HHS Public Access

Author manuscript

*J Urol*. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

*J Urol*. 2017 October ; 198(4): 890–896. doi:10.1016/j.juro.2017.04.103.

# Characteristics Associated With Treatment Response in Women Undergoing OnabotulinumtoxinA and Sacral Neuromodulation for Refractory Urgency Urinary Incontinence

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## Abstract

**Purpose—**To identify clinical and demographic characteristics associated with onabotulinumtoxinA and sacral neuromodulation treatment response in women with refractory urgency urinary incontinence.

**Material and Methods—**Data were analyzed from the Refractory Overactive Bladder: Sacral Neuromodulation vs Botulinum Toxin Assessment trial. Baseline participant characteristics and clinical variables associated with two definitions of treatment response: 1) reduction in mean daily urgency incontinence episodes over 6 months 2) ≥50% decrease in urgency incontinence episodes across 6 months were identified. Linear and logistic regression models were fit to estimate mean reductions in incontinence episodes and adjusted odds ratios for incidence of ≥50% decrease with 95% confidence intervals, respectively.

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**Conflict of Interest**

All authors except for C. Chermansky report no COI. Dr Chermansky participated in activities with Allergan and Medtronics resulting in funds spent for food/lodging less than $600.

**Results—**For both treatments, a greater reduction in mean daily urgency incontinence episodes was associated with higher Health Utility Index scores (P=0.002) and higher baseline incontinence episodes (P<0.001). Increased age was associated with less reduction in incontinence episodes (P<0.001). Increasing body mass index (aOR 0.82 per 5 points, 95% CI 0.70, 0.96) was associated with reduced achievement of ≥50% decrease in incontinence episodes after both treatments. Greater age (aOR 0.44 per 10 years, 95% CI 0.30, 0.65) and higher functional comorbidity index (aOR 0.84 per point, 95% CI 0.71, 0.99) were associated with reduced achievement of ≥50% decrease in urgency incontinence episodes in the onabotulinuntoxinA group only (P=0.016; P=0.031, respectively).

**Conclusion—**Increasing age, body mass index, and functional comorbidity are negatively associated with treatment response while greater incontinence frequency and health utility is associated with a greater response to third line treatments for refractory urgency incontinence.

### Keywords

functional comorbidity index; health utility index; onabotulinumtoxinA; refractory urgency urinary incontinence; sacral neuromodulation

## Introduction

Refractory urgency urinary incontinence (UUI) markedly impacts quality of life. Women with the condition have typically attempted treatment with several medications or experienced medication side-effects. Other treatments including behavioral therapy with pelvic muscle exercises require continued adherence which may decline over the long-term.[1] Women with UUI refractory to these primary treatment approaches may be offered third-line treatment options including posterior tibial nerve stimulation, sacral neuromodulation (SNM) or onabotulinumtoxinA. Understanding patient clinical and demographic characteristics which may be associated with third-line treatment response, especially in the setting of more invasive treatment approaches such as SNM and onabotulinumtoxinA, is important and may help improve treatment success.

In smaller studies of onabotulinumtoxin A, clinical and demographic factors associated with treatment efficacy included: female gender,[2] lower baseline overactive bladder symptom distress,[2] and higher baseline detrusor pressure.[3] Characteristics noted to be associated with efficacy of sacral neuromodulation included: higher baseline number of UUI episodes,[4] increasing age,[5–7] and medical comorbidity level.[6]

The Refractory Overactive Bladder: Sacral Neuromodulation versus Botulinum Toxin Assessment (ROSETTA) trial was an open-label randomized trial involving women with idiopathic refractory UUI randomized to onabotulinumtoxinA or sacral neuromodulation (SNM) and provided an opportunity to robustly characterize factors associated with treatment response.[8] The objective of this planned secondary analysis was to identify baseline clinical and demographic factors associated with treatment response in women participating in this multicenter randomized trial comparing efficacy of these two therapies.

## Materials & Methods

The design and primary results of the ROSETTA trial have been published.[8,9] The institutional review board of each clinical site and coordinating center approved the protocol and participants provided written informed consent. Major inclusion criteria for women participating in the ROSETTA trial included a minimum of six urgency urinary incontinence episodes (UUIE) on a baseline 3-day bladder diary, not taking or stopping UUI medications at least 3 weeks prior to their baseline evaluation, and urodynamic assessment within 18 months prior to randomization. Women with relevant neurologic diseases, history of using either of the two study interventions or elevated post-void residual volumes were excluded. Standardized demographic, clinical data and key procedural elements were collected at baseline.

Briefly, participants randomized to SNM underwent a first stage lead placement by experienced surgeons in the operating suite. During the 7–14 day testing phase, those participants with ≥50% improvement in mean UUIE on a 3 day bladder diary were categorized a priori as clinical responders and were eligible for placement of the permanent implantable pulse generator. Those without this improvement had the lead removed. Participants randomized to onabotulinumtoxinA received a one-time cystoscopic intradetrusor injection of 200 U performed in clinic. Women with ≥ 50% reduction in UUIE on a bladder diary one month post-injection were defined as onabotulinumtoxinA clinical responders.

Treatment response outcomes for this planned secondary analysis included: 1) reduction of mean daily UUIE over 6 months and 2) ≥50% decrease in UUIE on each of the completed diaries across 6 months as recorded in monthly 3-day bladder diaries. The analysis population for the first outcome included participants with at least one post-baseline diary, while the population for the second included participants with at least 4 completed diaries. Quality of life and symptom severity were assessed monthly with the Overactive Bladder Questionnaire Short Form (OABq-SF).[9] Other quality of life instruments administered at baseline and six months included the Sandvik questionnaire, the Urinary Distress Inventory-Short Form (UDI-SF), the Incontinence Impact Questionnaire-Short Form (IIQ-SF) and the Health Utility Index Mark-3 (HUI-3), a multi-attribute scale of overall health-related quality of life.[9]

Potential variables thought to be associated with treatment response were sociodemographic characteristics (age, race/ethnicity); medical history/functional status (body mass index, smoking status, menopausal status, Timed Up and Go); characteristics of urinary incontinence (UUIE, Sandvik score, UDI-SF); symptom impact and incontinence-related quality of life (OABq-SF, IIQ-SF); urodynamic variables and medical comorbidities including history of recurrent urinary tract infections and Functional Comorbidity Index (FCI).[9,10]

The analysis of reduction in mean UUIE utilized a modified intention to treat population including all participants providing at least one post-baseline bladder diary. Analysis of subjects achieving a ≥50% reduction in UUIE was limited to subjects with a minimum of 4

months of bladder diaries. To identify variables associated with reduction of mean daily UUIE over 1 to 6 months post-treatment (continuous outcome), linear mixed models were fit, for each potential predictor controlling for treatment group, age group (<65 years, ≥65 years), site, month post treatment, and interaction of treatment group with month. Participants were treated as a random effect to account for within-subject correlation in diary outcomes over time. To evaluate possible differences in effect size between treatment groups, interaction models were fit, in which a treatment-by-predictor term was also included. To identify baseline variables associated with ≥50% reduction in UUIE (dichotomous outcome), logistic regression models were fit for each potential predictor with all models controlling for treatment group and age group (<65 years vs ≥65 years), as factors included in the original randomization.

Initially each baseline variable was modeled individually to assess association to each of the two outcomes. Parameter estimates, odds ratios and 95% confidence intervals (CIs) are shown by treatment group based on treatment-stratified analyses. Variables in which either the main effect or interaction term had $p < 0.10$ (Wald test) were included as candidate terms in a combined multivariable model, which then underwent backward variable selection so that each term in the final multivariable model had $p < 0.10$. Results were not adjusted for multiple comparisons, so all p-values should be interpreted accordingly. All analyses were performed using SAS Version 9.4 (SAS Institute, Inc. Cary, NC).

## Results

One hundred ninety participants randomized to onabotulinumtoxinA and 174 randomized to SNM were included in this secondary analysis. Baseline characteristics were similar between treatment groups (Table 1). Overall, mean age (±SD) was 63.0 years (±11.6) and body mass index was 32.2 kg/m$^2$ (±8.2). At baseline, participants reported a mean of 5.30 (±2.67) UUIE per day, 96% reported their UUI symptoms as moderate, severe or very severe on the Sandvik questionnaire. Other characteristics are noted in Table 1.

On univariable analysis regarding the outcome of reduction in mean daily UUIEs over 6 months, the majority of baseline covariates were not associated however, increasing age and higher baseline OAB-SF Quality of Life (QoL) score were associated with less reduction of mean daily UUIE over 6 months (Table 2a). Hispanic/Latina ethnicity, presence of detrusor overactivity on cystometrogram, greater daily UUIE and total UI episodes per day, higher OABq-SF symptom bother scores and higher (better) HUI-3 scores were associated with greater reduction in mean daily UUIE. A greater effect was noted in the onabotulinumtoxinA group for UUIE and total UI episodes.

Multivariable analyses for reduction in mean daily UUIE over 6 months revealed that age and greater UUIE frequency for both onabotulinumtoxinA and SNM treatments (Table 3a) were associated with this outcome. Increasing age was associated with a lower treatment response, while higher frequency of UUIE at baseline was associated with an increased treatment response. Higher HUI-3 score, was also significantly associated with improved treatment response with some evidence of a greater reduction in the onabotulinumtoxinA group.

Similarly, univariable analysis regarding the achievement of ≥50% reduction in UUIEs revealed (Table 2b) that increased age, higher BMI, higher Functional Comorbidity Index (FCI) scores, worse (higher) baseline Incontinence Impact Questionnaire score and worse (higher) Sandvik score were all significantly associated with decreased odds while a greater volume at maximum cystometric capacity and higher HUI-3 score were associated with increased odds of achieving ≥50% reduction in UUIEs. A greater effect (lower odds ratio) was noted in the onabotulinumtoxinA group for FCI.

On multivariable analysis, increasing age and higher BMI were associated with a reduced odds of achieving a treatment response ≥ 50% reduction in UUIE, with the effect of age greater in the onabotulinumtoxinA group. Higher FCI score was associated with reduced odds of achieving a ≥ 50% reduction in UUIE only in the onabotulinumtoxinA group.

## Discussion

In this planned secondary analysis of women with refractory UUI randomized to onabotulinumtoxinA or SNM, increasing age was associated with less mean reduction (less efficacy), while higher baseline HUI-3 score and UUIE was associated with an increased mean reduction (greater efficacy) of UUIE/day, with the HUI-3 effect being greater in the onabotulinumtoxinA group. Similarly, regarding the outcome of ≥50% reduction in UUIE, increasing age and higher BMI were associated with a decreased odds of treatment response in all participants. A higher comorbidity index (FCI) score conferred decreased odds only in the onabotulinumtoxinA group. These 2 specific treatment outcomes were studied as they are commonly reported in the onabotulinumtoxinA and SNM literature.

Increasing age was independently associated with poorer treatment response to both treatments and in both treatment response definitions utilized in this study. The age association suggests that lower urinary tract changes occurring with aging, including decreased urethral closure pressure and detrusor contractility as well as increased detrusor overactivity, may predispose older women to a UUI phenotype which may be more refractory to treatment.[11–13]

To provide perspective, on average, a woman aged 55 years would have an increased mean reduction of 0.64 UUIE per day compared to a woman 65 years of age and in the onabotulinumtoxinA group, a woman 55 years would have roughly twice the odds of achieving a ≥50% reduction in UUIE than a woman 65 years old. The effect of age in previous reports on SNM treatments has varied. Prior SNM studies described older women gaining benefit from SNM but found higher continence rates and greater UUIE reduction in the younger group.[5,6] In contrast, Peters et al prospectively evaluated 328 patients (83% women) and found that SNM success was not age dependent.[14] The varied population and surgical approaches may have affected the latter results; study participants included those with only urgency/frequency irritative symptoms (not UUI), interstitial cystitis, and benign prostatic hypertrophy and encompassed both sacral and pudendal neuromodulation treatments.

Less information exists regarding the effect of age on onabotulinumtoxinA treatment response. One study reported results in 27 refractory UUI patients comparing outcomes of younger (55±15 years) to older (68±13 years) patients and found that although younger age predicted ≥50% UUIE reduction on univariate analysis, age was not significant on multivariable analysis.[15] Not previously reported, this current study found a differential treatment effect with respect to age and the ≥50% UUIE reduction treatment outcome. With increasing age, women undergoing onabotulinumtoxinA treatment had a reduced treatment response compared to those undergoing SNM. This differential effect of treatment type was not noted for the outcome of reduction in mean daily incontinence episodes over 6 months with increasing age mitigating both treatment responses.

The current study found that increased baseline BMI decreased odds of achieving ≥50% UUIE reduction, for example, the model estimated that a woman with a BMI of 25 would have roughly 50% greater odds of achieving ≥50% in UUIE than with a BMI of 35. This is consistent with prior epidemiologic literature associating increasing BMI and UUI severity.[16,17] Finding the association of BMI in predicting treatment success is important as it a modifiable risk factor. Each 5 point increase in baseline BMI decreased the odds of attaining ≥50% UUIE reduction by approximately 20%. Subak et al found that weight loss after bariatric surgery was associated with substantially reduced urinary incontinence over 3 years.[18] This raises the question of whether weight loss prior to refractory UUI treatment could improve treatment success. Further research is needed into the role of weight loss as a treatment for refractory UUI treatment.

Other characteristics associated with treatment response included baseline number of UUIE/day and HUI-3 in overall reduction in mean daily UUIE. Women with higher baseline UUIE/day, experienced greater mean reduction in UUIE/day. This finding reinforces previous findings, including those found in a randomized trial of anticholinergic therapy versus onabotulinumtoxinA[19] and another describing results of SNM testing.[4]

The Health Utilities Index Mark-3 (HUI-3) is an instrument used to measure general health status and health related quality of life (HRQoL).[9] It is scored on a scale of 0.00 to 1.00, where a value of 1.00 indicates perfect health and a score of 0.00 indicates death. The HUI-3 has been noted to provide valid measurements for utility scores in women with stress, urgency and mixed urinary incontinence[20] and in our study the HUI-3 demonstrated responsiveness to change in the treatment of refractory UUI in both onabotulinumtoxinA and SNM groups. For example, a woman with a baseline HUI-3 score of 0.7 would experience an average reduction of 0.5 episodes per day more compared to a woman with a baseline score of 0.4. This represents a difference of 0.3 in HUI-3, which is approximately the baseline standard deviation in our study population and which is 10 times the minimum important difference (MID) of 0.03.[21] Women with a higher health-related quality of life had a greater improvement in mean daily reduction in UUIE over 6 months in both treatment groups with greater reduction in the onabotulinumtoxinA group. This may reflect a differential impact of incontinence on general health status and HRQoL and a greater chance of treatment benefit. The trend toward a greater beneficial effect of HUI-3 on the success of onabotulinumtoxinA is unclear and further research is again warranted to understand the particular interaction between botulinum toxin and health status.

Finally with respect to FCI and its association with a ≥50% reduction in UUIE in the onabotulinumtoxinA group, women with higher numbers of medical comorbidities have a greater likelihood of increased incontinence severity.[22,23] In the current study, a woman with a baseline FCI score of 1 would have roughly 70% greater odds of achieving ≥50% reduction in UUIE than a woman with a baseline score of 4. Assessment of baseline physical function and HRQoL status as measured by the FCI is important as it may be used to control for baseline comorbidity, provide perspective of potential return to functional levels after a treatment and may be used as a predictor of outcome.[24] Incontinence treatment may be more difficult in women with increased morbidities due to the potential cumulative negative impact upon daily functioning and bladder control. This was previously noted in 105 men and women, where decreased SNM cure rates were associated with having 3 or more chronic medical conditions regardless of age.[6] It is unclear why we noted a differential treatment effect with onabotulinumtoxinA. As with the HUI-3, further evaluation is needed to better understand this specific finding.

This planned secondary analysis had several strengths. It allowed a robust assessment of a large number of women meeting standardized criteria for refractory UUI, with clearly defined preoperative clinical and demographic variables and validated outcome measures, with treatment outcomes. Study weaknesses include a follow-up interval limited to 6 months and the inclusion of only women participants.

## Conclusion

This study described patient characteristics associated with treatment response in women with refractory UUI. Unique to this study is its description of variables associated with differential treatment responses, including a health utility index, age and comorbidities. This information may help to individualize treatment approaches for these more invasive third-line therapies.

## Acknowledgments

UAB: Julie E. Burge, BS, Kathy S. Carter, RN, BSN, Patricia S. Goode, MD, Robert L. Holley, MS, MD, Ryanne R. Johnson, BSN, RNC, WHNP-BC, CRNP, L. Keith Lloyd, MD, Alayne D. Markland, DO, R. Jeannine McCormick, RN, BSN, MSN, CRNP, Nancy B. Saxon, RN, BSN, Robert E. Varner, MS, MD, Velria B. Willis, RN, BSN, CCRC, Robin R. Willingham, RN, BSN, Tracey S. Wilson, MD; Brown University: Alexandra Lynch, Ann Meers, Allegra Parrillo, Erika Spearin; UCSD: JoAnn Columbo; Kaiser Downey: Nancy Flores; Kaiser San Diego: Gisselle Zazueta-Damian; Cleveland Clinic: Andrea Aaby, Bradley Gill, MD, Ly Pung; Duke: Akira Hayes, MS, Amie Kawasaki, MD, Nicole Longoria, PA-C, Shantae McLean, MPH, CCRC, Nazema Y. Siddiqui, MD, Anthony G. Visco, MD, Alison C. Weidner, MD; University of New Mexico: Julie Middendorf, Karen Taylor; Oregon Health and Science University; University of Pennsylvania: Michelle Kinglee; University of Pittsburgh: Michael Bonidie MD, Christopher Chermansky, Judy Gruss, Karen Mislanovich, Pamela Moalli PhD, MD, Jonathan Shepherd MD, Gary Sutkin MD; RTI International: Maura Bearden, Katrina Burson, Allyson Drew, Marie Gantz, Kendra Glass, Rae Hope, Carolyn Huitema, Amy Kendrick, Daryl Matthews, Tracy Nolen, James Pickett, Kelly Roney, Amanda Shaffer, Yan Tang, Ryan Whitworth, Kevin Wilson, Anita Woodring

Funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institutes of Health Office of Research on Women's Health; ClinicalTrials.gov number, NCT01502956

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## Table 1

Baseline Characteristics of Study Participants

| Baseline Characteristics | All Participants | OnabotulinumtoxinA | Sacral Neuromodulation | P-value* |
|---|---|---|---|---|
| Sample size, N (%) | 364 | 190 | 174 | |
| Age (years), Mean (±SD) | 63.0 (11.6) | 62.9 (11.5) | 63.1 (11.8) | 0.832 |
| Hispanic ethnic group, N (%) | | | | 0.401 |
| Hispanic/Latina | 28 (7.7) | 18 (9.5) | 10 (5.7) | |
| Not Hispanic/Not Latina | 327 (89.8) | 167 (87.9) | 160 (92) | |
| Unknown/Not reported | 9 (2.5) | 5 (2.6) | 4 (2.3) | |
| Race, N (%) | | | | 0.805 |
| American Indian/Alaskan Native | 5 (1.4) | 4 (2.1) | 1 (0.6) | |
| Asian | 2 (0.5) | 1 (0.5) | 1 (0.6) | |
| Black/African American | 38 (10.4) | 22 (11.6) | 16 (9.2) | |
| More than one race | 3 (0.8) | 1 (0.5) | 2 (1.1) | |
| Other | 10 (2.7) | 6 (3.2) | 4 (2.3) | |
| Unknown | 3 (0.8) | 2 (1.1) | 1 (0.6) | |
| White | 303 (83.2) | 154 (81.1) | 149 (85.6) | |
| Body Mass Index ($kg/m^2$), Mean (±SD) | 32.2 (8.2) | 32.6 (8.7) | 31.7 (7.6) | 0.341 |
| Obese (BMI≥30 $kg/m^2$), N (%) | | | | 0.227 |
| Missing | 1 (0.3) | 1 (0.5) | 0 (0) | |
| No | 169 (46.4) | 82 (43.2) | 87 (50) | |
| Yes | 194 (53.3) | 107 (56.3) | 87 (50) | |
| Body Mass Index group, N (%) | | | | 0.443 |
| 0–18 ($kg/m^2$) | 3 (0.8) | 3 (1.6) | 0 (0) | |
| 19–25 | 76 (20.9) | 38 (20) | 38 (21.8) | |
| 26–30 | 90 (24.7) | 41 (21.6) | 49 (28.2) | |
| 31–35 | 79 (21.7) | 43 (22.6) | 36 (20.7) | |
| 36–40 | 59 (16.2) | 32 (16.8) | 27 (15.5) | |
| 41 + | 56 (15.4) | 32 (16.8) | 24 (13.8) | |
| Missing | 1 (0.3) | 1 (0.5) | 0 (0) | |
| Current smoker, N (%) | | | | 0.740 |
| No | 324 (89.0) | 168 (88.4) | 156 (89.7) | |
| Yes | 40 (11.0) | 22 (11.6) | 18 (10.3) | |
| Functional Comorbidity Index, Mean (±SD) | 3.71 (2.27) | 3.84 (2.26) | 3.57 (2.28) | 0.189 |
| Timed Up and Go (seconds), Mean (±SD) | 19.3 (27.0) | 17.8 (13.1) | 21 (36.5) | 0.750 |
| Post-menopausal, N (%) | | | | 1.000 |
| Not sure | 15 (4.1) | 8 (4.2) | 7 (4) | |
| Post-menopausal | 311 (85.4) | 162 (85.3) | 149 (85.6) | |
| Pre-menopausal | 38 (10.4) | 20 (10.5) | 18 (10.3) | |
| History of recurrent UTIs (>2 in past year), N (%) | | | | 0.648 |
| No | 315 (86.5) | 166 (87.4) | 149 (85.6) | |

| Baseline Characteristics | All Participants | OnabotulinumtoxinA | Sacral Neuromodulation | P-value* |
|---|---|---|---|---|
| Yes | 49 (13.5) | 24 (12.6) | 25 (14.4) | |
| Post void residual volume (ml), Mean (±SD) | 32.1 (40.0) | 31.2 (43.4) | 33 (36) | 0.483 |
| Volume at maximum cystometric capacity (dL), Mean (±SD) | 319 (142.6) | 305.1 (128.5) | 334.2 (155.5) | 0.076 |
| Cystometrogram with detrusor overactivity, N (%) | | | | 0.050 |
| No | 133 (36.5) | 60 (31.6) | 73 (42) | |
| Yes | 231 (63.5) | 130 (68.4) | 101 (58) | |
| Urgency urinary incontinence episodes per day, Mean (±SD) | 5.30 (2.67) | 5.39 (2.66) | 5.19 (2.68) | 0.508 |
| Stress urinary incontinence episodes per day, Mean (±SD) | 0.48 (0.94) | 0.46 (0.94) | 0.51 (0.96) | 0.714 |
| Total urinary incontinence episodes per day, Mean (±SD) | 5.87 (3.02) | 5.96 (3.01) | 5.78 (3.04) | 0.706 |
| Overactive Bladder Questionnaire (OABq)-short form (SF) symptom bother, Mean (±SD) | 75.3 (18.3) | 74.6 (19.5) | 76.1 (16.8) | 0.753 |
| OABq-SF quality of life, Mean (±SD) | 37.5 (22.3) | 38.2 (23) | 36.8 (21.6) | 0.625 |
| Urogenital Distress Inventory, Mean (±SD) | 60.1 (17.7) | 60.9 (18.3) | 59.2 (16.9) | 0.377 |
| Incontinence Impact Questionnaire, Mean (±SD) | 52.6 (26.7) | 52.7 (27.6) | 52.5 (25.8) | 0.950 |
| Sandvik Score, N (%) | | | | 0.734 |
| Slight | 3 (0.8) | 2 (1.1) | 1 (0.6) | |
| Missing | 11 (3.0) | 6 (3.2) | 5 (2.9) | |
| Moderate | 52 (14.3) | 27 (14.2) | 25 (14.4) | |
| Severe | 90 (24.7) | 52 (27.4) | 38 (21.8) | |
| Very severe | 208 (57.1) | 103 (54.2) | 105 (60.3) | |
| Health Utilities Index Mark-3, Mean (±SD) | 0.73 (0.29) | 0.71 (0.30) | 0.74 (0.28) | 0.509 |

Data are presented as mean and standard deviation or N and % for proportions

*Wilcoxon rank sum test (continuous variables) or Fisher's exact text (categorical variables) between groups

Functional Comorbidity Index (values range, 0–18, higher score with higher comorbidities), Overactive Bladder Questionnaire-Short Form, symptom bother and quality of life subscales (values range 0–100, with higher scores on the symptom severity scale indicating greater symptom severity and higher scores on quality of life scale indicating better quality of life), Urogenital Distress Inventory (values range 0–100, with higher scores indicating greater distress), Incontinence Impact Questionnaire (values range 0–100, with higher scores indicating worse quality of life impact), Sandvik Score (assessed on a scale of slight (1–2) to very severe (10–12) using the standard scoring algorithm, Health Utility Index Mark-3 (assessed on scale of 0.00 to 1.00, where a value of 1.00 indicates perfect health and a score of 0.00 indicates death.

*J Urol*. Author manuscript; available in PMC 2017 October 01.

## Table 2

**a: Univariable association of baseline characteristics and reduction of mean daily urgency urinary incontinence episodes 1 to 6 months after treatment**

| Characteristic | OnabotulinumtoxinA N=190 | | | Sacral Neuromodulation N=174 | | | P-value | P-value |
|---|---|---|---|---|---|---|---|---|
| | Coefficient | 95% CI | | Coefficient | 95% CI | | Main predictor effect | Treatment × Predictor |
| Age (decades)[1] | −0.285 | −0.595 | 0.026 | −0.139 | −0.445 | 0.168 | 0.050 | 0.533 |
| Hispanic/Latina ethnic group | 2.003 | 0.641 | 3.364 | 0.188 | −1.701 | 2.077 | 0.013 | 0.755 |
| Race | | | | | | | | |
| Black/African American | −0.186 | −1.459 | 1.088 | −0.550 | −1.876 | 0.777 | 0.699 | 0.230 |
| Other | −0.407 | −1.833 | 1.019 | 0.934 | −0.722 | 2.590 | | |
| White | Ref | | | Ref | | | | |
| Body Mass Index (kg/m$^2$) per 5 points[2] | −0.021 | −0.235 | 0.193 | −0.067 | −0.318 | 0.183 | 0.627 | 0.840 |
| Obese (BMI ≥30 kg/m$^2$) | −0.355 | −1.103 | 0.393 | 0.066 | −0.672 | 0.803 | 0.646 | 0.476 |
| Body Mass Index group | | | | | | | | |
| 0–25 (kg/m$^2$) | −0.115 | −1.299 | 1.069 | 0.382 | −0.910 | 1.674 | 0.980 | 0.137 |
| 26–30 | −0.377 | −1.570 | 0.815 | 1.028 | −0.169 | 2.225 | | |
| 31–35 | −0.778 | −1.957 | 0.402 | 1.003 | −0.259 | 2.265 | | |
| 36–40 | −0.950 | −2.187 | 0.287 | 1.304 | −0.056 | 2.664 | | |
| 41+ | Ref | | | Ref | | | | |
| Current smoker | −0.140 | −1.303 | 1.023 | −0.050 | −1.259 | 1.159 | 0.760 | 0.967 |
| Functional Comorbidity Index | −0.168 | −0.335 | −0.001 | 0.007 | −0.158 | 0.171 | 0.163 | 0.102 |
| Post-menopausal | −0.273 | −1.529 | 0.982 | −0.777 | −2.053 | 0.499 | 0.384 | 0.544 |
| History of Recurrent UTIs | 0.063 | −1.036 | 1.162 | 0.333 | −0.730 | 1.395 | 0.715 | 0.564 |
| log10 (Post Void Residual Volume in milliliter + 1) | 0.167 | −0.485 | 0.819 | 0.455 | −0.181 | 1.092 | 0.168 | 0.820 |
| Volume at maximum cystometric capacity (deciliter) | −0.037 | −0.325 | 0.251 | −0.097 | −0.339 | 0.146 | 0.432 | 0.306 |
| Cystometrogram with detrusor overactivity | 0.507 | −0.269 | 1.283 | 0.821 | 0.076 | 1.566 | 0.011 | 0.561 |
| Urgency urinary incontinence episodes per day | 0.642 | 0.540 | 0.744 | 0.535 | 0.418 | 0.651 | <0.001 | 0.083 |
| Stress urinary incontinence episodes per day | 0.330 | −0.058 | 0.717 | 0.041 | −0.341 | 0.422 | 0.170 | 0.394 |
| Total urinary incontinence episodes per day | 0.529 | 0.435 | 0.624 | 0.413 | 0.305 | 0.521 | <0.001 | 0.063 |
| OABq-SF Symptom-bother (per 10 points) | 0.189 | 0.007 | 0.371 | 0.171 | −0.045 | 0.387 | 0.013 | 0.856 |

**a: Univariable association of baseline characteristics and reduction of mean daily urgency urinary incontinence episodes 1 to 6 months after treatment**

| Characteristic | OnabotulinumtoxinA N=190 | | | Sacral Neuromodulation N=174 | | | P-value | P-value |
|---|---|---|---|---|---|---|---|---|
| | Coefficient | 95% CI | | Coefficient | 95% CI | | Main predictor effect | Treatment × Predictor |
| OABq-SF QoL (per 10 points) | −0.089 | −0.251 | 0.072 | −0.143 | −0.312 | 0.026 | 0.050 | 0.678 |
| Urinary Distress Inventory (per 10 points) | 0.164 | −0.036 | 0.364 | 0.088 | −0.128 | 0.303 | 0.069 | 0.740 |
| Incontinence Impact Questionnaire (per 10 points) | 0.022 | −0.115 | 0.159 | 0.126 | −0.020 | 0.271 | 0.131 | 0.305 |
| Sandvik Score | 0.035 | −0.093 | 0.163 | 0.043 | −0.084 | 0.169 | 0.361 | 0.932 |
| Health Utilities Index Mark-3 (per 0.30 points)[3] | 0.468 | 0.112 | 0.823 | 0.072 | −0.343 | 1.488 | 0.026 | 0.100 |

**b: Univariable association of baseline characteristics and ≥50% reduction in urgency urinary incontinence episodes among participants over 6 months**

| Characteristics | OnabotulinumtoxinA *N= 178 | | Sacral Neuromodulation *N=166 | | P-value | P-value |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | Odds ratio | 95% CI | Main predictor effect | Treatment × Predictor |
| Age (decades)[1] | 0.53 | 0.38,0.72 | 0.80 | 0.60,1.06 | <0.001 | 0.049 |
| Hispanic/Latina ethnic group | 1.31 | 0.38,4.91 | 0.31 | 0.055,1.60 | 0.567 | 0.641 |
| Race | | | | | | |
| Black/African American | 1.90 | 0.56,7.44 | 0.51 | 0.15,1.70 | 0.945 | 0.265 |
| Other | 1.46 | 0.41,5.58 | 0.58 | 0.12,2.51 | | |
| White | Ref | | Ref | | | |
| Body Mass Index (kg/m$^2$) per 5 points[2] | 0.84 | 0.68,1.01 | 0.76 | 0.60,0.95 | 0.009 | 0.384 |
| Obese (BMI ≥30 kg/m$^2$) | 0.46 | 0.22,0.92 | 0.59 | 0.30,1.14 | 0.026 | 0.965 |
| Body Mass Index group | | | | | | |
| 0–25 (kg/m$^2$) | Ref | | Ref | | 0.086 | 0.685 |
| 26–30 | 1.56 | 0.56,4.45 | 1.76 | 0.66,4.76 | | |
| 31–35 | 0.56 | 0.20,1.53 | 1.12 | 0.40,3.12 | | |
| 36–40 | 0.56 | 0.18,1.70 | 0.94 | 0.31,2.89 | | |
| 41+ | 0.58 | 0.20,1.71 | 0.42 | 0.12,1.38 | | |
| Current smoker | 0.77 | 0.27,2.26 | 0.98 | 0.34,2.85 | 0.734 | 0.870 |
| Functional Comorbidity Index | 0.76 | 0.64,0.90 | 0.98 | 0.85,1.14 | 0.022 | 0.038 |
| Post-menopausal | 1.10 | 0.30,3.64 | 0.44 | 0.12,1.42 | 0.442 | 0.536 |

**b: Univariable association of baseline characteristics and ≥50% reduction in urgency urinary incontinence episodes among participants over 6 months**

| Characteristics | OnabotulinumtoxinA *N= 178 | | Sacral Neuromodulation *N=166 | | P-value | P-value |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | Odds ratio | 95% CI | Main predictor effect | Treatment × Predictor |
| History of Recurrent UTIs | 0.79 | 0.30,2.10 | 1.67 | 0.66,4.39 | 0.683 | 0.242 |
| log10(Post Void Residual Volume in milliliter + 1) | 0.67 | 0.37,1.19 | 1.38 | 0.78,2.48 | 0.756 | 0.157 |
| Volume at maximum cystometric capacity (deciliter) | 1.22 | 0.94,1.62 | 1.20 | 0.97,1.50 | 0.038 | 0.474 |
| Cystometrogram with detrusor overactivity | 0.66 | 0.32,1.34 | 0.69 | 0.35,1.34 | 0.096 | 0.963 |
| Urgency urinary incontinence episodes per day | 1.00 | 0.88,1.14 | 0.96 | 0.84,1.09 | 0.377 | 0.739 |
| Stress urinary incontinence episodes per day | 1.05 | 0.74,1.56 | 0.66 | 0.42,0.99 | 0.236 | 0.088 |
| Total urinary incontinence episodes per day | 1.00 | 0.90,1.13 | 0.93 | 0.82,1.04 | 0.216 | 0.395 |
| OABq-SF Symptom-bother (per 10 points) | 1.00 | 0.85,1.19 | 0.94 | 0.77,1.14 | 0.682 | 0.693 |
| OABq-SF QoL (per 10 points) | 1.10 | 0.95,1.28 | 1.04 | 0.89,1.21 | 0.158 | 0.706 |
| Urinary Distress Inventory (per 10 points) | 0.93 | 0.77,1.11 | 0.93 | 0.77,1.13 | 0.310 | 0.872 |
| Incontinence Impact Questionnaire (per 10 points) | 0.88 | 0.77,1.01 | 0.89 | 0.78,1.02 | 0.013 | 0.993 |
| Sandvik Score | 0.84 | 0.73,0.95 | 0.90 | 0.81,1.01 | 0.001 | 0.442 |
| Health Utilities Index Mark-3 (per 0.30 points)[3] | 1.61 | 1.13,2.35 | 1.06 | 0.71,1.57 | 0.056 | 0.190 |

**c: Univariable association of baseline characteristics and Overactive Bladder Questionnaire Treatment Satisfaction at 6 Months**

| Characteristic | OnabotulinumtoxinA N=150 | | | Sacral Neuromodulation N=129 | | | P-value | P-value |
|---|---|---|---|---|---|---|---|---|
| | Coefficient | 95% CI | | Coefficient | 95% CI | | Main predictor effect | Treatment × Predictor |
| Age (decades)[1] | −5.64 | −9.47 | −1.80 | −1.63 | −5.61 | 2.35 | 0.010 | 0.093 |
| Hispanic/Latina ethnic group | −16.24 | −32.28 | −0.20 | −27.05 | −51.58 | −2.53 | 0.006 | 0.662 |
| Race | | | | | | | | |
| Black/African American | 14.67 | −0.72 | 30.07 | 8.52 | −8.73 | 25.76 | 0.017 | 0.616 |
| Other | −13.18 | −30.71 | 4.36 | −11.37 | −30.18 | 7.44 | | |
| White | Ref | | | Ref | | | | |
| Body Mass Index (kg/m$^2$) per 5 points[2] | −0.94 | −3.45 | 1.56 | 0.02 | −3.12 | 3.15 | 0.511 | 0.879 |
| Obese (BMI ≥30 kg/m$^2$) | −2.30 | −11.45 | 6.85 | 2.85 | −6.40 | 12.09 | 0.983 | 0.752 |
| Body Mass Index group | | | | | | | | |

**c: Univariable association of baseline characteristics and Overactive Bladder Questionnaire Treatment Satisfaction at 6 Months**

| Characteristic | OnabotulinumtoxinA N=150 | | | Sacral Neuromodulation N=129 | | | P-value | P-value |
|---|---|---|---|---|---|---|---|---|
| | Coefficient | 95% CI | | Coefficient | 95% CI | | Main predictor effect | Treatment × Predictor |
| 0–25 (kg/m$^2$) | Ref | | | Ref | | | | |
| 26–30 | 1.80 | −12.64 | 16.23 | 6.15 | −7.59 | 19.88 | 0.676 | 0.972 |
| 31–35 | 2.14 | −12.15 | 16.44 | 10.25 | −3.90 | 24.39 | | |
| 36–40 | −3.99 | −18.73 | 10.75 | 5.79 | −10.20 | 21.79 | | |
| 41+ | −1.33 | −16.09 | 13.43 | 1.75 | −14.00 | 17.50 | | |
| Current smoker | 0.59 | −14.22 | 15.40 | 2.15 | −14.46 | 18.77 | 0.997 | 0.953 |
| Functional Comorbidity Index | −1.06 | −3.18 | 1.07 | 0.38 | −1.67 | 2.44 | 0.756 | 0.326 |
| Post-menopausal | 6.90 | −8.46 | 22.27 | −3.75 | −20.09 | 12.60 | 0.498 | 0.985 |
| History of Recurrent UTIs | −1.20 | −14.90 | 12.49 | 3.47 | −8.89 | 15.83 | 0.756 | 0.340 |
| log10 (Post Void Residual Volume in milliliter + 1) | −2.74 | −10.48 | 4.99 | 0.39 | −7.52 | 8.29 | 0.507 | 0.768 |
| Volume at maximum cystometric capacity (deciliter) | −3.24 | −6.71 | 0.22 | 2.42 | −0.72 | 5.55 | 0.779 | 0.096 |
| Cystometrogram with detrusor overactivity | −0.09 | −9.82 | 9.64 | −3.69 | −12.95 | 5.56 | 0.494 | 0.614 |
| Urgency urinary incontinence episodes per day | −2.52 | −4.14 | −0.90 | −1.73 | −3.57 | 0.11 | <0.001 | 0.392 |
| Stress urinary incontinence episodes per day | −4.40 | −10.45 | 1.64 | −2.39 | −8.14 | 3.37 | 0.062 | 0.510 |
| Total urinary incontinence episodes per day | −2.45 | −3.94 | −0.95 | −1.86 | −3.62 | −0.10 | <0.001 | 0.431 |
| OABq-SF Symptom-bother (per 10 points) | 1.03 | −1.20 | 3.27 | 0.79 | −1.94 | 3.52 | 0.297 | 0.993 |
| OABq-SF QoL (per 10 points) | 0.07 | −1.89 | 2.02 | −0.83 | −2.89 | 1.24 | 0.594 | 0.495 |
| Urinary Distress Inventory (per 10 points) | −1.78 | −4.18 | 0.61 | 0.50 | −2.06 | 3.06 | 0.384 | 0.118 |
| Incontinence Impact Questionnaire (per 10 points) | −0.82 | −2.47 | 0.83 | 0.49 | −1.25 | 2.24 | 0.633 | 0.331 |
| Sandvik Score | −1.03 | −2.61 | 0.55 | −0.71 | −2.22 | 0.79 | 0.044 | 0.690 |
| Health Utilities Index Mark-3 (per 0.30 points)[3] | 7.28 | 2.74 | 11.82 | –1.74 | –7.15 | 3.67 | 0.052 | 0.047 |

Results based on linear mixed models with participant-month in the study (1 through 6) as the unit of analysis and month change from baseline in mean urgency urinary incontinence episodes per day as the outcome, with terms for treatment group, month, interaction of treatment group with month, categorical covariates for age group, and site, consistent with the randomization strata. Coefficient estimates and 95% confidence intervals based on stratified analyses

P-value (main) is based on an additive model, no interaction between predictor and treatment

P value (interaction) based on model in which predictor × treatment is included in model, note that p-values of greater than 0.1 for the predictor by treatment interaction are interpreted as absence of evidence that the effect of the predictor on the outcome differs by treatment arm.

[1]Age was included in the model as a continuous variable with units of years, but an increment of 10 years (decade) as used to generate meaningful effect estimates.

[2]BMI was included in the model as a continuous variable with units of kg/m$^2$, but an increment of 5 kg/m$^2$ as used to generate meaningful effect estimates.

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

[*]Participants with at least 4 completed bladder diaries

Logistic models fitted with Site and Age>=65 (except where predictor is age-related) as covariates. Odds ratios and 95% confidence intervals based on stratified analyses.

P-value (main) is based on an additive model, no interaction between predictor and treatment.

P-value (interaction) based on model in which predictor×treatment is included in model, note that p-values of greater than 0.1 for the predictor by treatment interaction are interpreted as absence of evidence that the effect of the predictor on the outcome differs by treatment arm.

[1]Age was included in the model as a continuous variable with units of years, but an increment of 10 years (decade) as used to generate meaningful effect estimates.

[2]BMI was included in the model as a continuous variable with units of kg/m$^2$, but an increment of 5 kg/m$^2$ as used to generate meaningful effect estimates.

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

P-values computed using Wald tests.

Results based on linear regression models with Overactive Bladder Questionnaire Treatment Satisfaction at 6 Months as the outcome, with terms for treatment group, categorical covariates for age group, and site, consistent with the randomization strata.

Coefficient estimates and 95% confidence intervals based on stratified analyses.

P-value (main) is based on an additive model, no interaction between predictor and treatment.

P value (interaction) based on model in which predictor×treatment is included in model, note that p-values of greater than 0.1 for the predictor by treatment interaction are interpreted as absence of evidence that the effect of the predictor on the outcome differs by treatment arm.

[1]Age was included in the model as a continuous variable with units of years, but an increment of 10 years (decade) as used to generate meaningful effect estimates.

[2]BMI was included in the model as a continuous variable with units of kg/m$^2$, but an increment of 5 kg/m$^2$ as used to generate meaningful effect estimates.

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

P-values computed using Wald tests.

## Table 3

**a. Multivariable associations between participant characteristics and reduction in mean daily urgency urinary incontinence episodes over months 1–6 after treatment**

| Characteristic | OnabotulinumtoxinA (n = 190) Coefficient | 95% CI | Sacral Neuromodulation (n = 174) Coefficient | 95% CI | P-value: Main predictor effect | P-value: Tx × Predictor |
|---|---|---|---|---|---|---|
| Health Utilities Index Mark-3 (per 0.30 points[1, 2]) | 0.50 | 0.23,0.77 | 0.09 | −0.21,0.40 | 0.004 | 0.051 |

| Characteristic | OnabotulinumtoxinA and Sacral Neuromodulation Coefficient | 95% CI | P-value: Main predictor effect | P-value: Tx × Predictor |
|---|---|---|---|---|
| Age (decades)[3] | −0.32 | −0.49,−0.15 | <0.001 | NA |
| Urgency urinary incontinence episodes per day | 0.62 | 0.54,0.70 | <0.001 | NA |

**b. Multivariable associations between participant characteristics and achieving ≥50% reduction of urgency urinary incontinence episodes over 6 months**

| Characteristic | OnabotulinumtoxinA (*N = 178) Adjusted Odds Ratio | 95% CI | Sacral Neuromodulation (*N = 166) Adjusted Odds Ratio | 95% CI | P-value: Main predictor effect | P-value: Tx × Predictor |
|---|---|---|---|---|---|---|
| Age (decades)[1, 2] | 0.44 | 0.30,0.65 | 0.78 | 0.57,1.08 | <0.001 | 0.016 |
| Functional Comorbidity Index, per point[2] | 0.84 | 0.71,0.99 | 1.07 | 0.92,1.25 | 0.374 | 0.031 |

| Characteristic | OnabotulinumtoxinA and Sacral Neuromodulation Adjusted Odds Ratio | 95% CI | P-value: Main predictor effect | P-value: Tx × Predictor |
|---|---|---|---|---|
| Body Mass Index (kg/m$^2$), per 5 points | 0.82 | 0.70,0.96 | 0.013 | NA |
| Incontinence Impact Questionnaire, (per 10 points) | 0.91 | 0.82,1.00 | 0.062 | NA |
| Sandvik Score | 0.92 | 0.84,1.01 | 0.068 | NA |

**c. Multivariable associations between participant characteristics and Overactive Bladder Questionnaire Treatment Satisfaction at 6 Months**

| | OnabotulinumtoxinA (n = 150) | | Sacral Neuromodulation (n = 129) | | P-value | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Coefficient** | **95% CI** | **Coefficient** | **95% CI** | **Main predictor effect** | **Tx × Predictor** |
| Age (decades)[1, 2] | −6.53 | −10.39,−2.68 | −0.69 | −4.86, 3.47 | 0.015 | 0.039 |
| Health Utilities Index Mark-3 (per 0.30 points)[2,3] | 6.84 | 2.48,11.19 | 0.41 | −4.79,5.60 | 0.039 | 0.059 |

| | OnabotulinumtoxinA and Sacral Neuromodulation | | | |
|---|---|---|---|---|
| **Characteristic** | **Coefficient** | **95% CI** | | |
| Race | | | | |
| Black/Afr Am | 14.62 | 3.41,25.83 | 0.017 | NA |
| Other | −6.91 | −19.87,6.05 | | |
| White | Ref | | | |
| Urgency urinary incontinence episodes per day | −1.89 | −3.25,−0.54 | 0.006 | NA |
| Stress urinary incontinence episodes per day | −4.65 | −8.81,−0.49 | 0.029 | NA |

Final model included the variables Health Utilities Index-3 score (per 0.1 points), age (decades) and urgency urinary incontinence episodes per day.

NA, Not applicable

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

[2]In the OnabotulinumtoxinA group for the Health Utilities Index Mark-3 effect, $p < 0.001$, and in the Sacral Neuromodulation group, $p=0.545$.

[3]Age was included in the model as a continuous variable with units of years, but an increment of 10 years (decade) as used to generate meaningful effect estimates.

[*]Participants with at least 4 completed bladder diaries

Final model included the variables age (decades), Functional Comorbidity Index (per point), body mass index ($kg/m^2$) per 5 points, Incontinence Impact Questionnaire (per 10 points) and Sandvik Score.
NA, Not applicable

[1]Age was included in the model as a continuous variable with units of years, but an increment of 10 years (decade) as used to generate meaningful effect estimates.

[2]In the OnabotulinumtoxinA group for the age effect, $p < 0.001$, and the Functional Comorbidity Index effect, $p=0.041$. In the Sacral Neuromodulation group, for the age effect, $p=0.137$ and for the Functional Comorbidity Index effect, $p=0.385$.

Final model included the variables Health Utilities Index-3 score (per 0.1 points), age (decades), urgency urinary incontinence episodes per day, stress urinary incontinence episodes per day, and race.

NA, Not applicable

[1]Age was included in the model as a continuous variable with units of years, but an increment of 10 years (decade) as used to generate meaningful effect estimates.

[2] In the OnabotulinumtoxinA group for the age effect, p=0.001, and the Health Utilities Index Mark-3 effect, p=0.002. In the Sacral Neuromodulation group, for the age effect, p=0.744 and for the Health Utilities Index Mark-3 effect, p=0.878.

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