retention following 100 units of BTX-A in 208 women with refractory OAB found patients with elevated postvoid residual (PVR) requiring intermittent self-catheterization (ISC) were older compared to those who emptied well postprocedurally (68.6 vs. 61.1 years, $p < 0.05$).[26]

Liao and Kuo[27] assessed treatment success and adverse events of 100 units BTX-A in 166 patients with idiopathic medication-refractory detrusor overactivity. In the comparison of frail elderly (>65 years with three or more frailty criteria), elderly, and younger patients, they found similar success rates at 3 months across groups (83%–91%) although success over time attenuated more rapidly in the frail elderly group (6.8% vs. 22%–23% success at 12 months). Elevated PVR was more common in the frail elderly group, and frail elderly who developed acute urinary retention took longer to return to spontaneous voiding (median 3.5 months vs 0.5-1 month). In a retrospective review, Suskind et al reported on 45 patients aged ≥60 years with and without frailty undergoing treatment for OAB, including 12 patients who received BTX-A. The mean age was 70.3 years. There was a significant improvement in patient-reported outcomes with no difference based on frailty across therapies.[28] The study did not evaluate adverse side effect rates specific to BTX-A.

3.2 | Summary of the evidence

BTX-A is efficacious for refractory UUI in older patients, but likely has a higher risk of UTI, elevated PVR, and retention, especially in the frail elderly.

3.3 | Considerations

In light of the above evidence, clinicians should consider the following when contemplating BTX-A for refractory OAB in the elderly:

- *Self-catheterization*: In addition to willingness, does the patient have the mobility and dexterity required to perform self-catheterization? If not, are caregivers available, able, and willing to perform if needed? If not, would the patient and/or caregiver accept a temporary indwelling catheter and associated follow-up visits for trials of the void?
- *UTI treatment burden*: Treatment of acute cystitis carries greater risk in older patients. Multiple antibiotics are included in the American Geriatric Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, including nitrofurantoin, ciprofloxacin, sulfamethoxazole-trimethoprim, and macrolides.[29] Furthermore, the risk of *Clostridium difficile* colitis is significantly higher with advanced age and antibiotic exposure. Asymptomatic bacteriuria increases with age, with incidence up to 21% in patients ≥65 compared to 1%–5% in younger cohorts.[30] Thus, it is important also to treat only clinically symptomatic UTIs.

4 | SACRAL NEUROMODULATION

SNM utilizes a percutaneously implanted lead through the S3 foramen to stimulate the S3 nerve root, which contains afferent sensory nerves from the pelvic floor and parasympathetic nerves to the bladder. While its precise mechanism of action is unknown, SNM is thought to treat lower urinary tract dysfunction via modulation of afferent signaling which in turn modulates voiding and continence reflexes.[31] SNM is FDA-approved for refractory UUI and frequency-urgency syndrome, as well as nonobstructive urinary retention.

4.1 | Safety and efficacy data in elderly patients

Traditionally, there has been hesitation among providers to offer SNM to older patients, reflected in several claims-based studies showing lower SNM utilization in older patients.[32,33] However, multiple contemporary retrospective studies show promising results in older patients. One recent retrospective series focused on SNM for refractory OAB in octogenarians.[34] Comparison of 37 (9.9%) patients aged ≥75 years against the younger cohort revealed no significant difference in test-phase success, need for multimodal therapy, or surgical revision rates with a minimum of 12 months of follow-up. Similarly, multiple other retrospective studies assessing the role of age in SNM have reported no significant differences in outcomes with older age.[35–38]

Conversely, a recent large multicenter retrospective study of 864 women undergoing SNM for refractory OAB found lower odds of implantation (OR 0.73) and postimplantation success (OR 0.78) per increasing decade of age; however, the study had very high implant rates (91% overall), with 90% of septuagenarians and 83% of octogenarians implanted.[39] Notably, no differences were found based on comorbidities. Ultimately, a 2021 systematic review of predictive factors in SNM treatment success found no consensus predictive factors could be identified, including age, citing retrospective study design and population heterogeneity as the limiting factor.[40] The review, however, did not assess frailty.

As with BTX-A, secondary analysis of ROSETTA represents the only age-stratified analysis of SNM from randomized clinical trial data. Komesu et al.[24] study found younger patients had a greater reduction in OAB-q SF score (−7.5) compared to older patients undergoing SNM; however, unlike BTX-A, there was no difference in UUI episodes or cure rate based on age. Notably, the ROSETTA trial also offers the only head-to-head comparison of BTX-A and SNM. Though not age-stratified, 24-month follow-up data showed no difference in UUI outcomes between the therapies in the overall cohort.[41]

4.2 | Summary of the evidence

SNM is an efficacious and safe option for the elderly without evidence of higher complication rates compared to younger cohorts.

4.3 | Considerations

There are several considerations specific to the elderly population when contemplating SNM for refractory OAB:

- *Incomplete emptying/underactive detrusor*: Older patients are prone to both incomplete emptying and OAB. Because SNM therapy is also indicated for nonobstructive urinary retention, it should be considered in patients with OAB/UUI and incomplete emptying when obstructive etiologies have been ruled out.
- *Ability to use the device*: For safe and effective therapy, patients (or their caregivers) must be able to navigate and adjust the device. Comfort with technology and/or

willingness to learn device use as well as dexterity and vision should be assessed when offering SNM.

- *Anesthesia/sedation risks*: Older patients are more vulnerable to postprocedural cognitive dysfunction and delirium risks following anesthesia and sedation.[42] Lightest sedation possible should be considered in older patients undergoing staged/full implants to minimize these risks.
- *Newer device technology*:
  a. *MRI compatibility*: Historically, available SNM leads were not MRI compatible. However, with the introduction of the Axonics SNM System (Axonics) in 2019 and Medtronic's InterStim SureScan MRI lead (Medtronic) in 2020, current SNM implants do not preclude full-body MRI.
  b. *New peripheral nerve evaluation (PNE) wires*: Although there is not yet published research to support it, improvements in PNE wire design may theoretically reduce the risk of wire displacement during the test phase. If the case, this should result in a more reliable test phase, allowing patients to undergo only one anesthetic following successful PNE rather than a traditional staged approach.
  c. *Rechargeable batteries*: Patients must be able to remember to charge the device at periodic intervals. In 2022, Medtronic and Axonics introduced recharge-free devices that are expected to provide up to 15 years of battery life with low energy settings, potentially eliminating the lifespan advantage rechargeable batteries had over older nonchargeable iterations (15 vs. 5 years).

5 | POSTERIOR TIBIAL NERVE STIMULATION

Posterior tibial nerve stimulation (PTNS) is another form of neuromodulation therapy, relying on indirect stimulation of the S3 nerve root via the posterior tibial nerve.[31] While protocols vary, it generally involves weekly sessions for 12 weeks followed by indefinite monthly maintenance sessions.

5.1 | Safety and efficacy data in elderly patients

The highest-quality evidence for PTNS in the older patient population comes from a multicenter randomized sham-controlled trial in a cohort of 220 patients with a mean age of 61 years, with 45% older than 65.[43] At 12 weeks, the treatment group experienced significantly more moderate or marked improvement in symptoms (58% vs. 22%, $p < 0.001$), with benefit maintained in the subset of patients continuing through 36-month extension trial follow-up.[44] A recent systematic review and meta-analysis of studies of PTNS for OAB, with a majority of included studies with populations, with mean age >50 years, reported a pooled response rate of 68%.[45] Adverse side effects appear few and minor, including pain at the needle site, bruising, and bleeding.

Multiple retrospective studies of PTNS have evaluated elderly patient cohorts, with a mean age in the 70–73 year range, showing similar success rates as clinical trials.[46–50] Several of these studies evaluated the impact of age on success, with none identifying older age as a predictive factor.[47,49,50]

Long-term studies, however, show adherence is poor. A retrospective study in over 400 patients treated with PTNS for OAB found just 57% continue after 12-week initial treatment, with 40% of those stopping maintenance therapy due to logistic reasons and physical strain.[46] A Northern California claims-based analysis of 1331 patients with a mean age of 69.8 years initiating PTNS for OAB found just 26% completed a 12-week initial course.[51] Interestingly, older age trended as a predictor of continuing therapy: patients completing maintenance were older (68.9 vs. 70.9 years, $p = 0.11$) and age >85 years trended as a positive predictor (OR 1.98, $p = 0.10$).

5.2 | Summary of the evidence

PTNS is efficacious in the elderly with minimal risk.

5.3 | Considerations

- *Challenging its role as third-line therapy*: As discussed above, PTNS therapy has few side effects with no major adverse events noted in the available literature. Systematic review and meta-analysis have concluded that efficacy is comparable to anticholinergic pharmacotherapy with a better adverse side effect profile.[52] For patients most vulnerable to pharmacotherapy risks, such as the frail elderly, we believe that PTNS should be considered for second-line therapy.
- *Implantable tibial nerve stimulators*: Several implantable tibial nerve stimulators are currently being investigated for FDA approval for OAB. They may eliminate the logistical issues of maintenance therapy with PTNS and offer more effective therapy with continuous or semicontinuous stimulation as well.[53] The future place of implantable stimulators in the

OAB algorithm is unknown, especially if PTNS is used as second-line therapy.

6 | SPECIAL SCENARIOS

6.1 | Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disease resulting from the degeneration of dopaminergic neurons in the substantia nigra and is characterized by resting tremor, rigidity, and shuffling gate. Lower urinary tract symptoms, including OAB/UUI, are extremely common in this population. Data on third-line OAB therapy in this population is limited but of particular interest, because PD patients are likely vulnerable to the effects of polypharmacy.

The risk of urinary retention following BTX-A is concerning, as Parkinsonian tremors may preclude ISC. A 2018 study in 47 patients with PD and OAB-wet found significant subjective improvement with 100-unit injections (79%) but with a 10.5% ISC rate.[54]

Neuromodulation is a promising therapy in PD patients. A recent study of PTNS in PD patients with DO reported significant improvements in patient-reported symptoms maintained over 2 years and a reduction in PVR.[55] SNM was traditionally avoided in PD patients due to MRI incompatibility, but small series suggest safety and efficacy comparable to non-PD refractory OAB populations.[56,57] Further research is needed to guide decision-making in this population, including work to stratify patients based on validated scales of PD severity.

6.2 | Cognitive impairment

Mild cognitive impairment prevalence is estimated at 15%–20% among those older than 60 years, with 15% progressing to dementia annually.[58] OAB and urinary incontinence are more prevalent and severe in patients with dementia, and the combination portends worse health outcomes.[59]

The AUA OAB guidelines note that OAB treatment requires patients have adequate cognitive ability to engage in the treatment process and communicate treatment response.[7] However, data on various OAB treatments in cognitively impaired patients is lacking. The level of engagement required with SNM is likely higher compared to other advanced OAB options due to need to navigate and adjust device technology. Anecdotally, we have seen successful treatment in patients with mild cognitive impairment as well as in patients with motivated and involved caregivers. Decisions on whether to offer to cognitively impaired patients should thus be on a case-by-case basis, and further research is necessary for this population.

7 | CONCLUSION

Advanced age and frailty should not preclude offering third-line therapies for refractory OAB, as available data support their efficacy and safety in these populations. There is no data to support one-third-line therapy over another in older patients; however, BTX-A likely has a higher risk of UTI and retention, especially in the frail elderly. PTNS involves the lowest risk and should be considered for second-line therapy in patients at risk for pharmacologic side effects, although adherence is poor, largely due to logistical burdens. Ultimately, treatment choices should be individualized and involve shared decision-making. Future studies in phenotyping OAB and artificial intelligence/machine learning may improve patient selection.

AUTHOR CONTRIBUTIONS

Jacqueline Zillioux conceived the review topic and performed the literature search and critical assessment. All authors contributed to manuscript writing and critical revision.

CONFLICTS OF INTEREST

Jacqueline Zillioux has grant funding from Medtronic for an independent investigator-initiated study, outside this study. Sandip P. Vasavada is a consultant for Allergan, Axonics, BlueWind, and Medtronic. Emily A. Slopnick declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable – no new data were generated.

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