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CLINICAL ARTICLE

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Predicting outcomes after intradetrusor onabotulinumtoxina for non-neurogenic urgency incontinence in women

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Abstract

Aims: Develop models to predict outcomes after intradetrusor injection of 100 or 200 units of onabotulinumtoxinA in women with non-neurogenic urgency urinary incontinence (UUI).

Methods: Models were developed using 307 women from two randomized trials assessing efficacy of onabotulinumtoxinA for non-neurogenic UUI. Cox, linear and logistic regression models were fit using: (1) time to recurrence over 12 months, (2) change from baseline daily UUI episodes (UUIE) at 6 months, and (3) need for self-catheterization over 6 months. Model discrimination of Cox and logistic regression models was calculated using c-index. Mean absolute error determined accuracy of the linear model. Calibration was demonstrated using calibration curves. All models were internally validated using bootstrapping.

Results: Median time to recurrence was 6 (interquartile range [IQR]: 2–12) months. Increasing age, 200 units of onabotulinumtoxinA, higher body mass index (BMI) and baseline UUIE were associated with decreased time to recurrence. The c-index was 0.63 (95% confidence interval [CI]: 0.59, 0.67). Median change in daily UUIE from baseline at 6 months was −3.5 (IQR: −5.0, −2.3). Increasing age, lower baseline UUIE, 200 units of onabotulinumtoxinA, higher BMI and IIQ-SF were associated with less improvement in UUIE. The mean absolute error predicting change in UUIE was accurate to 1.6 (95% CI: 1.5, 1.7) UUI episodes. The overall rate of self-catheterization was 17.6% (95% CI: 13.6%–22.4%). Lower BMI, 200 units of onabotulinumtoxinA, increased baseline postvoid residual and maximum capacity were associated with higher risk of self-catheterization. The c-index was 0.66 (95% CI: 0.61, 0.76). The three calculators are available at http://riskcalc.duke.edu.

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Conclusions: After external validation, these models will assist clinicians in providing more accurate estimates of expected treatment outcomes after onabotulinumtoxinA for non-neurogenic UUI in women.

KEYWORDS
ABC, BoNT-A, botox, prediction model, ROSETTA, urgency urinary incontinence, UUI

1 | INTRODUCTION

Urgency urinary incontinence (UUI) is the involuntary leakage of urine associated with the sudden, compelling need to void.[1] It is a common condition, impacting up to 30% of women older than 30 years old, with a projected increase in prevalence as the population ages.[2] The economic burden associated with UUI is tremendous, and its negative impact on quality of life is substantial; UUI is associated with increased rates of depression, falls, fractures, and decreased sleep quality.[3–6] Given the high side effect burden and discontinuation rates for medications, as well as the high failure rate for behavioral therapy, many women ultimately opt for third-line therapy, including intradetrusor injection of onabotulinumtoxinA (BoNT-A).[7]

The ideal BoNT-A dose that will simultaneously optimize efficacy for the longest duration and minimize complications for non-neurogenic UUI is unclear. Daily UUI episodes (UUIE) can remain improved over 6–12 months after 100, 150, and 200 units of BoNT-A, but evidence is conflicting regarding whether higher doses correspond with increased efficacy or longer duration of effect.[8] One dose varying trial found doses greater than 150 units led to minimal additional improvement in UUI symptoms.[8] Similarly, the association between higher doses of BoNT-A and UTI or catheterization remains unclear.[9] Some studies have suggested that efficacy and complications may be associated with certain patient characteristics, where greater improvement in UUIE at 6 months was noted in patients of younger age, lower body mass index (BMI), lower functional comorbidity index, greater baseline UUIE, greater baseline symptom bother, greater urodynamic cystometric capacity, and those with detrusor overactivity.[10,11]

Thus, it is likely that the optimal dosage of BoNT-A, while balancing its efficacy and risks, will differ based on a patient's unique characteristics. Prediction modeling can incorporate these characteristics and calculate a probability of outcomes and complications at the point of care. This makes prediction modeling considerably beneficial in patient counseling.[12] The objective of this study was to develop a clinical tool for predicting efficacy and complications after treatment with 100 or 200 units of BoNT-A at 6 and 12 months in women with non-neurogenic UUI.

2 | MATERIALS AND METHODS

This was a secondary analysis evaluating efficacy of BoNT-A in women with non-neurogenic UUI utilizing data from two previously conducted multicenter randomized controlled trials, Anticholinergic versus Botulinum Toxin Comparison study (ABC) and Refractory Overactive Bladder: Sacral Neuromodulation vs Botulinum Toxin Assessment (ROSETTA).[13,14] Both studies received institutional review board approval at all sites and all participants signed informed consent. This study followed the Transparent Reporting of Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD): The TRIPOD Statement.[15]

The ABC trial randomized women with idiopathic UUI to 100 units of BoNT-A or an anticholinergic medication, and compared change in UUIE over 6 months.[16] Women enrolled were anticholinergic naïve or refractory to 2 or less anticholinergic medications. After 6 months participants were followed for a total of 12 months if their Patient Global Symptom Control score (PGSC) was 4-5, indicating adequate control of symptoms. Women were not allowed off-protocol treatment or reinjection with BoNT-A during the 12 months. The ROSETTA trial randomized women with refractory UUI to 200 units of BoNT-A or sacral neuromodulation and estimated change in UUIE over 6 months.[17] Women enrolled were refractory to 2 or more anticholinergic medications. At 1 month, women who had <50% improvement in UUIE were allowed to receive nonstudy UUI treatment off-protocol. At 6 months participants were allowed a repeat dose of BoNT-A if their PGSC was 1–2, indicating inadequate control of urinary leakage.[17] Complete details of study protocols have been previously published.[16,17]

Women were included in this analysis if they received a BoNT-A injection as study treatment in one of the two trials, completed a baseline bladder diary and had at least one follow-up after their BoNT-A injection.

Three different models were fit utilizing this combined cohort and the same pool of candidate predictor variables. Models were developed to predict the following outcomes: (1) time to recurrence over 12 months, defined as a score of 1–3 on the PGSC, corresponding to "strongly disagree," "disagree," or "neutral" to the statement "this treatment has given me adequate control of my urine leakage," (2) change in daily UUIE at 6 months where a negative value is interpreted as improvement (i.e., reduction in incontinence episodes), and (3) the occurrence of adverse events including self-catheterization and urinary tract infection (UTI) over 6 months. Self-catheterization was initiated after BoNT-A therapy when the post-void residual (PVR) was >150 ml and participants were at least moderately bothered by incomplete emptying or the PVR was >300 ml. Postprocedural UTI was defined as a urine culture with $\geq 10^3$ CFU/ml in a symptomatic woman or treatment with antibiotics. If a patient received additional treatment for UUI, the last observation was carried forward for change in daily UUIE at 6 months; the remainder of the outcomes, time to recurrence and self-catheterization, were censored at the time of additional treatment.

We identified 18 candidate predictor variables that were shared between the two studies, would be clinically plausible predictors of outcomes, and might be available or easy to collect by clinicians at the time of counseling a patient about a BoNT-A injection. These predictors included age, BMI, maximum cystometric capacity, PVR, daily UUIE, daily total urinary incontinence episodes, Urogenital Distress Inventory-Short Form (UDI-SF) (ranging from 0 to 100 with higher scores indicating greater distress), Incontinence Impact Questionnaire-Short Form (IIQ-SF) (ranging from 0 to 100 with higher scores indicating worse quality of life), and Overactive Bladder Questionnaire-Short Form (OABq-SF) (ranging from 0 to 100 with higher scores indicating better quality of life and greater bother) as continuous variables; ethnicity, race (Black, white, other), smoking status, postmenopausal status, recurrent UTI history, diabetic history, prior anticholinergic use, and detrusor overactivity on urodynamics were treated as categorical variables. Race and ethnicity were included as candidate predictors given possible differences in continence mechanisms and urodynamic parameters involved in urinary incontinence.[18,19] BoNT-A dose was included as a predictor in every model to provide patients with outcomes for 100 and 200 units. Missingness in candidate predictor variables was assessed for missing at random and multiple imputation using chained equations were used to calculate missing values.[20] The final models were allowed to use imputed events for risk factors to predict outcomes, but the outcomes were based on actual, not imputed, events.

A Cox proportional survival model was used to predict time to recurrence. Variable selection was performed using p-value thresholds ranging from 0.05 to 0.5. Proportionality hazard assumption was met. Participants were censored at time of additional treatment or 12 months, whichever came first. The final model was selected based on clinical parsimony and optimized using fivefold cross validated Akaike Information Criterion (AIC) and concordance index, or c-index, for the receiver operating characteristics curve after 500 repeats to adjust for overfitting. For the change in daily UUIE outcome, the following models were explored: simple decision tree, linear regression with forward or backward selection using AIC as the stopping criteria, a generalized additive model, random forest, and LASSO and RIDGE regression. The final model predicting change in daily UUIE was selected using parsimony and mean absolute error of the prediction after fivefold cross validation with 500 repeats. For the categorical outcomes of self-catheterization and UTI, the following models were explored: simple decision tree, logistic regression with forward or backward selection using AIC as the stopping criteria, LASSO and RIDGE regression, generalized additive model and random forest models. The final model was selected based on parsimony and optimizing AIC and c-index after fivefold cross validation with 500 repeats. Nonlinearity and interactions between variables were explored for all outcomes and possible models to ensure comparison with nonlinear models. All final models were internally validated using bootstrapping with 1000 repeats to correct for bias and overfitting of the models.

Model discrimination for the time to event and categorical outcome models was corrected for bias using the c-index after bootstrapping with 1000 repeats to examine the performance of the final models. The c-index measures the models' ability to discriminate between different probabilities of the outcome. This means for a pair of individuals, where one has the outcome and the other does not, it is the ability of the model to produce a higher probability of the outcome for the individual with the outcome than without. Values closer to 1 indicate improved discrimination between individuals with and without the outcome, whereas a value of 0.5 indicates the model is no better than chance. Accuracy of change in daily UUIE model was calculated using mean absolute error, mean square error, and adjusted R^2 after bootstrapping with 1000 repeats. Mean absolute prediction error is the absolute difference between the predicted and actual observation, where lower values represent more accurate predictions. Mean square error is also a measure

of bias and variance of the model, but penalizes large errors more than small errors. For both mean absolute error and mean square error, the closer the value is to 0 the better the accuracy of the model. Calibration for all final models was demonstrated through calibration curves using the RMS package.[21] To correct for overfitting, the calibration curves were bootstrapped 1000 times and plotted as a bias-corrected loess smoothed curve. Statistical analysis was performed using R version 4.0.3.

3 | RESULTS

There were 307 women who met inclusion criteria; 118 women received 100 units (ABC) and 189 women received 200 units (ROSETTA). Appendix A illustrates baseline characteristics for women in the ABC and ROSETTA trials that served as candidate predictor variables. Three models were successfully fit to the combined cohort to predict the following (1) time to recurrence over 12 months based on PGSC of 1–3, (2) change in daily UUIE at 6 months, and (3) need for self-catheterization over 6 months. Due to high heterogeneity and poor predictability, a model to accurately predict UTI was not successfully fit. The distribution of predictors by outcomes are shown in Table 1 and Appendix B, and distributions of each of these outcomes within the ABC and ROSETTA trials are shown in Appendix A.

Data from 305 women (2 missing) were used to predict time to recurrence. Approximately 67% (95% confidence interval [CI]: 60.9%–71.8%) of women experienced recurrence by 12 months with a median time to recurrence of 6 months (interquartile range [IQR]: 2–12 months). The final model chosen used 8 predictors (Table 2). Baseline factors in the model associated with decreased time to recurrence included: increasing age, higher BMI, decreasing maximum cystometric capacity, higher UUIE, higher IIQ-SF, premenopausal status, prior anticholinergic use, and 200 units of onabotulinumtoxinA (Table 2 and Figure 2A). Bias-corrected discrimination was 0.63 (95% CI: 0.59–0.67). Calibration demonstrated the model predictions were accurate when an individuals' predicted probability ranged between 0.1 and 0.8 (Figure 1A). The model slightly overestimated time to UUI recurrence, when the predicted probability of recurrence was 0.4–0.8 Table 3.

Data from 292 women (15 missing) were used to predict change in daily UUIE with a median change from baseline in daily UUIE of −3.5 (IQR: −5.0, −2.3) at 6 months, where a negative value equates to improvement. The final model utilized linear regression with backward selection and had 10 predictors. Increasing age, increasing BMI, non-Latina, non-White race, other race, premenopausal status, no recurrent UTIs, higher IIQ-SF, lower UUIE, and 200 units of onabotulinumtoxinA were associated with less improvement in UUIE (Table 2 and Figure 2B). The bias-corrected mean absolute error in predicting change in UUIE was 1.6 (95% CI: 1.5–1.7) UUI episodes. The bias-corrected mean square error was 5.0 (95% CI: 4.7–5.2) and adjusted R^2 was 0.22. The model predictions were accurate when predicted change in UUIE was between −7 and −1 (Figure 1B). When change in UUIE was predicted to be −5.5 to −7 UUIE/day, the model underestimated the improvement observed.

Data from 307 women were used to predict need for self-catheterization over 6 months with 17.6% (95% CI: 13.6%–22.4%) of women requiring self-catheterization by 6 months. The final model used logistic regression with backward selection with six predictors. Lower BMI, premenopausal status, increased baseline PVR, increased maximum capacity, lower IIQ-SF, and 200 units of onabotulinumtoxinA were associated with higher risk of self-catheterization (Table 2 and Figure 2C). The bias-corrected concordance index was 0.66 (95% CI, 0.61–0.76). The model predictions were accurate when an individual's predicted probability ranged between 0 and 0.4 (Figure 1C). When the predicted probability of self-catheterization was 0.15 or less, the model underestimated the observed proportion in a small subset of samples. All three calculators are available publicly at http://riskcalc.duke.edu.

4 | DISCUSSION

The aim of this study was to create a clinical tool to predict both efficacy and complications after 100 and 200 units of BoNT-A in women with non-neurogenic UUI using data obtained from two multicenter randomized trials. Our goal was that this tool could be used to counsel patients regarding predicted treatment outcomes after a BoNT-A dose has been selected. Numerous studies have identified factors that may be predictive of treatment success or adverse events after BoNT-A.[22] However, properly weighing all factors when counseling patients is difficult. In this study we successfully developed models that can be used to predict: (1) time to recurrence over 12 months; (2) expected change in daily UUIE from baseline at 6 months; and (3) the need for self-catheterization over 6 months after BoNT-A. The c-index predicting time to recurrence and the need for self-catheterization were 0.63 (95% CI: 0.59–0.67) and 0.66 (95% CI: 0.61–0.76), respectively. While the accuracy of these models is modest, they compare favorably with

TABLE 1 Predictors and outcomes by recurrence

Predictors and outcomes	Total ($N = 307$)	No Recurrence ($N = 102$)	Recurrence ($N = 203$)
Cohort (BoNT-A Dose), *n* (%)			
ABC (100 units)[a]	118 (38.4%)	61 (59.8%)	56 (27.6%)
ROSETTA (200 units)[b]	189 (61.6%)	41 (40.2%)	147 (72.4%)
Missing	0 (0%)	0 (0%)	0 (0%)
Age (years), median (IQR)	62.2 (53.6, 69.9)	58.3 (52.3, 65.4)	64.0 (54.9, 71.5)
Missing	0 (0%)	0 (0%)	0 (0%)
Ethnicity, *n* (%)	40 (13.0%)	16 (15.7%)	24 (11.8%)
Missing	0 (0%)	0 (0%)	0 (0%)
Race, *n* (%)			
White	250 (81.4%)	82 (80.4%)	167 (82.3%)
Black	39 (12.7%)	15 (14.7%)	23 (11.3%)
Other	18 (5.9%)	5 (4.9%)	13 (6.4%)
Missing	0 (0%)	0 (0%)	0 (0%)
Current smoker, *n* (%)	36 (11.7%)	12 (11.8%)	23 (11.3%)
Missing	0 (0%)	0 (0%)	0 (0%)
Postmenopausal, *n* (%)	267 (87.0%)	87 (85.3%)	178 (87.7%)
Missing	0 (0%)	0 (0%)	0 (0%)
BMI, median (IQR)	31.8 (26.8, 37.5)	31.8 (26.7, 35.8)	31.6 (27.0, 38.0)
Missing	0 (0%)	0 (0%)	0 (0%)
Recurrent UTI history, *n* (%)[c]	26 (8.5%)	7 (6.9%)	19 (9.4%)
Missing	0 (0%)	0 (0%)	0 (0%)
Diabetes history, n (%)	52 (16.9%)	14 (13.7%)	38 (18.7%)
Missing	0 (0%)	0 (0%)	0 (0%)
Prior anticholinergic use, *n* (%)	260 (84.7%)	71 (69.6%)	187 (92.1%)
Missing	0 (0%)	0 (0%)	0 (0%)
Detrusor overactivity, *n* (%)	214 (69.7%)	69 (67.6%)	144 (70.9%)
Missing	0 (0%)	0 (0%)	0 (0%)
Maximum cystometric capacity (ml), median (IQR)	312 (220, 400)	347 (239, 460)	300 (210, 388)
Missing	0 (0%)	0 (0%)	0 (0%)
Post void residual (ml), median (IQR)	20.0 (5.00, 40.0)	20.0 (5.00, 41.8)	20.0 (8.00, 40.0)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline urgency incontinence episodes, median (IQR)	4.67 (3.33, 6.33)	4.00 (3.33, 5.67)	5.00 (3.33, 6.67)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline total incontinence episodes, median (IQR)	5.33 (4.00, 7.00)	5.00 (3.67, 6.33)	5.33 (4.00, 7.33)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline Urogenital Distress Inventory Short Form, median (IQR)[d]	61.1 (50.0, 72.2)	59.7 (50.0, 66.7)	61.1 (47.9, 72.2)
Missing	0 (0%)	0 (0%)	0 (0%)

(Continues)

TABLE 1 (Continued)

Predictors and outcomes	Total ($N = 307$)	No Recurrence ($N = 102$)	Recurrence ($N = 203$)
Baseline Incontinence Impact Questionnaire Short Form, median (IQR)[e]	52.4 (28.6, 71.4)	45.2 (28.6, 66.7)	57.1 (33.3, 76.2)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline Overactive Bladder Questionnaire Short Form Symptom Bother, Median (IQR)[f]	73.3 (56.7, 86.7)	66.7 (53.3, 83.3)	76.7 (60.0, 90.0)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline Overactive Bladder Questionnaire Short Form Quality of Life, Median (IQR)[f]	41.5 (23.1, 57.7)	50.8 (33.8, 64.6)	33.8 (21.5, 53.8)
Missing	0 (0%)	0 (0%)	0 (0%)
Clinical responder, *n* (%)[g]	249 (81.9%)	96 (94.1%)	153 (76.5%)
Missing	3 (1.0%)	0 (0%)	3 (1.5%)
Recurrence over 12 months, *n* (%)[h]	203 (66.6%)	0 (0.0%)	203 (100.0%)
Missing	2 (0.7%)	0 (0%)	0 (0%)
Time to recurrence over 12 months, median (IQR)[h]	6.00 (2.00, 12.0)	12.0 (12.0, 12.0)	4.00 (2.00, 6.00)
Missing	1 (0.3%)	0 (0%)	0 (0%)
Median change in UUI episodes at 6 months, median (IQR)	−3.50 (−5.00, −2.33)	−4.00 (−5.33, −3.00)	−3.00 (−4.67, −1.67)
Missing	15 (4.9%)	5 (4.9%)	9 (4.4%)
Self-catheterization, *n* (%)[i]	54 (17.6%)	14 (13.7%)	40 (19.7%)
Missing	0 (0%)	0 (0%)	0 (0%)

Abbreviations: BoNT-A, onabotulinumtoxinA; IQR, interquartile range; UUI, urgency urinary incontinence.

[a]ABC trial (Anticholinergic vs. Botulinum Toxin Comparison study, ClinicalTrials.gov No.: NCT01166438), which compared oral solifenacin to 100units of onabotulinumtoxinA.[13]

[b]ROSETTA trial (Refractory Overactive Bladder: Sacral Neuromodulation vs. Botulinum Toxin Assessment, ClinicalTrials.gov number NCT01502956), which compared sacral neuromodulation to 200 units of onabotulinumtoxinA.[14]

[c]Recurrent UTI defined as 3 or more urinary tract infections (bladder or kidney) that required treatment during the past year.

[d]Values range from 0 to 100, with higher scores indicating greater distress.

[e]Values range from 0 to 100, with higher scores indicating worse quality of life.

[f]Values range from 0 to 100, with higher scores on the symptom bother scale indicating greater severity of symptoms and higher scores on the quality-of-life scale indicating better quality of life.

[g]At 1 month ≥50% reduction in UUIE per day based on a 3-day bladder diary with UUIE averaged over 3 days (utilized to determine who would be allowed off-protocol nononabotulinumtoxinA treatment before 6 months in ROSETTA).

[h]Recurrence is defined as a score of 1–3 on the PGSC, corresponding to "strongly disagree," "disagree" or "neutral" to the statement "this treatment has given me adequate control of my urine leakage."

[i]Self-catheterization was initiated after onabotulinumtoxinA therapy when the PVR >150 ml and at least moderately bothered by the symptom of incomplete emptying or PVR >300 ml.

predictive models currently used in clinical practice, with concordance indices ranging from 0.6 to 0.8 and are likely better than an existing clinical guess.[23,24]

For time to recurrence of symptoms, baseline factors including older age, higher BMI, lower maximum cystometric capacity, higher baseline UUIE, higher IIQ-SF score, premenopausal status, prior anticholinergic use, and 200 units of onabotulinumtoxinA were all found to be associated with decreased time to recurrence. Our findings from the model predicting reduction in daily UUIE are similar to the results from the recurrence model with the notable addition of ethnicity, race and recurrent UTI history. There is inconsistent literature on the association of baseline factors and treatment response to BoNT-A, where some studies are even unable to elucidate any significant variables.[10,25,26] Recent systematic reviews concluded that although many different factors were identified, the quality of included studies was poor, limiting their conclusions.[22,27] Given this lack of high-quality studies on risk factors, our predictive models, based on high-quality multicenter trial data

TABLE 2 Coefficients for the prediction models

	Time to recurrence over 12 months ($n = 305$)			Change in daily UUIE at 6 months ($n = 292$)			Self-catheterization over 6 months ($n = 307$)		
Predictors[a]	**Adjusted hazard ratio**	**95% CI**	***p* value**	**Adjusted estimate**	**95% CI**	***p* value**	**Adjusted odds ratio**	**95% CI**	***p* value**
Intercept				−5.82	−7.94, −3.69	<0.001	0.09	0.01, 0.56	0.011
BoNT-A Dose (200 units)	1.13	0.79, 1.62	0.500	0.34	−0.22, 0.90	0.231	2.12	1.08, 4.16	0.029
Age (years)	1.03	1.01, 1.05	0.001	0.06	0.03, 0.09	<0.001			
BMI	1.01	1.00, 1.03	0.157	0.03	0.00, 0.07	0.039	0.99	0.95, 1.03	0.610
Maximum cystometric capacity (ml)[b]	1.00	1.00, 1.00	0.137				1.00	1.00, 1.00	0.042
Maximum cystometric capacity per 50 ml (ml)[b]	0.96	0.53, 1.02	0.137				1.12	1.01, 1.25	0.042
Maximum cystometric capacity per 100 ml (ml)[b]	0.92	0.82, 1.03	0.137				1.26	1.02, 1.56	0.042
Baseline UUIE	1.06	1.01, 1.11	0.028	−0.54	−0.64, −0.43	<0.001			
Baseline IIQ-SF[c]	1.01	1.00, 1.01	0.023	0.02	0.01, 0.03	0.003	1.00	0.99, 1.01	0.759
Postmenopausal	0.48	0.28, 0.84	0.009	−0.99	−1.94, −0.03	0.045	0.70	0.30, 1.60	0.392
Prior anticholinergic use	2.26	1.24, 4.12	0.008						
Ethnicity				−0.89	−1.70, −0.08	0.031			
Other race				1.33	0.00, 2.66	0.051			
White race				−0.13	−0.94, 0.69	0.758			
Recurrent UTI history				−0.64	−1.56, 0.27	0.171			
Post void residual (ml)[d]							1.16	1.00, 1.35	0.052

Abbreviations: BoNT-A, onabotulinumtoxinA; UUIE, urgency urinary incontinence episodes.

[a]Categorical variables including prior anticholinergic use, ethnicity, other race, white race, recurrent UTI history are all coded as 1 for the presence of the condition or descriptor and 0 for the lack of the condition or descriptor.

[b]The original models contained maximum cystometric capacity as a continuous variable. Coefficients for maximum cystometric capacity are presented per 50 and 100 ml for interpretability and were derived from the original model.

[c]Values range from 0 to 100, with higher scores indicating worse quality of life.

[d]Modeled as log(post void residual).

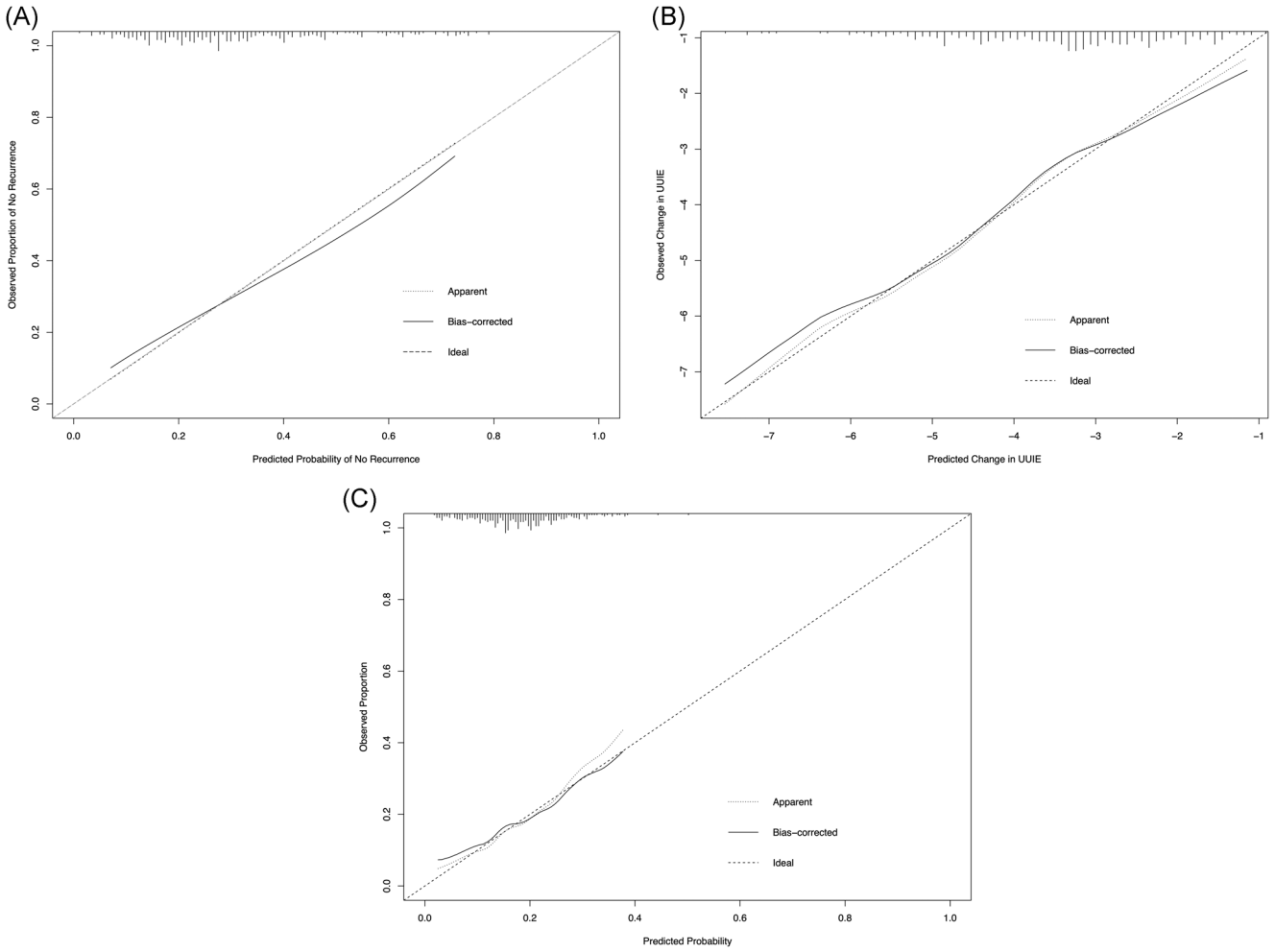

FIGURE 1 Calibration plots for models. (A) Calibration plot for the time to recurrence model over 12 months. (B) Calibration plot for the change in urgency urinary incontinence episode model at 6 months. (C) Calibration plot for the self-catheterization model over 6 months. Calibration curves fitted using the RMS package,[21] where apparent and bias-corrected curves are smoothed using loess. The bias-corrected curves are adjusted for optimism using bootstrapping with 1000 repetitions to correct for overfitting. Rug plots along the top *Y* axis show the relative prevalence of events at each probability. No, number; UUIE, urgency urinary incontinence episodes

with a goal of prediction, will likely be clinically useful.

Finally, for our self-catheterization model, lower BMI, premenopausal status, increased baseline PVR, increased maximum capacity, lower baseline IIQ-SF and 200 units of onabotulinumtoxinA were associated with higher risk of self-catheterization. Other studies have suggested advanced age and elevated preprocedure PVR as risk factors for postprocedure urinary retention and many other studies have investigated other risk factors.[7,28–30] Our data generally support these previous findings and both of our studies utilized similar criteria for postprocedure self-catheterization, which is a strength of our analysis. However, in a study aimed at optimizing prediction, caution should be taken when interpreting the associations herein as causal. Additionally, the rate of self-catherization is likely lower in clinical practice than in these published trials as higher PVRs are often tolerated in clinical practice. If this model is externally validated using a clinical data set with lower self-catheterization rates, it would not be surprising if the calibration intercept would be affected and simple recalibration might be necessary for a specific population.

Strengths of our study include that this is the first model to predict outcomes after BoNT-A of which we are aware. This study also utilized robust data from two large randomized trials to develop models to predict outcomes after two different doses of BoNT-A allowing prediction of outcomes after both 100 and 200 units. Thus far in multiple systematic reviews and meta-analyses there has been insufficient evidence to determine an optimal starting dose for BoNT-A.[7,9,31–33] It is possible that the increase risk of adverse events—elevated PVR and UTI—may modulate the effect of 200 units when compared to

TABLE 3 Model performance statistics[a]

	Time to recurrence over 12 months ($n = 305$)	Change in daily UUIE at 6 months ($n = 292$)	Self-catheterization over 6 months ($n = 307$)
R^2	0.11	0.25	0.03
Adjusted R^2	0.09	0.22	0.01
C-index (95% CI)	0.63 (0.59-0.67)	-	0.66 (0.61-0.76)
Brier score	0.20	-	0.14
Mean absolute error (95% CI)	-	1.59 (1.49-1.69)	-
Mean square error (95% CI)	-	4.95 (4.67-5.23)	-
Root mean square error (95% CI)	-	2.22 (2.16-2.29)	-
Akaike information criterion	2090.2	1305.4	284.65
LR χ^2 test	48.3	107.9	14.9
Log likelihood	−1037.1	−640.7	−135.33

Abbreviations: c-index, concordance index; LR, likelihood ratio; UUIE, urgency urinary incontinence episodes.

[a]All model statistics, except AIC, log likelihood and LR χ^2 test, were calculated after bootstrapping with 1000 repetitions.

100 units.[34–36] Given this some clinicians and patients may decide based on the patient's particular characteristics to start with 200 units. Having both 100 and 200 units within the calculator will allow clinicians and patients to understand their patient's particular response to either dose. Additionally, the study populations who received 100 and 200 units, were likely different owing to different study inclusion criteria in ABC and ROSETTA. Therefore, differences in the study populations may affect interpretations of the impact of BoNT-A dose on outcomes, as differences attributed to different doses may actually be reflective of hidden population differences. In a prior study utilizing these two cohorts, 200 units appeared to have less improvement in UUI episodes over 6 months, which was likely due to differences in baseline disease severity.[37] This difference in study populations and their differential response highlights the importance of including multiple markers of baseline disease severity in prediction calculators as well as the importance of future external validation of the models presented herein. Even more important is given these differences in study populations and BoNT-A dose, we strongly recommend the models are used after a BoNT-A dose has been selected and not used to compare outcomes between doses. Additionally, we followed up-to-date guidelines on fitting and validating these models, with robust resampling techniques used for variable selection, performance metrics and calibration.

Our data must be interpreted considering certain limitations including model performance. The outcome measure used to describe time to recurrence, PGSC, is a surrogate measure of recurrence, but has been used to determine a patient's need for re-treatment and was chosen as re-treatment was prespecified differently in each trial.[16,17,38] While these models perform similar to those currently in clinical use, albeit outside of the UUI literature, model performance can continue to improve, possibly by additional physiological testing or biomarkers. In the models presented herein maximum cystometric capacity, detrusor overactivity, and PVR were examined as potential factors to include. However, other urodynamic parameters could be examined such as maximum flow or bladder compliance.[39,40] Additionally, nonstandard testing, such as urethral function RNA testing, or nonurologic factors may also be useful to improve model accuracy.[41–43] Additionally, the performance of these models was not compared to clinical experts. Although prediction models are consistently superior to clinical judgment, this remains to be directly shown for these models, and this comparison is recommended in future studies.[12,44,45] To improve shared decision making, we have provided the active link for these calculators for immediate clinical use.

5 | CONCLUSIONS

These prediction models will allow providers and patients to be involved in shared decision making surrounding BoNT-A for non-neurogenic UUI.

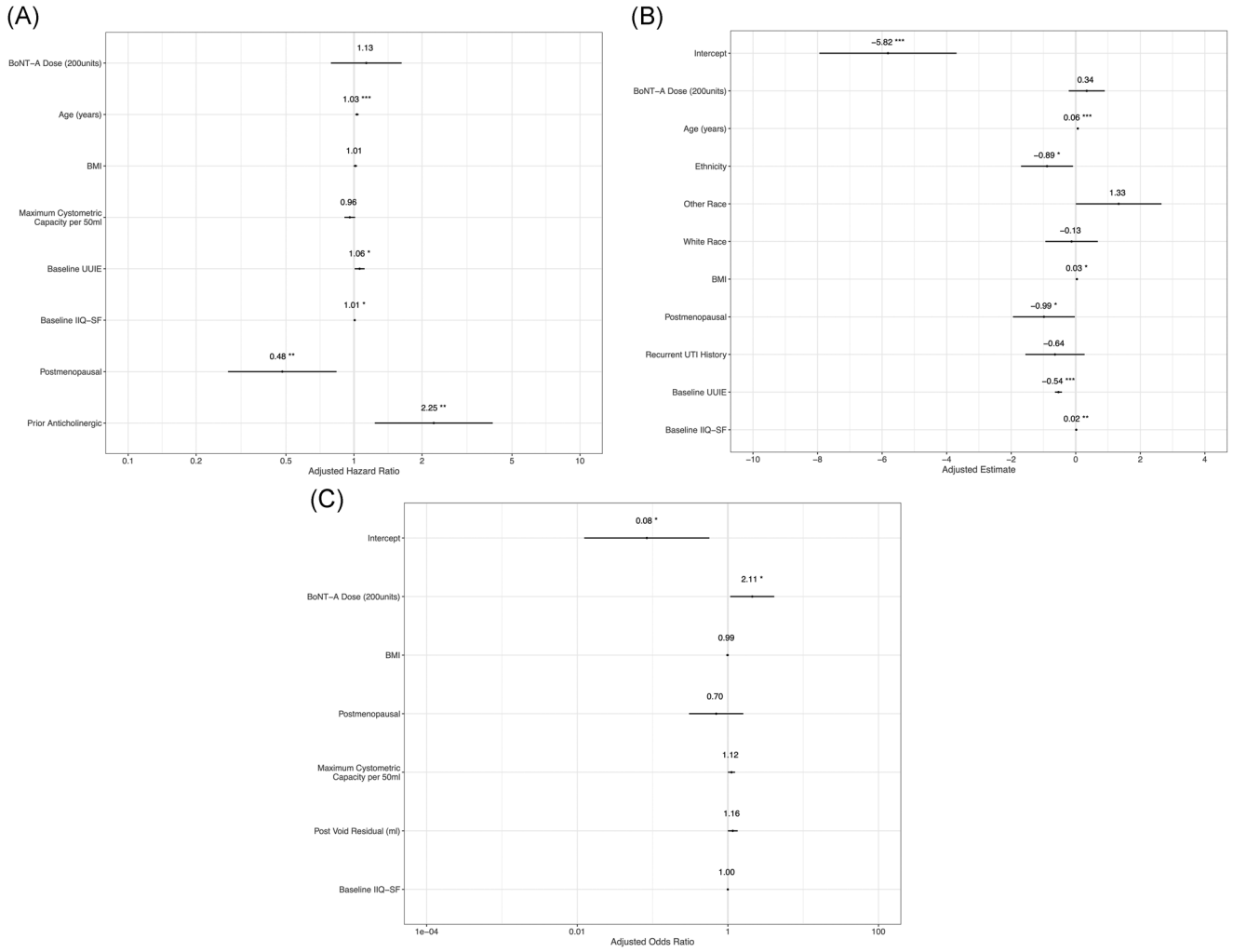

FIGURE 2 Associations for predictors in prediction models. (A) Adjusted hazard ratios and 95% confidence intervals for each variable in the time to recurrence model over 12 months. (B) Adjusted β coefficients and 95% confidence intervals for each variable in the change in urgency urinary incontinence episode model at 6 months. (C) Adjusted odds ratios and 95% confidence intervals for each variable in the self-catheterization model over 6 months. Appropriate ratios or coefficients and 95% confidence intervals for each variable in the three models developed to predict outcomes after onabotulinumtoxinA. Point estimates are represented by the black dot and 95% confidence intervals are represented by the black bands on either side of the black dot. *$p = 0.01–0.05$; **$p = 0.001–0.01$; ***$p < 0.001$. BoNT-A, onabotulinumtoxinA; IIQ-SF, Incontinence Impact Questionnaire Short Form; UUIE, urgency urinary incontinence episodes

We encourage researchers to test the model's performance in their intended population before general use.

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CONFLICT OF INTERESTS

Cindy L. Amundsen reports funding from BlueWind. Megan Bradley reports research support from Hologics and Axonics. David D. Rahn reports research support from Pfizer. All other authors report no conflict of interests.

ETHICS STATEMENT

This secondary analysis of deidentified data was considered IRB exempt at Duke University. Each institution enrolling participants in ABC and ROSETTA received IRB approval individually for these clinical trials. All participants were consented as a part of the original clinical trials (ABC and ROSETTA).

AUTHOR CONTRIBUTIONS

Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, visualization, writing-original draft: Whitney K. Hendrickson. *Formal analysis and methodology*: Gongbo Xie. *Writing-review & editing*: David D. Rahn, James A. Hokanson, Megan Bradley, Ariana L. Smith, and Vivian W. Sung. *Validation, writing-review & editing*: Cindy L. Amundsen and Anthony G. Visco. *Methodology, supervision, writing-review & editing*: Sheng Luo. *Conceptualization, methodology, supervision, writing-review & editing*: J. Eric Jelovsek.

DATA AVAILABILITY STATEMENT

Data was acquired through a data use agreement between Duke University and the Pelvic Floor Disorders Network.

LOCATION OF ANALYSIS

Original data utilized in this study was obtained at each institution listed involved in the Pelvic Floor Disorders Network. The analysis involved in the study herein occurred outside of the Pelvic Floors Disorders Network at Duke University.

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APPENDIX A

TABLE A1 Predictors and outcomes within each cohort and onabotulinumtoxinA dose

Predictors and outcomes	Total ($N = 307$)	ABC (100 units) ($N = 118$)[13a]	ROSETTA (200 units) ($N = 189$)[b]
Age (years), median (IQR)	62.2 (53.6, 69.9)	59.9 (52.6, 66.4)	63.7 (54.3, 71.2)
Missing	0 (0%)	0 (0%)	0 (0%)
Ethnicity, *n* (%)			
Latina	40 (13.0%)	22 (18.6%)	18 (9.5%)
Missing	0 (0%)	0 (0%)	0 (0%)
Race, *n* (%)			
White	250 (81.4%)	94 (79.7%)	156 (82.5%)
Black	39 (12.7%)	17 (14.4%)	22 (11.6%)
Other	18 (5.9%)	7 (5.9%)	11 (5.8%)
Missing	0 (0%)	0 (0%)	0 (0%)
Current smoker, *n* (%)	36 (11.7%)	14 (11.9%)	22 (11.6%)
Missing	0 (0%)	0 (0%)	0 (0%)
Postmenopausal, *n* (%)	267 (87.0%)	102 (86.4%)	165 (87.3%)
Missing	0 (0%)	0 (0%)	0 (0%)
BMI, median (IQR)	31.8 (26.8, 37.5)	30.7 (26.7, 35.7)	32.0 (27.0, 38.0)
Missing	0 (0%)	0 (0%)	0 (0%)
Recurrent UTI history, *n* (%)[c]	26 (8.5%)	2 (1.7%)	24 (12.7%)
Missing	0 (0%)	0 (0%)	0 (0%)
Diabetes history, *n* (%)	52 (16.9%)	18 (15.3%)	34 (18.0%)
Missing	0 (0%)	0 (0%)	0 (0%)
Prior anticholinergic use, *n* (%)	260 (84.7%)	71 (60.2%)	189 (100.0%)
Missing	0 (0%)	0 (0%)	0 (0%)
Detrusor overactivity, *n* (%)	214 (69.7%)	84 (71.2%)	130 (68.8%)
Missing	0 (0%)	0 (0%)	0 (0%)
Maximum cystometric capacity (ml), median (IQR)	312 (220, 400)	348 (257, 455)	295 (210, 388)
Missing	0 (0%)	0 (0%)	0 (0%)
Post void residual (ml), Median (IQR)	20.0 (5.00, 40.0)	20.0 (7.3, 50.0)	20.0 (5.00, 40.0)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline urgency incontinence episodes, median (IQR)	4.67 (3.33, 6.33)	4.33 (3.00, 6.33)	5.00 (3.67, 6.33)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline total incontinence episodes, median (IQR)	5.33 (4.00, 7.00)	5.33 (3.67, 7.00)	5.33 (4.00, 7.00)
Missing	0 (0%)	0 (0%)	0 (0%)

(Continues)

TABLE A1 (Continued)

Predictors and outcomes	Total ($N = 307$)	ABC (100 units) ($N = 118$)[13a]	ROSETTA (200 units) ($N = 189$)[b]
Baseline Urogenital Distress Inventory Short Form, median (IQR)[d]	61.1 (50.0, 72.2)	54.6 (45.8, 66.7)	61.1 (50.0, 72.2)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline Incontinence Impact Questionnaire Short Form, median (IQR)[e]	52.4 (28.6, 71.4)	47.6 (29.8, 71.4)	52.4 (28.6, 76.2)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline Overactive Bladder Questionnaire Short Form Symptom Bother, median (IQR)[f]	73.3 (56.7, 86.7)	66.7 (53.3, 83.3)	80.0 (63.3, 90.0)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline Overactive Bladder Questionnaire Short Form Quality of Life, median (IQR)[f]	41.5 (23.1, 57.7)	46.2 (32.7, 59.6)	32.3 (21.5, 56.4)
Missing	0 (0%)	0 (0%)	0 (0%)
Clinical responder, *n* (%)[g]	249 (81.9%)	90 (78.3%)	159 (84.1%)
Missing	3 (1.0%)	3 (2.5%)	0 (0%)
Recurrence over 12 months, *n* (%)[h]	203 (66.6%)	56 (47.9%)	147 (78.2%)
Missing	2 (0.7%)	1 (0.8%)	1 (0.5%)
Time to Recurrence over 12 months, median (IQR)[h]	6.00 (2.00, 12.0)	6.00 (2.00, 12.0)	6.00 (2.00, 12.0)
Missing	1 (0.3%)	1 (0.8%)	0 (0%)
Change in UUI episodes at 6 months, median (IQR)	−3.50 (−5.00, −2.33)	−3.67 (−4.92, −2.33)	−3.33 (−5.00, −2.08)
Missing	15 (4.9%)	8 (6.8%)	7 (3.7%)
Self-catheterization, *n* (%)[i]	54 (17.6%)	15 (12.7%)	39 (20.6%)
Missing	0 (0%)	0 (0%)	0 (0%)

Abbreviations: BoNT-A, onabotulinumtoxinA; IQR, interquartile range; UUI, urgency urinary incontinence.

[a]ABC trial (Anticholinergic versus Botulinum Toxin Comparison study, ClinicalTrials.gov number NCT01166438), which compared solifenacin to 100 units of onabotulinumtoxinA.[13]

[b]ROSETTA trial (Refractory Overactive Bladder: Sacral Neuromodulation vs Botulinum Toxin Assessment, ClinicalTrials.gov number NCT01502956), which compared sacral neuromodulation to 200 units of onabotulinumtoxinA.[14]

[c]Recurrent UTI defined as 3 or more urinary tract infections (bladder or kidney) that required treatment during the past year.

[d]Values range from 0 to 100, with higher scores indicating greater distress.

[e]Values range from 0 to 100, with higher scores indicating worse quality of life.

[f]Values range from 0 to 100, with higher scores on the symptom bother scale indicating greater severity of symptoms and higher scores on the quality-of-life scale indicating better quality of life.

[g]At 1 month ≥50% reduction in UUIE per day based on a 3-day bladder diary with UUIE averaged over 3 days (utilized to determine who would be allowed off-protocol non-BoNT-A treatment before 6 months in ROSETTA).

[h]Recurrence is defined as a score of 1–3 on the PGSC, corresponding to "strongly disagree," "disagree," or "neutral" to the statement "this treatment has given me adequate control of my urine leakage."

[i]Self-catheterization was initiated after BoNT-A therapy when the PVR > 150 ml and at least moderately bothered by the symptom of incomplete emptying or PVR > 300 ml.

APPENDIX B

TABLE B1 Predictors and outcomes by self-catheterization

Predictors and outcomes	Total ($N = 307$)	No self-catheterization ($N = 220$)	Self-catheterization ($N = 87$)
Cohort (BoNT-A dose), *n* (%)			
ABC (100 units)[a]	118 (38.4%)	103 (40.7%)	15 (27.8%)
ROSETTA (200 units)[b]	189 (61.6%)	150 (59.3%)	39 (72.2%)
Missing	0 (0%)	0 (0%)	0 (0%)
Age (years), median (IQR)	62.2 (53.6,69.9)	61.4 (53.4,70.4)	63.8 (56.9,68.4)
Missing	0 (0%)	0 (0%)	0 (0%)
Ethnicity, *n* (%)	40 (13.0%)	34 (13.4%)	6 (11.1%)
Missing	0 (0%)	0 (0%)	0 (0%)
Race, *n* (%)			
White	250 (81.4%)	202 (79.8%)	48 (88.9%)
Black	39 (12.7%)	36 (14.2%)	3 (5.6%)
Other	18 (5.9%)	15 (5.9%)	3 (5.6%)
Missing	0 (0%)	0 (0%)	0 (0%)
Current smoker, *n* (%)	36 (11.7%)	29 (11.5%)	7 (13.0%)
Missing	0 (0%)	0 (0%)	0 (0%)
Postmenopausal, n (%)	266 (86.6%)	221 (87.4%)	45 (83.3%)
Missing	0 (0%)	0 (0%)	0 (0%)
BMI, Median (IQR)	31.6 (26.8,37.5)	31.4 (26.6,38.0)	32.8 (27.7,36.0)
Missing	0 (0%)	0 (0%)	0 (0%)
Recurrent UTI history, *n* (%)[c]	26 (8.5%)	20 (7.9%)	6 (11.1%)
Missing	0 (0%)	0 (0%)	0 (0%)
Diabetes history, *n* (%)	52 (16.9%)	45 (17.8%)	7 (13.0%)
Missing	0 (0%)	0 (0%)	0 (0%)
Prior anticholinergic use, *n* (%)	260 (84.7%)	210 (83.0%)	50 (92.6%)
Missing	0 (0%)	0 (0%)	0 (0%)
Detrusor overactivity, *n* (%)	214 (69.7%)	183 (72.3%)	31 (57.4%)
Missing	0 (0%)	0 (0%)	0 (0%)
Maximum cystometric capacity (ml), median (IQR)	311 (220,400)	303 (212,393)	350 (248,442)
Missing	0 (0%)	0 (0%)	0 (0%)
Post void residual (ml), median (IQR)	20.0 (5.00,40.0)	20.0 (5.00,40.0)	26.5 (10.0,60.0)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline urgency incontinence episodes, median (IQR)	4.67 (3.33,6.33)	4.67 (3.33,6.33)	4.67 (3.42,6.33)
Missing	0 (0%)	0 (0%)	0 (0%)

(Continues)

TABLE B1 (Continued)

Predictors and outcomes	Total ($N = 307$)	No self-catheterization ($N = 220$)	Self-catheterization ($N = 87$)
Baseline total incontinence episodes, median (IQR)	5.33 (4.00,7.00)	5.33 (4.00,7.00)	5.00 (4.00,7.25)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline Urogenital Distress Inventory Short Form, median (IQR)[d]	61.1 (47.2,72.2)	61.1 (50.0,72.2)	61.1 (45.8,66.7)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline Incontinence Impact Questionnaire Short Form, median (IQR)[e]	52.4 (28.6,71.4)	52.4 (33.3,71.4)	52.4 (28.6,71.4)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline Overactive Bladder Questionnaire Short Form Symptom Bother, median (IQR)[f]	73.3 (56.7,86.7)	73.3 (60.0,86.7)	75.0 (53.3,85.8)
Missing	0 (0%)	0 (0%)	0 (0%)
Baseline Overactive Bladder Questionnaire Short Form Quality of Life, median (IQR)[f]	41.5 (23.1,57.7)	41.5 (23.1,58.5)	36.2 (23.5,56.1)
Missing	0 (0%)	0 (0%)	0 (0%)
Clinical responder, *n* (%)[g]	249 (81.9%)	209 (83.6%)	40 (74.1%)
Missing	3 (1.0%)	3 (1.2%)	0 (0%)
Recurrence over 12 months, *n* (%)[h]	203 (66.6%)	163 (64.9%)	40 (74.1%)
Missing	2 (0.7%)	2 (0.8%)	0 (0%)
Time to recurrence over 12 months, median (IQR)[h]	6.00 (2.00,12.0)	6.00 (2.00,12.0)	6.00 (2.00,11.8)
Missing	1 (0.3%)	1 (0.4%)	0 (0%)
Median change in UUI episodes at 6 months, median (IQR)	−3.50 (−5.00,−2.33)	−3.67 (−5.00,−2.33)	−3.33 (−4.67,−1.67)
Missing	15 (4.9%)	11 (4.3%)	4 (7.4%)
Self-catheterization, *n* (%)[i]	54 (17.6%)	0 (0.0%)	54 (100.0%)
Missing	0 (0%)	0 (0%)	0 (0%)

Abbreviations: BoNT-A, onabotulinumtoxinA; UUI, Urgency urinary incontinence

[a]ABC trial (Anticholinergic vs. Botulinum Toxin Comparison study, ClinicalTrials.gov number NCT01166438), which compared solifenacin to 100 units of onabotulinumtoxinA.[13]

[b]ROSETTA trial (Refractory Overactive Bladder: Sacral Neuromodulation vs Botulinum Toxin Assessment, ClinicalTrials.gov number NCT01502956), which compared sacral neuromodulation to 200 units of onabotulinumtoxinA.[14]

[c]Recurrent UTI defined as 3 or more urinary tract infections (bladder or kidney) that required treatment during the past year.

[d]Values range from 0 to 100, with higher scores indicating greater distress.

[e]Values range from 0 to 100, with higher scores indicating worse quality of life.

[f]Values range from 0 to 100, with higher scores on the symptom bother scale indicating greater severity of symptoms and higher scores on the quality-of-life scale indicating better quality of life.

[g]At 1 month ≥50% reduction in UUIE per day based on a 3-day bladder diary with UUIE averaged over 3 days (utilized to determine who would be allowed off-protocol nononabotulinumtoxinA treatment before 6 months in ROSETTA).

[h]Recurrence is defined as a score of 1–3 on the PGSC, corresponding to "strongly disagree," "disagree," or "neutral" to the statement "this treatment has given me adequate control of my urine leakage."

[i]Self-catheterization was initiated after onabotulinumtoxinA therapy when the PVR > 150 ml and at least moderately bothered by the symptom of incomplete emptying or PVR > 300 ml.