CLINICAL ARTICLE

Patient-tailored healthcare and tibial nerve neuromodulation in the treatment of patients with overactive bladder symptoms

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Abstract

Purpose: The aim of this study was to demonstrate features predictive of treatment response for patient-tailored overactive bladder (OAB) intervention with an implantable tibial neurostimulator using patient and technical prediction factors.

Materials and Methods: This study was designed as a follow-up study based on parameter settings and patients' preferences during the pilot and extended study of the implantable tibial nerve stimulator (RENOVA™ iStim system). For this study, we compared all treatment parameters (stimulation amplitude, frequency, and pulse width) and usage data (duration of treatment) during the different follow-up visits.

Results: We obtained usage data from a total of 32 patients who were implanted with the system between February and September 2015. Age, sex, body mass index (BMI) and previous experience with percutaneous tibial nerve stimulation (PTNS) treatment were considered as possible prediction factors for treatment success. However, only BMI was considered a statistically significant prediction factor ($p = 0.042$). A statistically significant increase in mean treatment level was seen in the responder group during the 3 month follow-up visit (mean: 6.7 mA, SD 0.416) as compared with the initial system activation visit (mean: 5.8 mA, SD 0.400) ($p = 0.049$). No other visits demonstrated statistically significant changes in both groups (responders and non-responders) during the defined timepoints.

Conclusion: This data underscores the need to use patient-tailored OAB treatment. BMI was found to be a negative predictive factor for treatment success. However, it was not possible to develop a specific responder model. A model predicting response to treatment could be useful for implementing shared decision making.

1 | INTRODUCTION

Overactive bladder (OAB) is a chronic condition that is characterized by urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology according to the International Continence Society terminology.[1]

The etiology and pathophysiology of OAB are still unclear. Over the years several new theories have emerged. However, still there is no clear understanding of the etiology and pathophysiology of OAB. This is one of the reasons why an appropriate long-term treatment for OAB has not yet been found. However, Peyronnet et al.[2] recently described a new method of managing OAB. They conclude that various OAB phenotypes exist based on several different studies.[2–8] These OAB subtypes are determined by the patient's comorbidities and existing theories/phenotypes.[2] These findings imply that a personalized approach should be considered when treating OAB patients versus the "one size fits all" strategy from a cost-effectiveness and long-term compliance point of view.

Implantable tibial nerve stimulation using a wearable unit that activates and regulates the implant provides an excellent setting for a personalized approach since all parameters and treatment regimens can be adjusted using the patient's preference and subjective response to optimize the treatment outcome. Although results of the prior pilot clinical trial were previously published,[9–11] this manuscript is the first to describe this new personalized patient-centric treatment approach, specifically related to treatment settings and usage. This report aims to demonstrate the positive aspects of patient-tailored OAB treatment using patient prediction and device-related technical options during treatment. As a result, we have looked at options for optimizing treatment for each individual, both at a patient-specific level (i.e., positive prediction factors) and at a device-specific level in terms of technical options. The following questions will be addressed: (a) Do patients use the ability to change their treatment parameters? (b) Do patients change their treatment regimen if allowed? (c) Is parameter assessment and adjustments during follow-up visits necessary in patient-tailored treatment? (d) Are there any predictive factors for treatment success based on technical or patient features for treatment of OAB with an implantable tibial neurostimulation device?

2 | MATERIALS AND METHODS

This study is based on a post hoc assessment of parameter settings and patient preferences during the previously published pilot and extended studies of the implantable tibial nerve stimulator (RENOVA™ system).[9,11,12] The study was approved by all ethical committees of the participating centers. All patients who were previously implanted with the RENOVA™ system were included in this study. However, only patients with available logs (usage data retrieved from the wearable external control unit), were included for final analysis. There were no other additional criteria for inclusion or exclusion. Subject enrollment for the pilot study was contingent upon satisfaction of all inclusion and exclusion criteria listed in the previous study.[9] Inclusion criteria included OAB wet or OAB dry based on completion by the subject of a consecutive 3-day voiding diary and patient who has failed conservative treatments after at least 6 months of treatment (i.e., lifestyle modification-fluid consumption, behavioral modification, and pharmacological therapy).[9]

The RENOVA™ system consists of a wireless miniature implant and a wireless wearable external control unit (nonimplantable component). The system transmits electrical pulses to the tibial nerve. The implant has two electrodes, positioned on each end of implant. After implantation and a period of healing, the device is activated (at 4 weeks postimplant) and the patient performs self-treatment at home with the wearable external control unit (ECU). The implantation procedure of this device has previously been described.[2] During the pilot study (activation – 6 months follow-up visit), the number of treatments per day was pre-defined in the study protocol described by Heesakkers et al. and van Breda et al.[9,11] Patients were not allowed to alter the frequency of usage during the pilot study. During the extended follow-up study (6–36 months post system activation), subjects could volitionally adjust the number of treatments per day according to the perceived responsiveness of self-experienced OAB symptoms.[12] Subjects were also allowed to alter treatment intensity (i.e., treatment level

and stimulation current) throughout the complete study (pilot and extended).

Stimulation parameters including pulse width (ms), frequency (Hz), minimum sensation level (MSL) in mA, maximum tolerable level (MTL) in mA, and treatment level (TL, recommended amplitude based on minimum sensation and maximum tolerable level) in mA, were established during the system activation (approximately 1-month postimplantation). During follow-up visits, after system activation, the system was adjusted based on the patient's comfort (i.e., pain) and treatment effect (number of UUI recorded in voiding diary). Patients could change their treatment intensity level (downwards and upwards) within the predefined range of MSL and MTL set on their device by altering treatment current intensity on their ECU.

In this study, treatment parameters were assessed during follow-up visits (activation, 1-month, 3-month, and 6 months follow-up). Logs retrieved during each follow-up visit provided parameter information during follow-up visits. Information regarding treatment settings and patient usage was retrieved from logs downloaded from the ECU during the follow-up visits to the clinic.

Statistical analysis was performed by using *IBM SPSS statistics 25*®. Logistic regression was used for a prediction model. Multivariant analysis and χ^2 tests were used to compare differences in minimum sensation level (MSL), maximum tolerable level (MTL), treatment level (TL), and the usage testing during different timepoints and responder versus nonresponder during 6 months follow-up timepoint. Responders were defined as; ≥50% reduction in the number of incontinence episodes/day, or a number of voids/day, or a number of episodes with a degree of urgency >2 or a return to <8 voids/day.

3 | RESULTS

3.1 | Baseline results

In this study, we obtained usage data from a total of 32 subjects who were implanted between February and September 2015 in three different hospitals (two in The Netherlands and one in the UK). Twenty-eight of the included subjects were females (88%), the median age of all study participants was 58 years (range 18–78). Forty-four percent ($n = 14$) of the participants had previous percutaneous tibial nerve stimulation (PTNS), median BMI was 27.2 (range 21.5–40.9). Most of the patients did suffer from urgency urinary incontinence (UUI) with urinary frequency (UF; 78%) followed by UF without incontinence (13%) and UUI without frequency (9%). At baseline (before implantation), patients with UUI had a

mean of 6 UUI episodes (SD 4.6) per day, and a mean of 12 (SD 3.0) voids per day. All baseline descriptive statistics are summarized in Table 1.

3.2 | Treatment regimens and parameters settings

During the first 6 months, the treatment regimen was fixed as described by Heesakkers et al.[9] However, during the extended study period patients ($n = 18$) regulated treatment (frequency of use), with a treatment frequency ranging between once every 6 weeks to 14 times per week. Most of the patients treated themselves between 4 and 6 times per week (72%). Due to the small number of patients included in the extended study no further analysis on the correlation between treatment frequency and treatment success could be determined.

During the system activation visit the median treatment level ($n = 29$) was set to 5.5 mA (range 1.58–8.0). Median treatment level during 6 month follow-up visit in responders ($n = 22$) was set to 6.75 mA (range 2.79–8.5, $n = 22$) which was equal (6.75 mA) to that of the nonresponders group ($n = 10$) (range 1.13–8.5, $n = 10$).

There was a statistically significant increase in the mean treatment level in the responder group during 3 months follow-up (mean: 6.7 mA, SD 0.416) as compared with their activation visit (mean: 5.8 mA, SD 0.400) ($p = 0.049$). No other visits demonstrated statistically significant changes in either group (responders and nonresponders) between the defined timepoints. Figure 1 shows mean treatment levels during the predefined

TABLE 1 Descriptive statistics ($n = 32$)

Gender (%)	Female: 88 Male: 12
Age (years)	58
BMI (median)	27.2
Type of OAB (%)	UUI & UF: 78
	UF only: 13
	UI only: 9
Leakages per day (baseline)	6/day
Number of voids (baseline)	12/day
Treatment sessions per week (extended study)	0–3 times 16.7%
	4–6 times: 72.2%
	7–10 times: 5.6%
	>10 times: 5.6%

Abbreviations: BMI, body mass index; OAB, overactive bladder; UF, urinary frequency; UUI, urgency urinary incontinence.

Meant treatment level (mA)

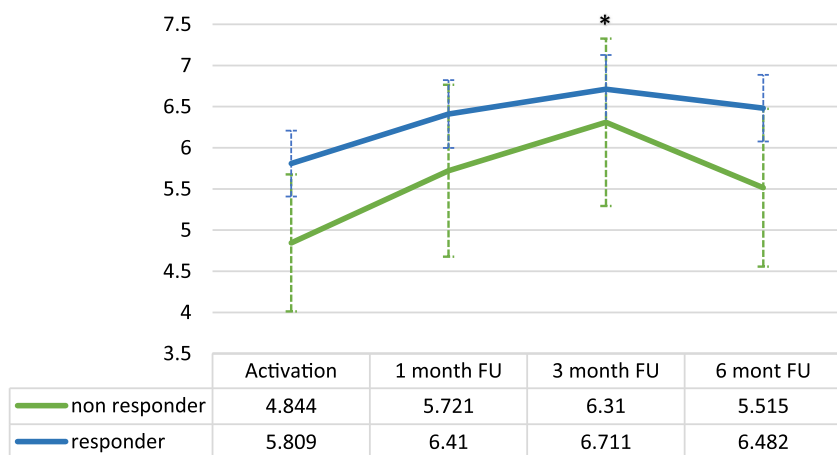|	Activation	1 month FU	3 month FU	6 mont FU
non responder	4.844	5.721	6.31	5.515
responder	5.809	6.41	6.711	6.482

FIGURE 1 Mean treatment level in mA during different timepoints, responder ($n = 22$) versus nonresponder ($n = 10$). Statistical significance between activation and 3 month follow-up in responders ($p = 0.049$)

timepoints (activation, 1 month, 3 months, and 6 months follow-up) in responders and nonresponders.

3.3 | Patient tailored treatment levels during home-treatment

During the first month of follow-up, all patients adjusted at least once the treatment intensity of their ECU ($n = 32$). During the 6 months of follow-up visit, logs demonstrated that 70% of the nonresponders used treatment adjustment at least once during the overall treatment versus 42% of the responders. During the first 2 min of treatment, again 70% of the nonresponders were altering treatment intensity as compared with only 32% of the patients in the responder group. After 2 min of therapy, only 32% of the responders were using treatment intensity alteration during 6 month follow-up comparing with 50% of the patients in the nonresponder group.

3.4 | Prediction factors

Age, sex, BMI, and previous PTNS were considered as possible prediction factors for treatment success. However, only BMI was considered a statistically significant negative prediction factor ($p = 0.042$), with higher BMI correlating with lower response level to treatment. Table 2 summarizes the prediction factors and their p-value.

4 | DISCUSSION

This study is the first to report the positive aspects of patient-tailored OAB treatment using patient prediction and device-related technical options during

TABLE 2 Prediction factors for being responder

Prediction factor	*p*-value
Age	0.51
Gender	0.40
BMI	0.042*
Previous PTNS	0.77

Abbreviations: BMI, body mass index; PTNS, percutaneous tibial nerve stimulation.

*$p < 0.05$ was considered statistically significant.

treatment. This study evaluates treatment settings, usage of home-based treatment, patient interaction with device, and prediction factors in the treatment of OAB by using a tibial nerve implantable neurostimulation system. Despite increasing reports of efficacy outcomes in smaller pilot studies,[12–14] treatment settings and their influence on therapy success have not been previously analyzed.

One of the major patient-specific findings in this study is that BMI was shown to be a negative prediction factor in the treatment success of tibial nerve stimulation with an implant. One device-specific explanation for this could be that the distance (skin to implant) is larger in patients with a higher BMI and therefore voltage could be attenuated in the higher tissue volume. Guidelines have previously stressed lifestyle intervention and positive outcomes on incontinence and specifically overactive bladder, and the importance of patient engagement for treatment success has long been recognized.[15,16] In this analysis, no other predictive factors for successful treatment were identified. Prior studies have also found no specific predictive factors for treatment success with percutaneous tibial nerve stimulation. Van Balken et al. found no factors to be predictive for treatment prognosis

inclusive of sex, age, weight, BMI, indication for PTNS, duration of symptoms, types of prior treatment, and stimulation parameters.[17] Their main negative prognostic factor for treatment success was poor mental health as reported by the SF-36 Mental Component Summary.

Based on the specific treatment modalities it was assumed that previous successful PTNS treatment is a positive predictive factor for treatment success in OAB with tibial implantation. However, we could not confirm this in our analysis. One possible explanation is the relatively small number of patients with previous successful PTNS ($n = 14$) which were included in this study. Also, success criteria definitions for PTNS have not been standardized and therefore historical PTNS success reporting could have led to miscategorization of some patients. For example, successful PTNS treatment might have been concluded based upon a subjective questionnaire but diary data did not demonstrate a 50% reduction in voiding/incontinence episodes as per predefined outcomes success criteria for the trial.

It is generally accepted that OAB usually requires long-term treatment to achieve control of symptoms.[18] Compliance and continuation of the therapy is therefore of great importance for therapeutic success. Nevertheless, long-term treatment persistence is typically low in chronic diseases, especially OAB.[19-21] Adherence and persistence to OAB treatment is challenging and therefore patient-centered treatment can potentially improve this aspect and allow optimal therapy result. The ability for the physician to refine treatment parameters during follow-up visits by adjusting stimulation parameters such as frequency (Hz), pulse width (ms), and the range of amplitudes to tailor the treatment for each patient based on individual patient's stimulation sensation as well as treatment efficacy will improve the quality of the patient-centered treatment. The logs provided by the system also allow the physician to monitor and verify treatment compliance including verifying technical issues. Thus, although there were no statistically significant differences in device-related technical options, that is, the treatment levels of the study cohort during follow-up (except for an increase in treatment level at 3-month follow-up), adjustments of treatment parameters were performed by each patient throughout the study to improve treatment success and improving patient well-being.

We believe that further investigation of the different parameters (i.e., frequency and pulse width) in correlation with treatment response should be reported by clinical trials. The ability to change their treatment intensity (amplitude) within a predetermined range is clearly important as demonstrated in this trial, with non-responders using this feature more frequently than

responders. Emphasizing the need for patient involvement with their therapy besides the various technical possibilities and highlighting the importance of patient-centric therapy.

A limitation of this study is the small sample size. A larger sample size perhaps would have allowed delineation of predictive factors correlated with treatment success. Having predictive factors could be of great importance in counseling the patient for personalized OAB treatment. These predictive factors in combination with the further ongoing research in the onset of OAB[2] could be the cornerstone of personalized OAB treatment instead of the "one-treatment-fits-all" theory, perhaps allowing earlier utilization of this therapy in the treatment paradigm.

5 | CONCLUSION

It was not possible to develop a specific responder model for OAB treatment using an implantable tibial neurostimulation system. A responder model could be useful for implementing shared decision making with the patient. Although similar to other neuromodulation reports, BMI was found to be a negative prediction factor for this treatment modality, no other predictive factors could be obtained. The need for patient-tailored healthcare is critical and might improve the long-term treatment outcome and compliance for each patient. Possibly new multicenter studies with a larger number of patients will shed light on a better predictive model in the treatment of OAB using an implantable tibial neurostimulation device.

ETHICS STATEMENT
The study was approved by all ethical committees of the participating centers.

PATIENT CONSENT STATEMENT
Consent to Participate was obtained by written procedure.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES
On request from the authors.

CLINICAL TRIAL REGISTRATION

Clinical trial number: CP-03-001.

AUTHOR CONTRIBUTIONS

Manon te Dorsthorst: Data collection and management, data analysis, and manuscript writing/editing. Alex Digesu, Phillip van Kerrebroeck, Sohier Elneil, and Jetske van Breda: Manuscript writing/editing and data collection. Frank Martens, Dick Janssen, and Michael van Balken: Manuscript writing/editing. John Heesakkers: Manuscript writing/editing, data collection, and protocol/project development.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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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(2):167-178.
2. Peyronnet B, Mironska E, Chapple C, et al. A comprehensive review of overactive bladder pathophysiology: on the way to tailored treatment. *Eur Urol.* 2019;75(6):988-1000.
3. Hubeaux K, Deffieux X, Ismael SS, Raibaut P, Amarenco G. Autonomic nervous system activity during bladder filling assessed by heart rate variability analysis in women with idiopathic overactive bladder syndrome or stress urinary incontinence. *J Urol.* 2007;178(6):2483-2487.
4. Bunn F, Kirby M, Pinkney E, et al. Is there a link between overactive bladder and the metabolic syndrome in women? A systematic review of observational studies. *Int J Clin Pract.* 2015;69(2):199-217.
5. Klausner AP, Steers WD. Corticotropin releasing factor: a mediator of emotional influences on bladder function. *J Urol.* 2004;172(6 Pt 2):2570-2573.
6. Hanna-Mitchell AT. Do we need to know more about the effects of hormones on lower urinary tract dysfunction? ICI-RS 2014. *Neurourol Urodyn.* 2016;35(2):299-303.
7. Malykhina AP, Wyndaele JJ, Andersson KE, De Wachter S, Dmochowski RR. Do the urinary bladder and large bowel interact, in sickness or in health? ICI-RS 2011. *Neurourol Urodyn.* 2012;31(3):352-358.
8. Aragón IM, Herrera-Imbroda B, Queipo-Ortuño MI, et al. The urinary tract microbiome in health and disease. *Eur Urol Focus.* 2018;4(1):128-138.
9. Heesakkers JPFA, Digesu GA, van Breda J, Van Kerrebroeck P, Elneil S. A novel leadless, miniature implantable tibial nerve neuromodulation system for the management of overactive bladder complaints. *Neurourol Urodyn.* 2018;37(3):1060-1067.
10. te Dorsthorst MJ, Heesakkers JPFA, van Balken MR. Long-term real-life adherence of percutaneous tibial nerve stimulation in over 400 patients. *Neurourol Urodyn.* 2020;39(2):702-706.
11. van Breda HMK, Martens FMJ, Tromp J, Heesakkers JPFA. A new implanted posterior tibial nerve stimulator for the treatment of overactive bladder syndrome: 3-month results of a novel therapy at a single center. *J Urol.* 2017;198(1):205-210.
12. Te Dorsthorst M, Digesu GA, Tailor V, et al. 3-year follow-up, of a new implantable tibial nerve stimulator for the treatment of overactive bladder syndrome (OAB). *J Urol.* 2020;204(3):545-550.
13. MacDiarmid S, Staskin DR, Lucente V, et al. Feasibility of a fully implanted, nickel sized and shaped tibial nerve stimulator for the treatment of overactive bladder syndrome with urgency urinary incontinence. *J Urol.* 2019;201(5):967-972.
14. Sievert KD, Milinovic L, Foditsch E, et al. New novel chronic tibial neuromodulation (CTNM) treatment option for OAB significantly improves urgency (UI)/urge urinary incontinence (UUI) and normalizes sleep patterns: Initial results. *European Urology, Supplements.* 2017;16(3):e994.
15. Subak LL, Wing R, West DS, et al. Weight loss to treat urinary incontinence in overweight and obese women. *N Engl J Med.* 2009;360(5):481-490.
16. Link CL, Steers WD, Kusek JW, McKinlay JB. The association of adiposity and overactive bladder appears to differ by gender: results from the Boston Area Community Health survey. *J Urol.* 2011;185(3):955-963.
17. van Balken MR, Vergunst H, Bemelmans BL. Prognostic factors for successful percutaneous tibial nerve stimulation. *Eur Urol.* 2006;49(2):360-365.
18. Abrams P, Kelleher CJ, Kerr LA, Rogers RG. Overactive bladder significantly affects quality of life. *Am J Manag Care.* 2000;6(11 Suppl):S580-S590.
19. Yu YF, Nichol MB, Yu AP, Ahn J. Persistence and adherence of medications for chronic overactive bladder/urinary incontinence in the California Medicaid Program. *Value Health.* 2005;8(4):495-505.
20. Sexton CC, Notte SM, Maroulis C, et al. Persistence and adherence in the treatment of overactive bladder syndrome with anticholinergic therapy: a systematic review of the literature. *Int J Clin Pract.* 2011;65(5):567-585.
21. Andrade SE, Walker AM, Gottlieb LK, et al. Discontinuation of antihyperlipidemic drugs: do rates reported in clinical trials reflect rates in primary care settings? *N Engl J Med.* 1995;332(17):1125-1131.