A Prospective Study to Evaluate Efficacy Using the Nuro Percutaneous Tibial Neuromodulation System in Drug-Naïve Patients With Overactive Bladder Syndrome

Kathleen Kobashi, Victor Nitti, Eric Margolis, Peter Sand, Steven Siegel, Salil Khandwala, Diane Newman, Scott A. MacDiarmid, Fangyu Kan, and Elizabeth Michaud

OBJECTIVE To evaluate changes from baseline in urgency urinary incontinence episodes, urinary frequency and quality of life through 12 weeks of percutaneous tibial neuromodulation (PTNM) therapy using NURO in drug-naïve overactive bladder syndrome (OAB) subjects.

METHODS Eligible subjects underwent 12 weekly PTNM sessions with the NURO system. Changes in voiding symptoms were evaluated with bladder diaries from baseline through 12 weeks. Analyses were conducted for subjects with data at baseline and follow-up visits (sessions 1, 4, 8, and 12). Safety was evaluated through adverse events (AE) related to the device, procedure, and therapy.

RESULTS Of 154 subjects enrolled in the study,120 subjects met study criteria and received PTNM. The mean age was 64.8 years, mean duration of OAB diagnosis was 3.4 years and 86% female subjects. No subjects tried OAB medication prior to enrollment. At baseline, patients had 3.5 ± 2.5 (mean ± SD) UUI episodes/day. Statistically significant improvement in urgency urinary incontinence episodes from baseline was observed at each follow-up visit ($P < .0001$), with a reduction of 2.4 ± 2.1 episodes after session 12 from baseline. Subjects with urinary frequency at baseline had 11.5 ± 2.9 voids/day. After session 12, a statistically significant reduction of 1.7 ± 2.5 voids/day was observed ($P < .0001$). Ninety-six percent (116/120) of subjects completed the study with diary data for the primary objective with an average of 11.6 sessions. There were no serious or unanticipated AEs. The most common AEs were medical device site pain (3.3%, 4/121) and extremity pain (3.3%, 4/121).

CONCLUSION PTNM using NURO is an effective and safe treatment for drug-naïve patients with OAB. UROLOGY 131: 77–82, 2019. © 2019 Elsevier Inc.

Overactive bladder syndrome (OAB) is a prevalent condition defined by a constellation of symptoms that include urinary urgency with or without resultant incontinence, often with associated urinary frequency and nocturia.[1] The prevalence estimates vary depending upon the definition used and population considered, with the overall incidence ranging from 16% to 23%.[2,3] Multiple studies have demonstrated an increased prevalence of OAB with advancing age.[2,4] OAB poses a significant and costly public health concern that can have a tremendous effect on the quality of life of an individual.[5]

The AUA/SUFU OAB Guidelines recommend starting with dietary and behavioral modification and progressing to pharmacotherapy and third-line therapies including neuromodulation; however, the guidelines acknowledge that each patient should not be required to go through each line of treatment in the order specified.[6] An assessment is needed to determine the best treatment option for each patient based on allergies, sensitivity to various adverse drug events, patient ability and motivation to comply and availability of and access to specific treatments.[6] Review of the literature suggests that few patients remain on medications long-term with discontinuation rates for

ClinicalTrials.gov identifier: NCT02857816.

Conflicts of Interest: Medtronic, Minneapolis, MN, provided funding for this study in its entirety. Development of study design, data analysis/statistical support, and creation of the manuscript was performed by the listed authors who include members of the Medtronic team.

From the Virginia Mason Medical Center, Seattle, WA; the David Geffen School of Medicine at UCLA, Los Angeles, SA; the Urologic Research and Consulting LLC, Engelwood, NJ; the NorthShore University Health-System, Evanston, IL; the Minnesota Urology, Woodbury, MN; the Advanced Urogynecology of Michigan PC, Dearborn, MI; the Division of Urology, Penn Medicine, University of Pennsylvania, Philadelphia, PA; the Alliance Urology Specialists, Greensboro, NC; and the Medtronic, Minneapolis, MN

Address correspondence to: *Kathleen Kobashi, M.D., Virginia Mason Medical Center, 1100 Ninth Avenue, C7-URO, Seattle, WA 98101. E-mail: Kathleen.Kobashi@virginiamason.org*

Submitted: March 4, 2019, accepted (with revisions): June 3, 2019

antimuscarinic agents and beta-3 agonists ranging from 38% to 88% and nearly 68%, respectively at 1 year.[7-9] The most common reasons why patients discontinue antimuscarinic medications include lack of efficacy, side effects,[10] and cost.[11] Additionally, with recent reports regarding the potential for cognitive side effects with antimuscarinics, many patients are seeking alternative treatments.[12,13] Potential side effects reported for beta-3 agonists include hypertension, nasopharyngitis, urinary tract infections, and headache.[14]

Percutaneous tibial neuromodulation (PTNM), also known as percutaneous tibial neurostimulation (PTNS), is considered a third-line therapy in the AUA/SUFU Guidelines. Its consideration as a third-line option notwithstanding, the rate of patient discontinuation of medications in conjunction with the desire of many individuals to avoid medications all together prompted this study. This study endeavored to evaluate a minimally invasive well-tolerated[15,16] option using the NURO system (Medtronic, Minneapolis, MN) in a drug-naïve patient population, a group that has not been well studied with this modality. Based upon the parameters utilized in the pharmacologic literature, the study assessed absolute change from baseline, with specific attention to UUI episodes.

MATERIALS AND METHODS

This prospective, multicenter, single-arm study evaluated changes from baseline in OAB symptoms as measured by bladder diaries and quality of life through 12 PTNM sessions. All eligible subjects had a diagnosis of OAB with at least 3 episodes of UUI on a 3-day paper bladder diary. Subjects had not undergone treatment for OAB with antimuscarinic or beta 3-agonist medications or any third-line therapy options. Institutional review board approval and subject informed consent were obtained prior to subject participation. Study design and subject disposition is shown in Figure 1.

The NURO system received FDA clearance in 2013 with the following system components: an external neurostimulator (model 3533) and associated accessory kit (model 3533K). During PTNM, the needle electrode is placed into the lower, inner aspect of either leg. Electrical pulses are delivered through the needle to stimulate the afferent fibers of the tibial nerve. A patient typically receives 12 weekly 30 minute treatments. Those who respond may continue with longer term (maintenance) therapy.

After confirmation of all eligibility criteria, subjects received 12 weekly PTNM sessions with the NURO System followed by a final study visit. Motor and/or sensory response(s) were obtained at all PTNM sessions. Voiding symptoms were assessed by 3-day bladder diaries at baseline and directly following PTNM sessions #1, #4, #8, and #12. Subjects who met eligibility criteria and received PTNM therapy were analyzed for changes in UUI episodes per day from baseline, and in subjects with UF (defined as >8 voids/day at baseline), the change in voids per day from baseline was also analyzed.

The Overactive Bladder Quality of Life Questionnaire (OABq) was used to assess the impact of OAB on health-related quality of life (HRQL) with its subscales (Coping, Concern, Sleep, and Social), and symptom bother[17] at baseline and following PTNM sessions #1, #4, #8, and #12. The questionnaire used in the study included a 1-week recall for symptom assessment.

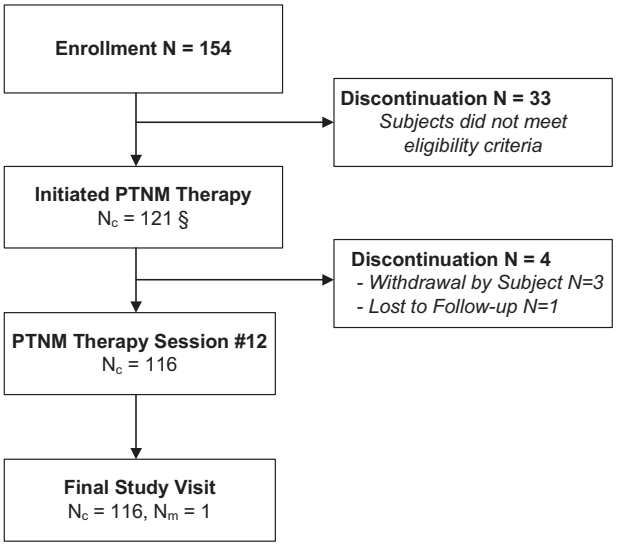

Figure 1. Study design and disposition of subjects counts at each visit indicate the number of subjects who have completed the visit (denoted as N_C) and number of subjects who have missed the visit (denoted as N_M). § One subject received PTNM treatment but did not meet eligibility criteria.

Safety was evaluated through adverse events (AE) related to the device, procedure and therapy (all considered device-related AEs). All device-related AEs were reported for subjects who received PTNM therapy.

The purpose of this study was to evaluate the reduction from baseline in the number of UUI episodes per day after PTNM session #12. Reduction in average UUI episodes per day from baseline was calculated for each subject (within subject) after the PTNM session #12 and was summarized for all subjects. The following assumptions were used for the sample size calculations: reduction of 0.75 UUI episodes/day from baseline, 1-sample *t* test with 2-sided $\alpha = 0.05$, 90% power, and an estimated standard deviation of 2.2 incontinence episodes/day. Based on these assumptions, a sample size of 93 subjects was required to demonstrate a statistically significant reduction from baseline. To account for an attrition of approximately 20% during the course of the study, a sample size of up to 120 qualified subjects was planned for this study.

Statistical Analyses

The primary objective of the study was to evaluate the change in UUI episodes per day after PTNM session #12. Calculation of change from baseline was computed by subtracting baseline values from PTNM session #12 values. Subjects with diary data from both baseline and PTNM session #12 were included in the primary analysis for this objective. Supporting analysis was conducted which included those subjects with diary data from both baseline and PTNM session #12, as well as those who failed to provide the relevant data for PTNM session #12, and those who withdrew early due to a device-related AE, unsuccessful treatment or any other reasons. For those who withdrew early due to device-related AEs or unsuccessful treatment, the data that corresponded to PTNM session #12 was set to their baseline values; for those who withdrew from the study due to any other reason or failed to provide data for the PTNM session #12, the Last Observation Carried Forward method was used to impute the missing data. To assess efficacy over time, outcomes were evaluated for subjects with data available at

baseline and each follow-up where diary data were collected (PTNM session #1, #4, #8, and #12).

Secondary objectives of the study included assessment of the reduction in number of voids per day from baseline following PTNM session #12 in UF subjects and changes in QOL as measured by the OABq Questionnaire. In both secondary objectives, primary and supporting analysis was performed as described in the primary objective.

Descriptive statistics were used to summarize device-related AEs.

For all analyses to assess the changes from baseline, paired *t* test or Wilcoxon signed-rank test was used after testing for data normality by calculating Shapiro-Wilk W statistic. All statistical tests were examined for significance at the 0.05 level. SAS software package (version 9.4, SAS Institute, Cary, NC) was used for all analyses.

RESULTS

One hundred and fifty-four (154) subjects at 12 sites enrolled in the study. One hundred-twenty (120) were qualified and 121 subjects received PTNM therapy, with 1 not meeting eligibility criteria. The subject who did not meet eligibility criteria was included only within the safety analysis. The most common reason for screen failures in the study were subjects who did not qualify with 3 episodes of UUI on the 3-day voiding diary. Overall, subjects who received PTNM therapy underwent an average of 11.6 sessions. Among 121 subjects who received PTNM treatment, 4 subjects discontinued therapy prior to reaching Session #12, and 1 subject missed the final study visit and was lost to follow-up (as shown in Fig. 1). Of 116 subjects who provided data at both baseline and PTNM Session #12, 107 subjects completed 12 sessions; 7 subjects completed 11 sessions; and 1 subject each completed 10 and 9 sessions, respectively. Ten sites contributed data for analysis; however, no site exceeded 20% of the total number of qualified subjects. Demographics for the 120 subjects who received PTNM therapy are shown in Table 1. Subjects had a mean age of 64.8 years with a mean duration of OAB diagnosis of 3.4 years at the time of enrollment, with no subjects having tried an OAB medication or advanced therapy treatment for OAB. The majority of subjects (73.3%) had tried a conservative therapy for OAB prior to study enrollment. Conservative therapies for OAB included physical therapy, pelvic floor muscle training, behavior modification, and dietary programs. At baseline, subjects had an average of 3.5 ± 2.5 UUI episodes/day.

Table 1. Baseline demographics

Demographics	Total (*n* = 120)
Gender	
Female	103 (85.8%)
Male	17 (14.2%)
Race	
White	105 (87.5%)
Black	13 (10.8%)
Asian	1 (0.8%)
Other	1 (0.8%)
Age, mean ± SD, y	64.8 ± 11.6
Years since OAB diagnosis	3.4 ± 5.1
Body mass index	30.1 ±7.1
Baseline UUI episodes/day*	3.5±2.5 (*n* = 119)
Baseline voids/day‡	11.5±2.9 (*n* = 86)
Secondary diagnoses	
Urinary frequency	81 (67.5%)
Urinary retention	5 (4.2%)
Stress incontinence	39 (32.5%)
Fecal incontinence	8 (6.7%)
Most common history of conservative therapies	
Bladder retraining	27 (22.5%)
Kegel exercises	80 (66.6%)
Dietary and fluid restrictions	39 (32.5%)
Weight loss	27 (22.5%)
Smoking cessation	15 (12.5%)
Pelvic floor physical therapy	15 (12.5%)

SD = standard deviation.
* One subject did not have evaluable diary at baseline.
‡ Voids include only those subjects who qualified for UF (≥8 voids/day) at baseline.

Ninety-six percent (116/120) of subjects completed the study and provided diary data for the primary objective. For the primary objective, change in UUI episodes/day after PTNM session #12 from baseline, a statistically significant reduction of 2.4 ± 2.1 (median: 2.0) UUI episodes/day was observed ($P < .0001$; Fig. 2). Supporting analysis was completed (not shown) and was consistent with the results from the primary analysis. Reduction

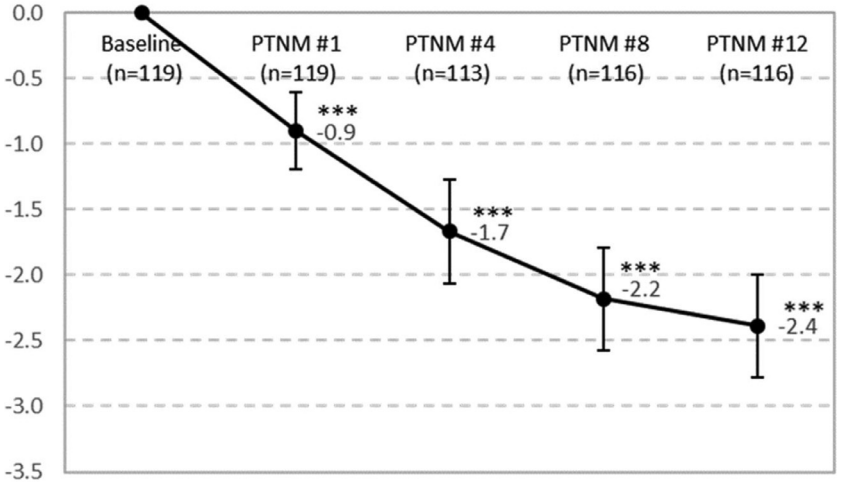

Figure 2. Change in UUI episodes per day by visit. Baseline = 3.5 UUI episodes per day. Error bars are 95% confidence intervals (CI). ***$P < .0001$.

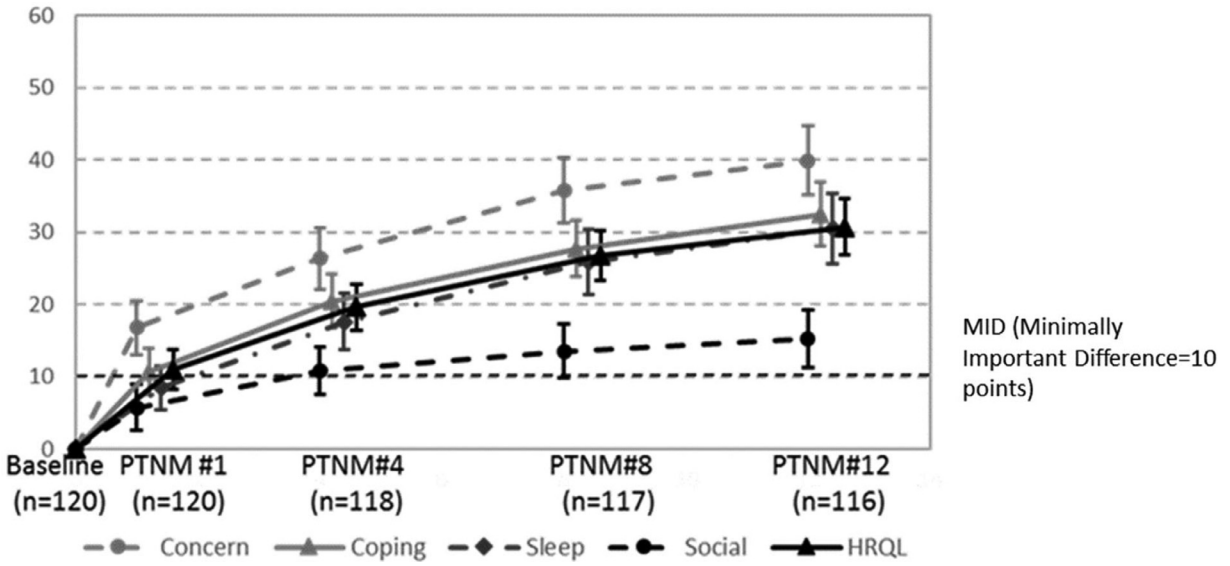

Figure 3. Change in HRQL and its subscales by visit. Baseline = 45(Concern); 53.1(Coping); 52.1(Sleep); 80.4(Social); 56.1(HRQL). All paired tests comparing follow-up to baseline had a $P < .0001$. Error bars are 95% CI. A positive change indicates improvement in QOL.

in UUI episodes from baseline over time is also shown in Fig. 2, indicating increasing efficacy over time through 12 therapy sessions. The UUI responder rate (>50% reduction in UUI episodes from baseline) increased over time with a rate of 77.6% following PTNM Session #12 and a complete continence rate of 39.7%.

One of the secondary objectives was to evaluate change in voids in UF subjects. UF subjects had 11.5 ± 2.9 voids/day at baseline. After completing the PTNM session #12, a statistically significant reduction of 1.7 ± 2.5 (median: 1.3) voids/day was observed ($P < .0001$).

When evaluating changes in QOL with the OABq tool, HRQL and its subscales, as well as symptom bother showed significant improvement from baseline (all $P < .0001$) after PTNM session #12 (Fig. 3). The minimally important difference for the HRQL and subscales are 10 points.[17] As shown in Figure 3, average improvements from baseline for Concern, Coping, Sleep, and HRQL are 3-4 times greater than minimally important difference at PTNM session #12. Change in OABq domains from baseline over time are also shown in Figure 3, indicating increasing QOL improvement over time up to 12 therapy sessions.

There were no serious adverse device events or unanticipated adverse device events. A total of 20 device-related AEs occurred in 14% of subjects (17/121), with most being transient and including device site pain (3.3%, 4/121) and pain in extremity (3.3%, 4/121). None of the device-related AEs required any medical intervention. There were 1408 PTNM sessions that occurred in the study resulting in 0.014 events per session. All device-related AEs were resolved at the completion of the study.

DISCUSSION

Favorable outcomes were observed in all objectives assessed in the study. Additionally, there was a notable improvement of both the primary and secondary outcome measures over the 12-week study period. This cohort demonstrated high compliance regarding study visits, along with bladder diary and questionnaire completion. Additionally, the unmistakable increase in improvement of UUI, UF, and OABq responses noted in this study over time would emphasize the importance of completing all 12 PTNM sessions before assuming that maximal therapeutic success has been reached.

At 14%, the percentage of patients who experienced a device-related AE was consistent with the literature,[16,18] and resulted in 0.014 events per PTNM session. AEs experienced in this study were transient and did not require intervention. As a comparison, the rate of AEs reported with antimuscarinics ranges from 9.7% to 63%,[19] and although serious side effects are rare, this may, at least in part, be a reason for the high discontinuation rate of medications.

According to current AUA/SUFU OAB Guidelines,[6] PTNM is positioned as a therapy for patients who have failed or not tolerated oral medications. Given the cost and potential side effects of oral medications and the lack of serious adverse device events with PTNM, it seems reasonable to investigate PTNM in the drug-naïve population. Utilizing parameters set by prior pharmacologic studies, eligibility criteria for this study were set to target patients with UUI. Though direct comparison between patients who fail medication prior to PTNM and those who go directly to PTNM was not a part of this study, using similar criteria theoretically allows for an opportunity to investigate the role of PTNM in the drug-naïve patient.

This brings focus to the important issue of compliance with therapy. Though the high treatment completion rate in this cohort may have been related to patient commitment to the trial, oversight by research staff, and a treatment period of 12 weeks, it remains a fact that the discontinuation rate of antimuscarinics is high. Reported rates at 1 year range from 38.2% in an open label study[7] to 88.6% in a retrospective assessment of medical claims data.[8] The converse persistence rates at 1 year are consistent with the above, ranging from 5% to 35% dependent

upon the medication studied.[10,20] This phenomenon was not limited to antimuscarinic agents with the 52-week persistence rate on mirabegron, a beta-3 agonist, reported to be only 31.7%.[9] Given the limited durability of medication compliance, an alternative to pharmacotherapy is attractive. Long term data on the use of PTNM is limited in the published literature. Recently, Sirls et al reported 75.6% compliance with 12 weekly PTNM therapy sessions and 54.9% of patients continuing with maintenance therapy.[21] Peters et al investigated long-term use of PTNM in 50 patients in the STEP[22] who had completed 12 PTNM sessions in the SUmiT Trial.[16] In this study, 29 patients completed the 3-year follow-up visit.[22] Given the early effects of the therapy, understanding compliance with long-term treatment may be a future area of interest to understand the durability of treatment effect and therapy adherence.

This represents the first evaluation of PTNM in the drug-naïve patient and a limitation of the study is its single-arm design. Though the efficacy was very encouraging, a randomized study with a sham arm in a drug-naïve population might provide even more guidance regarding the use of PTNM in these patients. A logical assessment of the published literature might suggest that PTNM (also called percutaneous tibial nerve stimulation, or PTNS, in the literature) would be favored in such a study.

Though not inclusive of a drug-naïve patient population, Peters et al demonstrated superiority of PTNS over a validated sham for both subjective and objective parameters in the SUmiT trial.[16] At 12 weeks follow-up, 54.5% vs 20.9% ($P < .001$) of patients reported moderate to marked improvement in their symptoms in the PTNS and sham groups, respectively. Also, by 12 weeks, a mean reduction in the number of voids/day of −2.4 (PTNS) and −1.5 (sham) ($P = .01$), and a median reduction in UUI episodes per day of −1.3 (PTNS) and −0.3 (sham) ($P = .002$) were noted, which is similar to that which was noted in this study.

Direct comparison of PTNS and tolterodine in the randomized controlled OrBIT study showed a statistically significant improvement in both arms with a cured/improved rate of 79.5% with PTNS and 60.5% with tolterodine.[18] However, this population was not drug-naïve. A recent meta-analysis on antimuscarinic agents showed an efficacy with medications[19] that was similar to PTNS, and a systematic review and meta-analysis of PTNS for OAB also concluded that the efficacy of PTNS was comparable to the effect of medications but with a better side effect profile.[23] Given the available data, there is clearly a role for PTNM that might warrant consideration earlier in the treatment algorithm than third line.

Finally, durability of symptom relief is an important consideration, particularly given the high rate of discontinuation of medications by 1 year. Though the standard of care for PTNM is only 12 weeks, and there is not sufficient long-term maintenance data to warrant a standard schedule, sustained efficacy has been reported in 2 extension studies. With an average treatment interval of 21 days, the OrBIT trial extension showed a sustained decrease in daily voids, UUI episodes, and nocturia at 12 months.[24] Similarly, the STEP Study, utilizing an average of 1.1 maintenance treatments per month, showed sustained efficacy and safety out to 3 years in a limited number of patients who continued follow-up in the study.[22] Improvement in the understanding of therapeutic durability and standardization of maintenance therapy would be valuable information and warrant further study.

CONCLUSION

This study demonstrated successful outcomes regarding both safety and efficacy using PTNM, a minimally invasive neuromodulation technique, to treat OAB in drug-naïve patients. While pharmacotherapy may still be an option for some patients with OAB, our findings suggest a role for PTNM as a second line option after conservative and behavioral therapies for patients who wish to avoid medication.

Acknowledgments. The study investigators thank Kira Stolen, Ph.D.; Kellie Berg, M.S.; Colleen Haberman, M.S.; and Sudha Iyer, Ph.D. for their contributions.

References

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21:167–178.
2. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20:327–336.
3. Coyne KS, Sexton CC, Bell JA, et al. The prevalence of lower urinary tract symptoms (LUTS) and overactive bladder (OAB) by racial/ethnic group and age: results from OAB-POLL. *Neurourol Urodyn*. 2013;32:230–237.
4. Coyne KS, Sexton CC, Vats V, et al. National community prevalence of overactive bladder in the United States stratified by sex and age. *Urology*. 2011;77:1081–1087.
5. Reynolds WS, Fowke J, Dmochowski R. The burden of overactive bladder on US public health. *Curr Bladder Dysfunct Rep*. 2016;11:8–13.
6. Gormley EA, Lightner DJ, Burgio KL, et al. *Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: Aua/Sufu Guideline*. American Urological Association Education and Research, Inc; 2019. https://www.auanet.org/guidelines/overactive-bladder-(oab)-guideline. Accessed 10 May 2019.
7. Abrams P, Malone-Lee J, Jacquetin B, et al. Twelve-month treatment of overactive bladder drugs aging. 2001; 18: 551-560.
8. Yu YF, Nichol MB, Yu A, Ahn J. Persistence and adherence of medications for chronic overactive bladder/urinary incontinence in the California Medicaid program. *Value Health*. 2005;8:495–505.
9. Wagg A, Gerhard C, Fahey A, et al. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU Int*. 2012;110:1767–1774.
10. Kim TH, Lee KS. Persistence and compliance with medication management in the treatment of overactive bladder. *Investig Clin Urology*. 2016;57:84–93.
11. Campbell UB, Stang P, Barron MS. Survey assessment of continuation of and satisfaction with pharmacological treatment for urinary incontinence. *Value Health*. 2008;11:726–732.

12. Gray SL, Anderson M, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia. *JAMA Intern Med*. 2015; 175:401–417.
13. Thomas TN, Walters MD. AUGS consensus statement: association of anticholinergic medication use and cognition in women with overactive bladder. *Female Pelvic Med Reconstr Surg*. 2017;23: 177–178.
14. Nitti VW, Auerbach S, Martin N, et al. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. *J Urol*. 2013;189:1388–1395.
15. Govier FE, Litwiller S, Nitti V, et al. Percutaneous afferent neuromodulation for the refractory overactive bladder: results of a multicenter study. *J Urol*. 2001;165:1193–1198.
16. Peters KM, Carrico DJ, Perez-Marrero RA, et al. Randomized trial of percutaneous tibial nerve stimulation versus sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial. *J Urol*. 2010;183:1438–1443.
17. Coyne KS, Gelhorn H, Thompson C, et al. The psychometric validation of a 1-week recall period for the OAB-q. *Int Urogynecol J*. 2011;22:1555–1563.
18. Peters KM, Macdiarmid SA, Wooldridge LS, et al. Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results from the overactive bladder innovative therapy trial. *J Urol*. 2009;182:1055–1061.
19. Chapple C, Khullar V, Gabriel Z, et al. The effects of antimuscarinic treatments in overactive bladder: a systematic review and meta-analysis. *Eur Urol*. 2005;48:5–26.
20. Shaya FT, Blume S, Gu A, et al. Persistence with overactive bladder pharmacotherapy in a Medicaid population. *Am J ManagCare*. 2005;11:S121–S129.
21. Sirls ER, Killinger KA, Boura JA, et al. Percutaneous tibial nerve stimulation in the office setting: real-world experience of over 100 patients. *Urology*. 2018;113:34–39.
22. Peters KM, Carrico DJ, Wooldridge LS, et al. Percutaneous tibial nerve stimulation for the long-term treatment of overactive bladder: 3-year results of the STEP study. *J Urol*. 2013;189: 2194–2201.
23. Burton C, Sajja A, Latthe PM. Effectiveness of percutaneous posterior tibial nerve stimulation for overactive bladder: a systematic review and meta-analysis. *Neurourol Urodyn*. 2012;31: 1206–1216.
24. MacDiarmid SA, Peters KM, Shobeiri SA, et al. Long-term durability of percutaneous tibial nerve stimulation for the treatment of overactive bladder. *J Urol*. 2010;183:234–240.