Feasibility of using a novel non-invasive ambulatory tibial nerve stimulation device for the home-based treatment of overactive bladder symptoms

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Short title: Ambulatory transcutaneous tibial nerve stimulation for the overactive bladder

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Abstract

Objectives

To evaluate safety, acceptability and pilot efficacy of transcutaneous low frequency tibial nerve stimulation (TNS) using a novel home-based neuromodulation device.

Patients and methods

In this single centre pilot study, 48 patients with OAB (24 with neurogenic and 24 with idiopathic OAB) were randomized to use a self-applicating ambulatory skin-adhering device stimulating transcutaneously the tibial nerve behind the medial malleoulus for 30 minutes, either once daily or once weekly, for 12-weeks. Changes in OAB symptoms and quality of life (QoL) were measured at baseline, weeks 4, 8, and 12 using validated scoring instruments (ICIQ-OAB and ICIQ-LUTSqol), 3-day bladder diary data and a Global Response Assessment (GRA) at week 12. Compliance was assessed through weekly phone calls and a usage diary.

Results

Thirty-four patients completed the study (idiopathic OAB n=15, neurogenic OAB n=19). No significant adverse effects were noted. Patients found using the device acceptable, rating the treatment as easy to use, comfortable, and were very satisfied with this treatment modality. Eighteen patients (53%) reported a moderate or marked improvement in symptoms according to the GRA. Between baseline and week -12, ICIQ-OAB part A sub-scores improved from mean (SD) 9.3 (2.5) to 7.5 (3.1), and from 9.1 (1.9) to 5.9 (1.7) in the daily and the weekly arms, respectively. ICIQ-OAB part B sub-scores improved from 29.6 (8.1) to 25.6 (9.5) (p=0.2) in the daily arm, and

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from 29.7 (5.9) to 19.1 (8.5) in the weekly arm. ICIQ-LUTSqol part A sub-scores improved from mean (SD) 51 (12.8) to 44.2 (13.1) and 44.9 (9.0) to 35.9 (8.8) in the daily and the weekly arms, respectively. ICIQ-LUTSqol part B subscores improved from 130.3 (43.7) to 105.5 (57.8) in the daily arm, and from 102.1 (40.1) to 63.9 (42.8) in the weekly arm. 3-Day bladder diary improvements were also noted as 24 hour urinary frequency improved from 11.5 at baseline to 8.8 at week 12 in the daily arm in both arms combined. Improvements were observed in patients with both idiopathic and neurogenic OAB.

Conclusion

This novel ambulatory transcutaneous TNS device is safe and acceptable for use in patients reporting OAB symptoms for home-based neuromodulation. Preliminary evidence suggests efficacy, however this needs to be confirmed in a larger study.

ClinicalTrials.gov Identifier: NCT02790307

Introduction

Tibial nerve stimulation (TNS) has emerged as an effective alternative for the management of the overactive bladder (OAB). Consisting of intermittent electrical stimulation of the tibial nerve, the efficacy of this treatment has been demonstrated in several studies, including a multicentric, double-blind, randomised sham-controlled study of patients with idiopathic OAB [1, 2]. More recently, the treatment has appeared in National Institute for Health and Care Excellence (NICE) guidance as a second-line option for the management of female urinary incontinence [3] [4].

In clinical practice, the tibial nerve is most often stimulated percutaneously (PTNS) by inserting a needle, however this entails regular visits to an outpatient clinic over 8 to 12 weeks. Being resource intense in terms of time, financial and staff commitments, this treatment is often not a feasible option from the point of view of health care delivery. Moreover, the treatment may not be an option for patients requiring to travel long distances, those having disabilities requiring special transport arrangements and those unable to commit to a 3 month block of treatment. Adverse effects such as pain, bruising, tingling or bleeding at the insertion site is reported in upto 8% of patients, and this may limit acceptability of this treatment [5]. Perhaps reflecting these limitations, the results of a long-term follow up study of patients undergoing PTNS treatment showed poor compliance to PTNS over time [6].

Non-invasive alternatives, whereby the tibial nerve is stimulated transcutaneously (TTNS) at a home-based setting, have therefore been explored [7]. Early results have been promising, demonstrating improvements in OAB symptom scores and urodynamic parameters [7, 8]. So far, these studies have been using a TENS

(transcutaneous electrical nerve stimulation) machine for stimulating the tibial nerve at frequencies between 10 to 40 Hz, which can be administered by the patient at home using pre-determined stimulation settings [9]. Using a TENS machine however restricts the mobility of patients during the time that the nerve is being stimulated. Recently, a self-applicating skin-adhering ambulatory device, known as geko™ (Firstkind Limited, Buckinghamshire, UK) (figure. 1) has been developed and has received a CE mark for the prevention of deep vein thrombosis through chronic popliteal fossa stimulation, with no reported safety concerns [10]. This device has recently been piloted in a study exploring outcomes in a cohort of patients reporting faecal incontinence, with promising results [11]. Whether this device has a role in managing urinary incontinence is uncertain, and therefore the aim of this study was to evaluate the safety, acceptability and pilot efficacy of the geko™ device for transcutaneous stimulation of the tibial nerve in patients with OAB.

Materials and methods

Patients

Patients with OAB symptoms attending a tertiary centre teaching hospital who found conservative first-line management options either ineffective or intolerable were enrolled in this randomised open label parallel-arm 12 week pilot trial of once daily versus once weekly 30 minute stimulation of the tibial nerve.

All participants provided written informed consent prior to enrolment. Patient eligibility was based on meeting the criteria for an overactive bladder, defined by the International Continence Society as an average urinary frequency ≥ 8 voids and ≥ 1

urgency episode (with or without incontinence) per 24 hours [12]. Patients with neurological disease reporting OAB symptoms were enrolled if their Expanded Disability Status Scale (EDSS) score was ≤ 6.5. Exclusion criteria included use of botulinum toxin A treatment within the previous year or neuromodulation (TNS or sacral neuromodulation), patients with sensory loss in the gaitor region (cutaneous sensation to nociception was assessed in the lower limb), presence of urinary tract infection or any other documented LUT pathology. Participants on antimuscarinic medications for OAB went through a 2-week run-in washout period during which time medications were discontinued.

Intervention

Patients were assigned to one of two treatment arms using the sealed envelope stratified randomisation service (https://www.sealedenvelope.com/randomisation/internet/). A dedicated member of the study team recruited participants and collected baseline and follow-up data. It was not deemed possible to include a control group as TTNS relies upon supra-sensory threshold stimulation and often a motor response to confirm device placement and effect.

Patients were provided an antiseptic wipe to clean the area and a pad for simple skin exfoliation. They were trained to use the device and attach over the tibial nerve by a self-adhesive gel 1 cm behind the medial malleolus in a vertical position (figure 1). The area of stimulation was up to 5 cm cephalad to the medial malleolus. Patients were asked to apply the device over the same ankle if possible.

The device has default stimulation parameters delivering a constant 27mA current, at a frequency of 1Hz. The pulse width was increased between a range of 7 settings (between 70 and 560μs) and was sequentially increased depending upon the maximum tolerable sensory and best sensory-motor response (toe flexion and fanning, tingling sensation). Patients were encouraged to use the device at home and to carry on with daily activities with no restriction to ambulation, however bathing and driving with the device were discouraged.

Outcome measures

The primary objective of the study was to assess safety and acceptability of the device and this was measured through a customized compliance diary in which entries could be made by patients to record compliance as well as their experiences whilst using the device and any adverse effects. Additionally, a member of the research team made weekly phone calls to ensure patients were applying correctly and achieving adequate sensory-motor responses during stimulations.

Treatment response was assessed using the Global Response Assessment (GRA) at week 12 of treatment, and the International Consultation on Incontinence Questionnaires for the overactive bladder and LUTS-related quality of life (ICIQ-OAB and ICIQ-LUTSqol) at baseline, week 4, 8 and 12. The GRA was based on a similar questionnaire used previously where patients were asked to assess their response to treatment using an ordinal scale of 0 to 3, referring to none, mild, moderate or marked improvement, respectively [1]. Patients reporting moderate or marked improvement were considered to have responded to treatment [1]. The ICIQ-OAB score is a 6-item questionnaire that assesses OAB symptom severity and bother and the ICIQ-LUTSqol score is a 20-item health related quality of life questionnaire.

In both questionnaires, part A assesses symptom severity and part B assesses the accumulative bother to the patient. Higher scores in each suggests worse symptom profiles and negative impact on QoL, respectively. Patients were also asked to complete 3-day bladder diaries to capture the mean 24hour urinary frequency episodes and number of urinary leakage episodes at the four time points.

Statistical analysis

A feasibility sample size of 48 patients was adopted and no formal power calculation was performed as is the convention for pilot studies with no prior data to base a sample size on [13]. All data were presented as means with SDs. Paired student t-tests were used to provide an estimate of within group responses between baseline and 12 weeks.

The study received ethics approvals from the Surrey Borders NRES Committee London (Ref: 12/LO/1613) and the Medicines and Healthcare Products Regulatory Agency (MHRA).

Results

Forty-eight patients met the eligibility criteria (neurogenic OAB (Multiple Sclerosis, MS)) (n=24) and idiopathic OAB (n=24)) and were 1:1 randomised to receive once daily (n=24) or once weekly (n=24) treatment. Participants randomized into the daily and weekly groups were comparable for age, sex, diagnosis and symptom severity. The mean age (range) for the daily and weekly arms were 46.4 (32-73) and 46.9 (20-81) years, female to male patients 18:6 and 20:4, and the number of patients with

incontinence of 20 and 18 in the two respective arms. Thirty-four patients completed 12-weeks of treatment and the reasons for withdrawing are outlined in Figure 2.

Patient compliance and acceptability

Compliance for using the device amongst participants randomized to receive daily treatment was 90.5% (76 out of the 84 daily applications) compared to 100% amongst patients randomized to receive weekly treatment (12 out of the 12 weekly applications). The participants throughout the course of treatment noted no significant concerns and the responses to the satisfaction survey are shown in table 1. Five patients found the electrical stimulation uncomfortable and discontinued treatment (Figure 2). There were no significant safety concerns raised during the 12 weeks course of treatment. One patient developed mild skin redness at the site of stimulation, likely to be due to sensitivity to the adhesive, and was withdrawn from the study (Figure 2).

Changes in OAB symptoms

Eighteen (53%) (daily treatment (n=9), weekly (n=9)) participants reported a moderate or significant improvement in symptoms on the GRA. No differences were noted between responders and non-responders with regards to age, gender, diagnosis, degree of disability (in the neurological group). Sixty-five percent (13/20) of neurological patients with OAB and 36% (5/14) of patients with idiopathic OAB responded to the intervention (Table 2).

Improvements were observed in both ICIQ-OAB and ICIQ-LUTSqol scores between baseline and over the course of 12 weeks treatment in both the weekly and daily arms

(Figure 3). In the daily arm, mean (SD) ICIQ-OAB part A subscores improved between baseline and week 12 from 9.3 (2.5) to 7.5 (3.1), and from 9.1 (1.9) to 5.9 (1.7) in the weekly arm. ICIQ-OAB part B subscores improved from 29.6 (8.1) to 25.6 (9.5) in the daily arm, and from 29.7 (5.9) to 19.1 (8.5) in the weekly arm (Figure 3).

ICIQ-LUTSqol part A subscores improved from 51 (12.8) to 44.2 (13.1) in the daily arm and from 44.9 (9.0) to 35.9 (8.8) in the weekly arm. ICIQ-LUTSqol part B subscores improved from 130.3 (43.7) to 105.5 (57.8) in the daily arm, and from 102.1 (40.1) to 63.9 (42.8) in the weekly arm (Table 3).

Improvements were also noted in the 3-day bladder diary mean. 24 hour urinary frequency improved from 11.5 at baseline to 8.8 at week 12 in the daily arm in both arms combined. And the mean number of leakages reduced from 2.5 to 1.3 at week 12 (Table 3).

Discussion

This study evaluates the feasibility of using a novel ambulatory device (Geko^{TM}) for transcutaneously stimulating the tibial nerve in patients reporting OAB symptoms. Participants largely found the treatment satisfactory, tolerable and convenient to use. Compliance was assessed through the use of a diary which provided a written record of all the stimulation sessions. Patients receiving the treatment every day were

compliant 90% of the time, whereas those receiving weekly treatment were 100% compliant. Being a new indication for the device, patients were contacted on a weekly basis to assess safety, and the device was found to be safe to use over the ankle with no significant adverse events reported. These results are in line with previous studies where the device was used to stimulate the tibial nerve for managing fecal incontinence [11], and over the popliteal fossa for preventing deep venous thrombosis [10].

Several studies have previously demonstrated the efficacy of TTNS for the management of OAB. In an earlier study, Amarenco et al., investigated Transcutaneous Electrical Nerve Stimulation (TENS) for 44 patients with demonstrated detrusor overactivity (DO), showing increased mean cystometric capacity and mean volume at involuntary detrusor contractions during stimulation [7]. Schreiner et al. carried out a placebo controlled, randomized trial of 12 weeks of TTNS versus pelvic floor muscular training alone, to treat idiopathic urgency incontinence demonstrating significant efficacy of TTNS over placebo [14].

Satisfactory compliance was confirmed with the submission of a compliance diary for those patients who completed the therapy. The device was found to be safe as no significant adverse effects were noted, although 5 patients experienced some discomfort with the stimulation. This may be due to the slow frequency of the stimulation which is more noticeable than faster frequency stimulation as used with other devices, and also due to possible recruitment of cutaneous afferent nerves which does not occur with PTNS. Patients rated the device as easy to use and operate, and would recommend the treatment to a friend for use.

Fifty-three percent of our patients completing 12-weeks of treatment reported a moderate to significant improvement using the GRA scale. This is comparable to the improvements seen in a phase 3 multicentric randomized study comparing PTNS treatment with sham stimulation (SUmiT study) where 54.5% of the patients in the treatment arm reported moderate or marked improvements in bladder symptoms using the same GRA scale [1].

The preliminary results of this study seem to suggest a benefit in bladder diary paramters, OAB scores and LUT symptom related quality of life scores, however this exploratory phase 2 study was not designed to evaluate efiacy and therefore conclusions cannot be drawn. The improvements observed in both arms of the study would help inform the design of a properly powered study to evaluate efficacy of this device. Unexpectedly, benefits were observed as early as four weeks into the treatment, however continued to improve at week 8 and at week 12 of treatment. Greater improvements noted in the weekly treatment arm was surprising, and a future study should include in the design an evaluation of different frequencies of treatment sessions.

It appeared in our study that neurological patients more often responded to treatment (65%) compared to patients with idiopathic OAB (36%). There were no significant differences in tolerability between groups. This supports previous observations of the benefits of TNS in patients with neurological disease. Several studies have already demonstrated the efficacy of PTNS in different patient groups with neurological disease [15-20]. De Seze et al performed a multicentric study of 70 patients with MS

reporting symptoms of OAB using a TENS machine which was applied for 20 minutes daily and noted by day 30 significant improvements in urgency and frequency [8]. Likewise, benefits of TTNS have been demonstrated in patients with Parkinson's disease [20].

Our study was limited by the high attrition rate. There were several reasons for patients dropping out including device-related (n=8), perceived lack of improvement in OAB symptoms (n=2) and local discomfort (n==5) where the nerve stimulation was felt to be unpleasant or too intense. Participants were permitted to adjust the strength of stimulation to achieve the balance of a device setting high enough for sufficient sensory-motor response and yet not too high where it may become unpleasant.

There are several advantages of transcutaneous TTNS over PTNS because of the convenience of home-based neuromodulation, without the need for regular outpatient visits. Using a self-contained skin-adhering device such as the device used in this study has the added advantage of permitting ambulation during the treatment, without restricting activity of the patient. As the study lacked a sham arm, a placebo effect could not be entirely excluded, especially considering the early benefits in OAB and quality of life scores noted in patients receiving weekly treatment. Whereas a sham arm may be possible when studying PTNS [1] it is a challenging prospect in a randomized double blinded TTNS study and therefore future studies would need to be designed comparing TTNS against established treatments. Furthermore, a future study should be designed to compare different stimulation parameters such as pulse intensity and frequency, for optimization of stimulation settings [21].

The prospects of a portable, non-intrusive, cost-effective, transcutaneous mode of stimulation delivery has clear advantages and warrants further investigation for this morbid and prevalent condition.

Conclusions

This study demonstrates that the use of a novel non-invasive ambulatory tibial nerve stimulation device was both safe and acceptable for patients with high levels of compliance. Low frequency stimulation of the tibial nerve at 1 Hz was shown, for the first time in a clinical study, to improve storage symptom severity from both quality of life questionnaire and 3-day bladder diary data. Further studies are however required to evaluate the efficacy and optimal treament frequency of transcutaneous TNS using this novel device for the management of OAB.

Acknowlegdements

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Figure One: The geko™ device applied over the ankle behind the medial malleolus

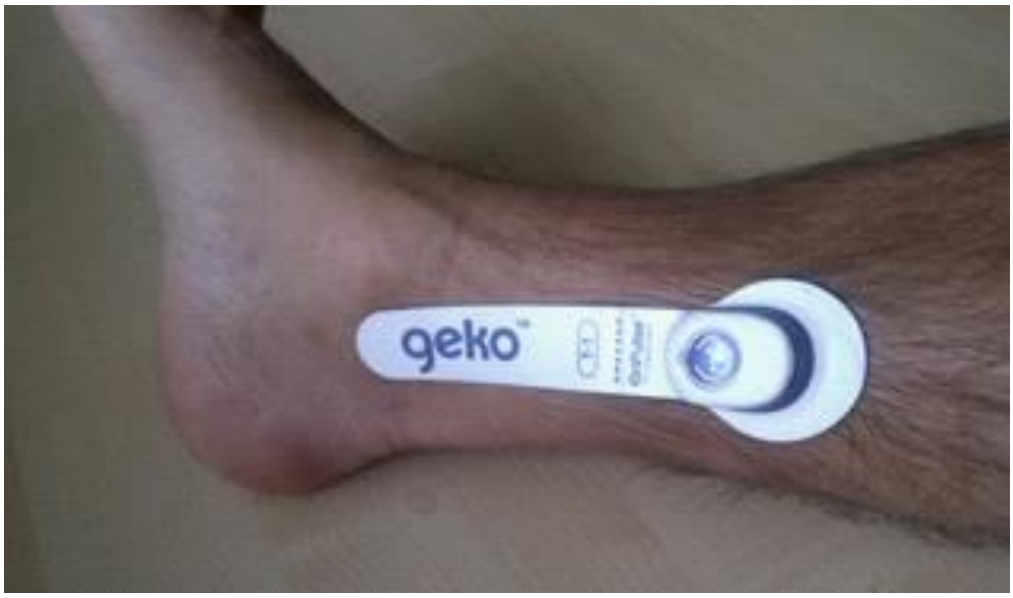


Figure two: Summary flow chart of patients (n=48) participating in the study.

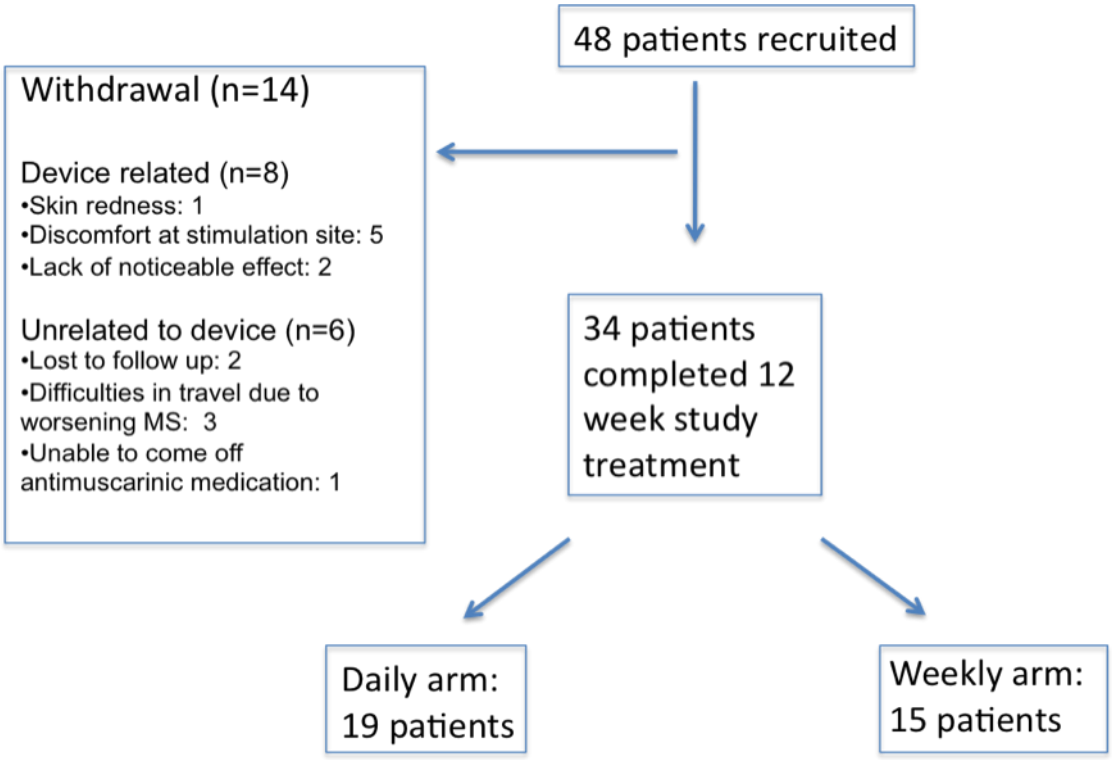
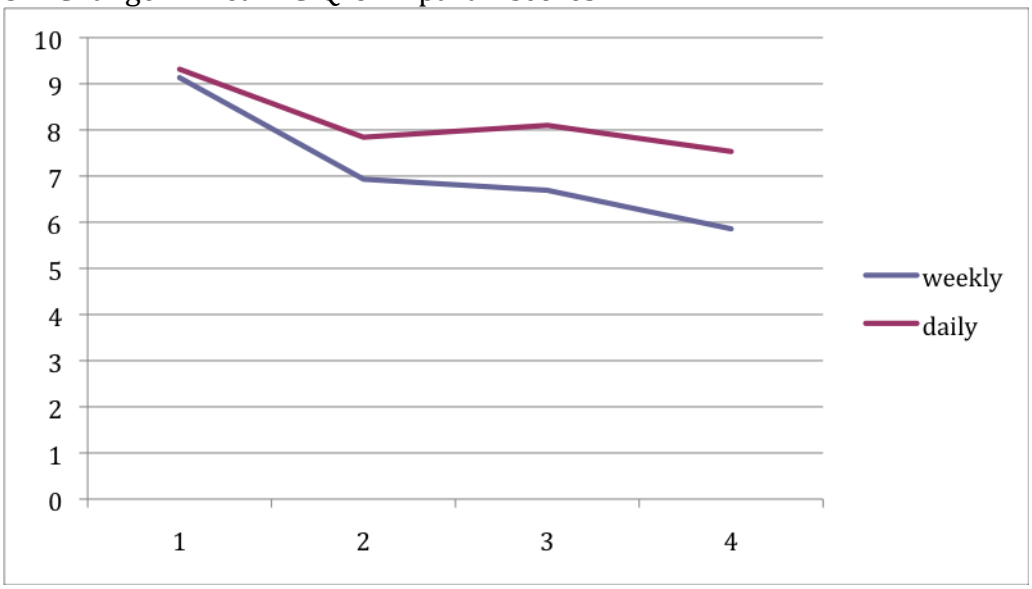


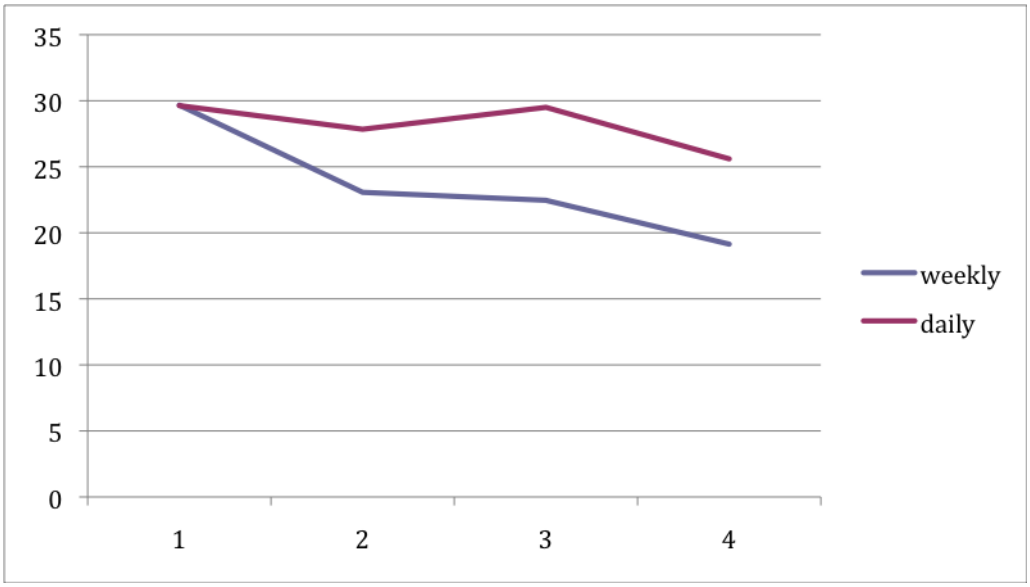
Figure three A and B: Changes in mean ICIQ-OAB scores over the course of 12 weeks in patients receiving weekly and daily treatment

3A: Change in mean ICIQ-OAB part A scores



x-axis: 1: baseline, 2: week-4, 3: week-8, 4:week-12.

3B: Change in mean ICIQ-OAB part B scores



x-axis: 1: baseline, 2: week-4, 3: week-8, 4:week-12.

ICIQ-OAB: International Consultation on Incontinence Questionnaire Overactive Bladder

Table 1: Results of a customised patient satisfaction survey where results were recorded using a Likert scale (score of 1=strongly disagree, 4=neutral, 7=strongly agree) (n=34)

Question	**Mean score**
The device instructions are easy to understand	6.2
The device is easy to attach and remove	6
The device is easy to operate	6
The device is comfortable to use	5.2
I have full mobility when I am wearing the device	5.8
The device improved my symptoms	4.8
Overall I am satisfied with the device	4.8
I would recommend the device to a friend for this use	5.4

Table 2: Demographic characteristics of responders and non-responders of 34 patients completing 12 weeks of transcutaneous tibial nerve stimulation

	Responders (n=18)	**Non-Responders** (n=16)
Mean age (years)	42 (12.6)	48.3 (8.4)
Mean EDSS score (Neurological patients)	4 (2.5-6)	3.7 (2.5-6)
Weekly:daily arm (n)	9:9	6:10
Idiopathic OAB:MS (n)	5:13	9:7

EDSS: Expanded Disability Status Scale
MS: Multiple sclerosis

Table 3: Changes in overactive bladder symptoms, quality of life scores and bladder diary parameters in patients undergoing 12 weeks of transcutaneous tibial nerve stimulation

	Daily and Weekly combined	**Daily treatment (n=19)**	**Weekly treatment (n=15)**
ICIQ-OAB part A score mean (SD)			
Baseline	9.2 (2.2)	9.3 (2.5)	9.1 (1.9)
Week 4	7.1 (2.9)	7.8 (3.2)	6.9 (2.7)
Week 8	7.5 (2.6)	8.1 (2.4)	6.7 (2.9)
Week 12	6.7 (2.5)	7.5 (3.1)	5.9 (1.7)
ICIQ-OAB part B score mean (SD)			
Baseline	29.6 (7.1)	29.6 (8.1)	29.7 (5.9)
Week 4	25.8 (8.9)	27.8 (9.7)	23.1 (7.6)
Week 8	25.7 (9.4)	29.5 (7.6)	22.5 (10.1)
Week 12	22.5 (9.3)	25.6 (9.5)	19.1 (8.5)
ICIQ-LUTSqol part A score mean (SD)			
Baseline	48.4 (11.0)	51 (12.8)	44.9 (9.0)
Week 4	44.2 (13.0)	46.7 (15.8)	40.8 (8.4)
Week 8	42 (12.7)	46.4 (16.3)	38.3 (8.4)
Week 12	40.5 (10.6)	44.2 (13.1)	35.9 (8.8)
ICIQ-			

LUTSqol part B score mean (SD)			
Baseline	113.7 (45.4)	130.3 (43.7)	102.1 (40.1)
Week 4	99.3 (51.1)	111.6 (59.4)	85.6 (38.0)
Week 8	95.6 (51.7)	114.7 (60.1)	79.3 (41.6)
Week 12	84.7 (53.1)	105.5 (57.8)	63.9 (42.8)
Bladder diary mean 24HR frequency episodes			
Baseline	11.5	10.8	12.2
Week 4	10.3	10.2	10.4
Week 8	10.8	10.2	11.7
Week 12	89.8	8.210	9.5
Bladder diary mean 24HR number of leakages			
Baseline	2.5	2.8	2.3
Week 4	1.6	1.8	1.4
Week 8	1.9	1.8	2.1
Week 12	1.3	1.6	0.9

ICIQ-OAB: International Consultation on Incontinence Questionnaire Overactive Bladder questionnaire

ICIQ-LUTSqol: International Consultation on Incontinence Questionnaire Lower urinary tract symptoms quality of life questionnaire

SD: standard deviation