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Refractory Urgency Urinary Incontinence Treatment in Women: Impact of Age on Outcomes and Complications

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Abstract

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Background—Women with refractory urgency urinary incontinence (UUI) (i.e. unresponsive to behavioral and pharmacologic interventions) are treated with onabotulinumtoxinA or sacral neuromodulation.

Objectives—To compare treatment efficacy and adverse events (AEs) in women <65 and ≥65 years old treated with onabotulinumtoxinA or sacral neuromodulation (SNM).

Study Design—This study was a planned secondary analysis of a multi-center, randomized trial which enrolled community-dwelling women with refractory UUI to onabotulinumtoxinA or SNM treatments. The primary outcome: Change in mean daily UUI episodes (UUIEs) on bladder diary over 6 months. Secondary outcomes: ≥75% UUIE reduction, change in symptom severity/quality of life, treatment satisfaction and treatment-related AEs.

Results—Both age groups experienced improvement in mean UUIEs/day following each treatment. There was no evidence that mean daily UUIE reduction differed between age groups for onabotulinumtoxinA (adjusted coefficient, −0.127,95%CI −1.233, 0.979; P=0.821) or SNM (adjusted coefficient −0.698, 95% CI −1.832, 0.437; P=0.227). Among those treated with onabotulinumtoxinA, women < 65 had 3.3-fold greater odds of ≥ 75% resolution than women ≥ 65 (95% CI 1.56 –7.02). Women <65 had greater reduction in OABq-SF symptom bother scores compared to women ≥ 65 by 7.49 points (95% CI −3.23, −11.74), regardless of treatment group. There was no difference between quality of life improvement by age. Older women had more UTIs following onabotulinumtoxinA and SNM (OR 1.9, 95% CI 1.2-3.3). There was no evidence of age differences in SNM revision/removal or catheterization following onabotulinumtoxinA.

Conclusion—Younger women experienced greater absolute continence, symptom improvement, and fewer UTIs; both older and younger women had beneficial UUIE reduction, similar rates of other treatment adverse events and improved quality of life.

Keywords

OnabotulinumtoxinA; Sacral neuromodulation; InterStim; Urgency Incontinence; older women

Introduction

Urgency urinary incontinence (UUI) is characterized by involuntary urinary leakage that occurs with a sudden, compelling desire to void that is difficult to defer. Refractory UUI is defined as UUI that has not responded to behavioral therapies with lack of response or intolerance to at least two medications.[1] UUI prevalence increases with age[2] and its attendant consequences, including diminished social interaction, increased fall–related injury and reduced quality of life, profoundly affects older women.[1,3]

Studies of refractory UUI treatments have demonstrated efficacy of both onabotulinumtoxinA and sacral neuromodulation (SNM).[1,4,5] However, efficacy and safety data for these treatments in the older population are limited. Older patients have been under-represented in clinical research because of exclusion and under-recruitment, likely due to concerns regarding participants' multiple co-morbidities and risk of adverse events.[6] It is important to evaluate treatment effects and complications associated with

onabotulinumtoxinA and SNM in older women, as age-bias has hampered study of outcomes in this population.

The Refractory Overactive Bladder: Sacral Neuromodulation vs Botulinum Toxin Assessment (ROSETTA) study is a 9-center open-label randomized trial involving 381 community dwelling women with idiopathic refractory UUI randomized to onabotulinumtoxinA or sacral neuromodulation.[7] Its 6 month results have been published.[7] The trial intentionally included older women and stratified participants by age and treatment, allowing for a more detailed evaluation of the impact of age on refractory UUI treatments. The objective of this planned secondary analysis was to compare symptom control and adverse events (AEs) over the first 6 months following refractory UUI treatment in women ≥65 years compared to women ≥65 years.

Materials and Methods

Design

The design and primary results of the randomized trial comparing 6-month outcomes have been published.[7] The current comparative cohort study evaluated age-related treatment efficacy and complications relative to these treatments.

Participants and Procedures

Women were recruited from nine sites participating in the NIH-sponsored Pelvic Floor Disorders Network and were stratified by age into women ≥65 versus ≥ 65 years, the typical age for Medicare eligibility. Inclusion criteria for participants included women with persistent UUI symptoms despite undergoing at least one supervised behavioral or physical therapy intervention and use of ≥ 2 incontinence medications (or inability to tolerate or contraindications to the medications). Participants were required to have a minimum of six UUI episodes on a baseline 3-day bladder diary. Participants had stopped UUI medications for a minimum of 3 weeks prior to baseline evaluation and had urodynamic assessment within 18 months prior to randomization. Women with relevant neurologic diseases, elevated post-void residuals, or a history of using either onabotulinumtoxinA or SNM were excluded. All sites received local IRB approval (UNMH IRB#11-423).

After obtaining written consent, standardized demographic and clinical data and key procedural elements were collected. Medical comorbidities were assessed with the Functional Comorbidity Index (FCI) questionnaire.[8] Definitions of clinical terms, methods of evaluation, and procedural elements, were standardized across sites as described previously.[7]

Interventions

Participants were randomized 1:1 to onabotulinumtoxinA or SNM. SNM participants underwent a first stage lead placement by experienced surgeons in the operating suite. During the 7-14 day testing phase, participants with ≥50% improvement in mean UUI episodes (UUIEs) on a 3-day bladder diary were categorized a priori as clinical responders and were eligible for placement of the permanent implantable pulse generator. A ≥ 50%

reduction in UUIE from baseline is the threshold used in clinical practice to proceed with pulse generator implantation based on FDA recommendations. Those without this improvement underwent lead removal.

Participants randomized to onabotulinumtoxinA received a cystoscopic intradetrusor injection of 200 U of onabotulinumtoxinA performed in clinic. Women with ≥ 50% reduction in UUIEs on a bladder diary one-month post-injection were a priori defined as clinical responders and were eligible for future injections as specified by the study protocol.[7] After injection, onabotulinumtoxinA participants were followed for urinary retention and those with a post void residual >300 ml or >200 ml with symptoms of incomplete voiding were instructed to perform clean intermittent catheterization post-treatment.

Outcomes and Data Collection

The primary treatment outcome for the current study was change from baseline in mean number of daily UUIEs averaged over 6 months, as recorded for 3 days on monthly bladder diaries. Other outcomes included the proportion of subjects with ≥75% reduction in daily UUIEs through 6 months and questionnaire results. Quality of life and symptom severity were assessed monthly with the Overactive Bladder Questionnaire Short Form (OABq-SF).[9] Other measures assessed at baseline and six months included the Sandvik questionnaire,[10] a measure of incontinence severity, the Urinary Distress Inventory Short Form,[11] the Incontinence Impact Questionnaire Short Form,[11] the Health Utility Index Mark-3 (HUI-3),[12] and the Life Space Assessment (LSA),[13] a measure of participants' mobility patterns. The Patient Global Impression of Improvement (PGI-I)[14] and the Overactive Bladder Satisfaction of Treatment (OAB-SATq)[15] were measured only at six months. OAB-SATq subcategories measure treatment satisfaction, adverse effects, treatment endorsement, and convenience.

Safety and AE secondary outcomes were collected monthly, including the proportion of onabotulinumtoxinA participants with urinary retention requiring catheterization at 2 weeks and one, three, and six months. Additional information was collected regarding the proportion of SNM participants requiring surgical revisions due to surgical site infection, pain, or lead migration, and the proportion in each group receiving urinary tract infection (UTI) treatment, either culture positive and/or due to symptoms.

Statistical Analysis

The analysis of reduction in mean UUIE utilized a modified intention to treat population that included all eligible participants who provided at least one post-baseline bladder diary assessment. The analysis of those participants who achieved ≥75% reduction in UUIE episodes on each available bladder diary was limited to participants with a minimum of 4 months of completed diaries. The analysis of quality-of-life measures was based on the full intention to treat population who had at least one post-baseline measure on the outcome measure. The safety and AE analysis was based on the full intention to treat population.

Analyses of reduction in mean UUIE used a multivariable linear mixed model with participant-month in the study (1 through 6) as the unit of analysis and reduction from baseline in mean UUIE per day from the monthly diary as the outcome, with terms for

treatment group, month, age group, interaction of treatment group with month, interaction of treatment group with age group, and site. Participant was treated as a random effect to account for within-person correlation in diary outcomes over time. Additional baseline covariates considered for inclusion were race, body mass index (BMI), FCI, diabetes (type 1, 2), degenerative disc disease, daily UUIE, IIQ, Sandvik severity score, HUI-3, and smoking, with only those covariates found to be associated with the outcome at $p \geq 0.10$ included in the multivariable model; in building the multivariable model, candidate covariate terms were removed in stepwise fashion to achieve a final model that included all covariates with $p < 0.10$. Analysis for discrete outcome of ≥75% reduction in UUIEs used an analogous process with a multivariable logistic regression model. Analysis of continuous measures of quality-of-life and efficacy, such as change in OAB symptom bother or change in HUI, used the same linear mixed model described above but without consideration of covariates beyond treatment group, age group, month, and site. Aggregate binary measures were evaluated using contingency tables, with differences between treatment groups assessed with the Mantel–Haenszel tests accounting for randomization strata.

The study was designed to conduct formal analyses for only the primary outcome at the 0.05 level of significance, and all other results and p-values are considered descriptive. Consequently, no adjustments have been made for multiple comparisons. Analyses were performed with the use of SAS software, version 9.3 (SAS Institute). All inferences and descriptive p-values are based on 2-sided tests.

Results

Study Population

Three hundred sixty-four women with refractory UUI were followed for six months following randomization to intravesical onabotulinumtoxinA or SNM and were stratified by age as ≥65 years old (N=191) and ≥ 65 years (N=173). Participant baseline characteristics are noted in Table 1. Younger women had a higher mean BMI, were more often non-White, and were more often smokers. Older women had higher mean FCI (i.e. more co-moribidities), better (higher) mean OABq quality of life, and better (lower) mean IIQ scores. In subjects ≥65 years, 100 were treated with onabotulinumtoxinA and 91 were treated with SNM; in women ≥ 65 years, 90 were treated with onabotulinumtoxinA and 83 treated with SNM (Table 2).

Incontinence Outcomes

There was no evidence of a difference in mean daily reduction of UUIE between younger and older women within either the onabotulinumtoxinA (P=0.821) or SNM (P=0.227) groups (Table 2). Variables independently associated with UUIE reduction over 6 months included baseline HUI-3 scores and baseline daily mean number of UUIE. Higher (i.e. better) HUI-3 scores predicted greater reduction of mean UUIE for younger, not older women; for each 0.3 increase in HUI-3 score, there was a mean reduction of 0.54 UUIE/day. Higher baseline UUIE/day predicted greater reduction for both younger and older women with a mean reduction of 0.62 UUIE/day following treatment.

Younger women had a 3.3 times greater odds of attaining ≥ 75% resolution of UUIE than women ≥ 65 years (95% CI 1.56 – 7.02) in the 6 months following onabotulinumtoxinA treatment (Table 3). In women undergoing SNM there was no evidence of an age difference (P=0.72). In addition to age, variables associated with ≥ 75% UUIE reduction included presence of degenerative disc disease and IIQ and Sandvik severity scores. Presence of degenerative disc disease decreased the odds of achieving ≥75% UUIE reduction in women treated with onabotulinumtoxinA (adjusted OR 0.15, 95% CI 0.06 – 0.39). This effect was not observed in women treated with SNM, nor did this variable differentially affect older versus younger women. A similar pattern was observed for IIQ score, where higher (i.e. worse) baseline scores predicted lower odds of ≥ 75% resolution in women treated with onabotulinumtoxinA, but not in women treated with SNM. Higher (i.e. worse) Sandvik severity scores at baseline decreased the odds of ≥75% UUIE reduction for both older and younger women treated with either treatment.

Symptom Specific Quality of Life Outcomes

Improvements in OAB symptom bother and satisfaction scores in women ≥65 were greater than women ≥ 65 years with no evidence of a difference between treatment groups (Appendix). OAB-satisfaction endorsement and convenience scores reflected better outcomes in women ≥ 65 treated with onabotulinumtoxinA; scores in women undergoing SNM did not differ by age. LSA scores worsened in women ≥65 years treated with onabotulinumtoxinA; but there was no evidence of differences between age groups in women treated with SNM. Older women more commonly had UTIs following both onabotulinumtoxinA and SNM treatments (an approximate 2-fold increase, Appendix), and a similar trend (Appendix) in older women occurred regarding recurrent UTIs, though this did not reach statistical significance. No evidence of age differences was noted regarding device revision/removal following SNM, or need for catheterization following onabotulinumtoxinA.

Comments

This planned secondary analysis of data obtained from women with refractory UUI undergoing treatment with onabotulinumtoxinA or SNM is particularly important for older women since significant changes in the lower urinary tract may accompany aging. These changes include decreased detrusor contractility and decreased urethral vascular density and pressure[16,17] which may affect micturition efficiency and continence and could differentially impact both chemical and electrical neuromodulation treatment modalities.

In this study, older women differed from younger women with respect to several baseline variables. Though statistically significant, it is unclear whether all these were clinically significant. For example, the difference in FCI scores between groups did not meet a conservative estimate of a minimal clinically important difference of one half the standard deviation.[18] The IIQ score, however, exceeded the minimally important difference.[19] This suggests that these older women, despite similar distress and symptom severity scores, were less clinically impacted at baseline than younger women, perhaps representing age or generational differences in symptom perception.

With respect to post-treatment incontinence outcomes, there was no difference in mean daily UUIE reduction over 6 months in younger compared to older subjects, regardless of treatment. Similarly, a previous study which evaluated onabotulinumtoxinA dose response in women with idiopathic OAB, also found no age differences on multivariate analysis.[20] In contrast, a study of participants undergoing SNM reported that although both younger and older groups had a significant decrease in UUIE, greater improvement was noted in the younger cohort.[21]

Variables noted in the current study that did influence mean UUIE reduction included the HUI-3 and UUIEs at baseline. Though there were no differences in HUI-3 scores at baseline, younger women with higher scores (reflecting better health status) had greater UUIE reduction regardless of treatment modality. Higher baseline UUIEs also predicted greater UUIE reduction irrespective of age or treatment modality, an effect also noted in a trial of anticholinergic therapy versus 100units onabotulinumtoxinA for UUI.[5] This finding may reassure older women contemplating refractory UUI treatment that UUIE improves despite relatively high baseline levels.

Diary outcomes also included evaluation of ≥ 75% UUIE reduction over 6 months. A significantly higher proportion of younger women, compared to older women, treated with onabotulinumtoxinA experienced ≥75% reduction. This age effect was not seen with SNM, although a previous SNM study did note cure rates (defined as no leakage episodes) that were higher in younger patients compared to older patients (65% versus 37%, $p<0.05$).[21] Very little other data exist with regard to refractory UUI cure rates between older and younger women, but in general cure rates may be less in older women.

Regardless of age, women with degenerative disc disease treated with onabotulinumtoxinA therapy had reduced odds of attaining ≥75% reduction in UUIE. In theory, degenerative disc disease, especially with disc prolapse, could affect bladder function.[22,23] Interestingly, a prior study evaluating factors associated with use of percutaneous nerve evaluation (PNE) results in SNM found that prior intervertebral disc surgery was associated with 3.7 times higher odds of a successful test.[24] Perhaps women with self-reported, ongoing disc disease have more afferent/efferent sacral irritation that interferes with the peripheral effect of OnabotulinumtoxinA, an effect not seen in SNM. As degenerative disc disease is a variable included in the FCI, the potential for co-linearity between disc disease and FCI existed in our current analysis. A multivariable analysis was performed including FCI score rather than disc disease as a predictor of ≥75% UUIE reduction. Total FCI score did not predict ≥75% UUIE reduction in this model (onabotulinumtoxinA, adjusted OR 0.86, 95% CI 0.73,1.02; SNM adjusted OR 0.99, 95% CI 0.83,1.18), confirming the importance of disc disease independently decreasing the effectiveness of onabotulinumtoxinA. Other predictors of ≥ 75% reduction in UUIE included baseline IIQ and Sandvik scores. Greater UUI severity reflected in baseline IIQ and Sandvik scores were negative predictors of ≥ 75% reduction. IIQ was only predictive in onabotulinumtoxinA patients and higher Sandvik severity scores were predictive for both treatments.

With regard to quality of life outcomes, there were few differences in treatment response based on the majority of study questionnaires comparing younger and older women. Both

age groups met the questionnaires' minimally important differences in improvement. Age differences were present only for OABq-SF symptom, OAB-SATq and LSA scores post-treatment. Mean OABq-SF symptom bother score improvements were statistically better in the younger age group; however, the clinical significance of this difference is unclear as it did not meet the minimally important difference established for the OAB questionnaire.[19] Paradoxically, LSA scores showed less improvement in younger women compared to older women treated with onabotulinmutoxinA. This relationship between onabotulinumtoxinA and LSA did not seem to affect younger women's satisfaction scores with botulinum toxin treatment. OAB-SATq convenience and endorsement domains were higher in younger women treated with onabotulinumtoxinA. Perhaps diminished LSA (reflecting diminished mobility) was outweighed by the other benefits of onabotulinumtoxinA, resulting in higher treatment satisfaction in younger women.

Treatment-related AEs included UTIs, the need for clean intermittent self- catheterization (CISC) and revision/removal of SNM associated devices. As reported in our previous ROSETTA publication,[7] UTIs were more common following onabotulinumtoxinA compared to SNM (35% versus 11% overall). Furthermore, here we show that women ≥ 65 were more commonly treated for a UTI than women ≥65 years and that the same trend held true for recurrent UTIs (≥ 2 UTIs over 6 months). UTIs in older women in ROSETTA, like women in the general population, increased with age. Ten percent of community-dwelling women report having had a UTI within a year,[25] with numbers increasing to 25% of women > 85 and 34% of women > 95 years.[26] The nearly 2-fold increase in UTIs in older women in this study did not seem to affect OAB-Sat Adverse Event Scores, where no differences were found based on age groups. Whether UTI occurrence affected age differences in OAB-Sat Endorsement or Convenience remains unclear. CISC was performed at some point within the first 6 months of onabotulinumtoxinA treatment in approximately 18-23% of patients with no differences found between age groups. This differs from the report by Miotla, who found elevated post-void residuals and higher CISC occurrence in patients older than 68 years.[27] SNM removal/revisions were uncommon occurring in less than 5% of patients and no differences were found between age groups.

In conclusion, this is the largest prospective study comparing outcomes and AEs in older and younger women undergoing onabotulinumtoxinA or SNM for the treatment of refractory UUI. The study design allowed robust comparison of outcomes by age groups which, on average, differed by nearly 20 years. Study outcomes based on bladder diary and validated questionnaires permitted evaluation of the patient experience from several important dimensions including UUI episodes, changes in symptom specific quality of life, patient endorsement, and AEs. Weaknesses include the possibility that medically frail, cognitively impaired and institutionalized women were under-represented given the rigorous data acquisition and follow-up required of trial participants. In summary, both older and younger women with refractory UUI responded positively to both treatments. There were differences between age groups in UTIs and certain UUI diary parameters and questionnaire domains. Further follow-up is required to weigh longer-term benefits, including cost-effectiveness, versus adverse consequences of these refractory UUI treatments.

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Appendix. Quality of Life Outcomes & Procedure-Related Adverse Events

Outcome Measure	Parameter Estimated	Effect Measurements				P-value	
		Onabotulinumtoxin A <65	Onabotulinumtoxin A ≥65	Neuromodulation <65	Neuromodulation ≥65	Age x Treatment Interaction	Main Age Effect
Change in OAB Symptom Bother	Age/Tx[a] Mean (SE)	−49.8 (2.1)	−44.3 (2.2)	−42.4 (2.3)	−32.8 (2.3)	0.341	0.0006
	Age Difference (CI)	−7.5 (−3.2, −11.7)					
Change in OAB Quality of Life	Age/Tx Mean (SE)	42.3 (2.1)	41.6 (2.1)	40.0 (2.2)	33.7 (2.6)	0.185	0.121
	Age Difference (CI)	3.2 (−0.9, 7.5)					
Change in Life Space Assessment	Age/Tx Mean (SE)	−4.22 (2.4)	1.64 (2.5)	5.75 (2.6)	1.26 (2.5)	0.032	0.081 (O) 0.199 (N)
	Age Difference (CI)	−5.9 (−12.4, 0.7)		4.5 (−2.4, 11.4)			
Change in Urinary Distress Inventory	Age/Tx Mean (SE)	−24.3 (2.64)	−20.1 (2.76)	−22.1 (2.92)	−22.2 (2.82)	0.422	0.446
	Age Difference (CI)	−2.1 (−7.5, 3.3)					
Change in Incontinence Impact	Age/Tx Mean (SE)	−28.2 (2.8)	−25.7 (3.0)	−30.1 (3.1)	−21.2 (3.0)	0.261	0.062
	Age Difference (CI)	−5.6 (−11.4, 0.3)					
Change in Health Utility Index	Age/Tx Mean (SE)	−0.02 (0.03)	−0.04 (0.03)	0.01 (0.03)	0.00 (0.03)	0.8026	0.671
	Age Difference (CI)	0.01 (−0.04, 0.07)					
OAB-sat Treatment Satisfaction	Age/Tx Mean (SE)	73.7 (3.1)	61.3 (3.2)	61.6 (3.4)	58.1 (3.3)	0.160	0.011
	Age Difference (CI)	9.2 (1.9, 14.5)					
OAB-sat Adverse Effects	Age/Tx Mean (SE)	89.2 (2.6)	87.3 (2.7)	81.9 (2.8)	88.5 (2.8)	0.108	0.406
	Age Difference (CI)	−2.2 (−7.4, 3.0)					
OAB-sat Endorsement	Age/Tx Mean (SE)	85.3 (3.0)	70.4 (3.2)	69.2 (3.4)	65.9 (3.2)	0.059	0.006 (O) 0.466 (N)
	Age Difference (CI)	15.0 (6.5, 23.4)		3.30 (−5.5, 12.1)			
OAB-sat Convenience	Age/Tx Mean (SE)	71.5 (2.6)	63.3 (2.9)	69.8 (3.0)	70.7 (3.0)	0.100	0.032 (O) 0.814 (N)
	Age Difference (CI)	8.2 (0.7, 15.7)		−1.0 (−9.1, 7.1)			
PGI-I Urinary Leakage	Age/Tx Incidence, n (%)	59 (76.6%)	42 (63.6%)	44 (66.7%)	47 (70.2%)	0.156	0.452
	Age OR (CI)	0.8 (0.5, 1.4)					
PGI-I Bladder Function	Age/Tx Incidence, n (%)	59 (73.8%)	41 (62.2%)	45 (69.2%)	47 (71.2%)	0.259	0.349
	Age OR (CI)	0.8 (9.5, 1.3)					
Any Urinary Tract Infection	Age/Tx Incidence, n (%)	31 (30.7%)	39 (43.3%)	10 (10.8%)	12 (15.3%)	0.690	0.014
	Age OR (CI)	1.9 (1.2, 3.3)					

Outcome Measure	Parameter Estimated	Effect Measurements				P-value	
		OnabotulinumtoxinA <65	OnabotulinumtoxinA ≥65	Neuromodulation <65	Neuromodulation ≥65	Age x Treatment Interaction	Main Age Effect
Recurrent Urinary Tract Infection	Age/Tx Incidence, n (%)	12 (11.9%)	15 (16.5%)	2 (2.0%)	6 (6.8%)	0.402	0.066
	Age OR (CI)	2.01 (0.96, 4.24)					
Revision or Removal	Age/Tx Incidence, n (%)	NA	NA	2 (2.0%)	4 (4.6%)	NA	0.258
	Age OR (CI)	2.8 (0.5, 16.7)					
Intermittent catheterization	Age/Tx Incidence, n (%)	23 (22.8%)	16 (17.6%)			NA	0.535
	Age OR (CI)	0.79 (0.4, 1.7)					

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Condensation

OnabotulinumtoxinA and sacral neuromodulation both effectively treated older and younger women with refractory urgency urinary incontinence, though certain aspects of incontinence and questionnaire improvements differed.

Table 1

Baseline Characteristics

	≥65 years N=191	≥65 years N=173	P value
Treatment Group N (%)			1.000
• OnabotulinumtoxinA	100 (52.4)	90 (52.0)	
• Neuromodulation	91 (47.6)	83 (48.0)	
Age Mean (SD)	54.1 (7.9)	72.9 (5.5)	≥0.001
BMI Mean (SD)	33.0 (8.4)	31.3 (7.9)	0.034
Ethnicity N (%)			0.221
• Non-Hispanic	168 (88.0)	159 (91.9)	
• Hispanic/Latina	19 (9.9)	9 (5.2)	
• Unknown/Not reported	4 (2.1)	5 (2.9)	
Race N (%)			0.014
• White	151 (79.1)	152 (87.9)	
• Black/African-Am	29 (15.2)	9 (5.2)	
• Asian	1 (0.5)	1 (0.6)	
• American Indian/Pacific Islander	3 (1.6)	2 (1.2)	
• Other	5 (2.6)	5 (2.9)	
• More than 1 race	2 (1.0)	1 (0.6)	
• Unknown	0 (0)	3 (1.7)	
Smoker N (%)			≥0.001
• No	159 (83.2)	165 (95.4)	
• Yes	32 (16.8)	8 (4.6)	
Functional Comorbidity Index, mean (SD)	3.47 (2.3)	3.98 (2.21)	0.020
Diabetes type 1 & 2 N (%)			0.093
• Don’t know	1 (.5)	0 (0)	
• No	164 (85.9)	137 (79.2)	
• Yes	26 (13.6)	36 (20.8)	
Degenerative Disc Disease N (%)			0.625
• Don’t know	2 (1.0)	1 (0.6)	
• No	146 (76.4)	127 (73.4)	
• Yes	43 (22.5)	45 (26.0)	
Recurrent UTIs (≥3 past year) N (%)			0.759
• No	164 (85.9)	151 (87.3)	
• Yes	27 (14.1)	22 (12.7)	
UUIE Mean (SD)	5.11 (2.53)	5.5 (2.8)	0.178

	≥65 years N=191	≥65 years N=173	P value
Sandvik Score[a] Number (%)			0.090
• Slight	1 (0.5)	2 (1.2)	
• Moderate	32 (16.8)	20 (11.6)	
• Severe	54 (28.3)	36 (20.8)	
• Very Severe	97 (50.8)	111 (64.2)	
• Missing	7 (3.7)	4 (2.3)	
OABq-SF[b] Symptom Severity Mean (SD)	76.2 (18.0)	74.3 (18.6)	0.370
OABq-SF[b] Quality of Life Mean (SD)	35.1 (21.7)	40.2 (22.7)	0.044
Life Space Assessment Mean (SD)	86.4 (28.9)	82.2 (25.1)	0.051
HUI-3[c] Mean (SD)	0.7 (0.3)	0.7 (0.3)	0.773
UDI[d] Mean (SD)	60.9 (18.5)	59.1 (16.7)	0.533
IIQ[e] Mean (SD)	58.8 (25.5)	45.7 (26.4)	≥0.001

[a] scale of slight=1-2, moderate=3-6, severe=8-9, very severe=10-12

[b] overall scores range 0-100; higher symptom severity scores indicate more symptoms, higher quality of life scores indicate better quality of life

[c] represents overall health; score for death=0.00, score for perfect health=1.00

[d] range 0-100, higher scores represent greater distress

[e] range 0-100, higher scores indicate worse quality of life

[f] t-tests used for continuous variables and chi-squared testing used for proportions

Table 2

Multivariable Model Results for Mean Reduction in UUI Episodes Over 6 Months

Outcome: Reduction in UUI Episodes Over 6 Months					
Predictor	**≥ 65 years Adjusted Coefficient (95% CI) N=191**	**≥ 65 years Adjusted Coefficient (95% CI) N=173**	**PredictorMain Effect p-value**	**Predictor x Age Interaction p-value**	**Predictor x Treatment Interaction p-value**
Age ≥ 65[a,b]					
OnabotulinumtoxinA (N=100)	−0.1 (−1.233, 0.979)	Reference	0.821	—	0.148
Neuromodulation (N=91)	−0.698 (−1.832, 0.437)	Reference	0.227		
HUI-3 (per 0.3 pts[C]**)**	0.537 (0.266,0.808)	0.111 (−0.188,0.410)	0.002	—	—
UUI episodes at baseline	0.621 (0.540, 0.702)		≥0.001	—	—

[a] Age category and an age-category-by-treatment-group interaction term were included in the multivariable model irrespective of p-value. For other predictors and interactions, terms were selected by backwards selection subject to p ≥ 0.1, as described in Methods. Coefficient estimates represent the mean daily reduction in UUIE episodes associated with a unit increase in the predictor.

[b] Age ≥ 65, onabotulinumtoxinA N=100 and neuromodulation N=91. Age ≥ 65, onabotulinum toxin N=90, neuromodulation N=83

[c] HUI-3 baseline standard deviation in our study population

[d] Multivariable linear mixed model used for analysis

Table 3

Multivariable Model Results for ≥ 75% Reduction in UUI Episodes Over 6 Months

Outcome: ≥75% Reduction in UUI Episodes					
Predictor	**≥ 65 years Adjusted Odds Ratio (95% CI)**	**≥ 65 years Adjusted Odds Ratio (95% CI)**	**Predictor Main Effect p-value**	**Predictor x Age Interaction p-value**	**Predictor x Treatment Interaction p-value**
Age ≥ 65					
OnabotulinumtoxinA	3.31 (1.56, 7.02)	Reference	0.002	—	0.059
Neuromodulation	1.16 (0.51, 2.61)	Reference	0.721		
Degenerative Disc Disease					
OnabotulinumtoxinA	0.150 (0.059, 0.386)		<0.001	—	0.016
Neuromodulation	0.798 (0.304, 2.096)		0.647		
IIQ (per each 10 points)					
OnabotulinumtoxinA	0.866 (0.756, 0.992)		0.038	—	0.062
Neuromodulation	1.058 (0.898, 1.247)		0.499		
Sandvik (per each 1 point)	0.835 (0.762, 0.916)		<0.001	—	—

A multivariable logistic regression model was used for analysis. Age category and an age-category-by-treatment-group interaction term were included in the multivariable model irrespective of p-value. For other predictors and interactions, terms were selected by backwards selection subject to $p < 0.1$, as described in Methods. Odds ratios represent the increased odds of a ≥75% reduction in UUI episodes associated with a unit increase in the predictor.