



Tibial nerve stimulation in the treatment of overactive bladder syndrome: technical features of latest applications

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Purpose of review

Overactive bladder syndrome (OAB) is a chronic condition, which can be treated by tibial nerve stimulation. The present review will focus on the technical aspects, advantages, drawbacks, and limitations of the latest available applications of posterior tibial nerve stimulation.

Recent findings

We describe the technical aspects of recent developed implants and techniques of tibial nerve stimulation in a transcutaneous, percutaneous, and minimal invasive way. All different treatment options have advantages and disadvantages based on type of surgery, energy transfer, impedance, treatment setting options, risk of migration, and patient usability, which are described in this review. Only devices with data that are publicly available were included.

Summary

New technologies are on their way in the field of tibial nerve stimulation for the treatment of OAB. Technical aspects are important to demonstrate safety and efficacy and user friendliness in order to obtain high acceptance of the various devices.

Keywords

implant, neuromodulation, overactive bladder syndrome, tibial nerve stimulation, urge incontinence

INTRODUCTION

Overactive bladder syndrome (OAB) is a chronic condition, which has for patients a large social burden. It is a problem which affects the quality of life of patients significantly and comes with large financial costs for patients and our healthcare system [1,2]. According to the ICS terminology, patients with OAB have urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology [3].

OAB can be treated by tibial nerve stimulation. Acupuncture is perhaps the oldest form of neuromodulation since the practice of stimulating energy streams comes very close to genuine tibial nerve stimulation [4,5]. This technique was introduced more than 2000 years ago in Chinese medicine [5]. Wilhelmus Ten Rhyne was the first physician who published about this way of treatment in his 'Dissertatio de Arthritide: Mantissa Schematica: De Acupunctura: Et orationes tres'. During this treatment with fine needles on certain preestablished points, one tries to restore the 'energetic harmony'

by stimulating the Sanyinjiao point (SP-6) [6]. In case of tibial nerve stimulation, the tibial nerve is stimulated most likely at exactly the same spot as SP-6. It is likely that with electro-acupuncture, the same physiological effects are obtained as with posterior tibial nerve stimulation [7].

The present review will focus on the technical aspects, advantages, drawbacks, and limitations of the latest available applications of posterior tibial nerve stimulation. We will investigate the ideal form

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Curr Opin Urol 2020, 30:513–518

DOI:10.1097/MOU.0000000000000781

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KEY POINTS

- We investigated the ideal form of tibial nerve stimulation based on latest applications.
- Almost all new developments focus on small, battery-free devices, which are easy to operate and can be positioned in the least invasive or noninvasive ways.
- Bluewind RENOVA system and the Stimguard are close to an ideal implant based on advantages and disadvantages.
- Treatment of OAB with new technologies in the field of tibial nerve stimulation still need safety and efficacy data on the long-term.

of tibial nerve stimulation based on latest applications. The ideal form of tibial nerve stimulation is in our opinion home-based treatment and easy to operate for the patient. An implant, from our point of view should be easy to implant and should have an external energy source. Preferable, the implant has a long lifespan without surgical re-interventions, no leads and a minimal chance of migration. Moreover, there should be no interference with other diagnostics or treatments and accessible in terms of costs of the treatment.

PERCUTANEOUS TIBIAL NERVE STIMULATION

Since the introduction of percutaneous tibial nerve stimulation (PTNS) in 1999, a lot of studies evaluated the efficacy and therapeutic outcomes of PTNS in the treatment of OAB. During the past years, the way of performing the treatment has not been changed. Pulse width and frequency are fixed, respectively at 200 μ s and 20 Hz. However, pulse intensity can be changed during treatment up to 9 mA [8].

Most studies are performed by using the Urgent PC system. However recently Kobashi *et al.* published their data about a new minimally invasive option using the NURO system (Medtronic, Minneapolis, MN). In their single-arm study they investigated the efficacy of percutaneous tibial neuromodulation (PTNM) after 12 weekly sessions (30 min) [9[¶]]. They included 121 patients in their study (mean age 64.8), 116 patients completed all 12 sessions. Urge urinary incontinence (UUI) episodes decreased significantly with 2.4 after 12 sessions. A UUI responder rate (defined as >50% reduction in UUI episodes comparing to baseline) of 77.6% was shown and a complete continence rate of 39.7%. There were no serious adverse events noted. Adverse events mentioned were mainly device site pain (3.3%, 4/121) and pain in the extremity (3.3%, 4/

121) [9[¶]]. Parameter settings were not included in the published data.

Similar to the Urgent-PC, the NURO system still holds the main disadvantage of the time investment for the patients. First, patients have to undergo 12 weekly treatments, followed by maintenance treatments depending on their clinical symptoms. Typically, maintenance PTNS is performed once a month in the hospital, as PTNS cannot be done by patients in their own environment [10]. Another objection for patients could be the 'needle' in the ankle during every treatment.

However, recent research from Cardozo *et al.* describes patient's preferences in the treatment of refractory overactive bladder. In their study they found that 98% of their study population ($N=127$) was willing to try PTNS and that in 57% PTNS was the most preferred therapeutic option after oral medication, compared to 34% for sacral neuromodulation and 9% for Botulin toxin injection [11].

TRANSCUTANEOUS TIBIAL NERVE STIMULATION

GEKO

The GEKO (Firstkind Limited, Buckinghamshire, UK) was introduced as a self-applicating skin-adhering ambulatory device. The tibial nerve is transcutaneous stimulated like with TENS however the GEKO is self-applicating which increases the mobility of patients during treatment comparing to other TENS systems. It was originally developed for the prevention of deep vein thrombosis [12,13]. Recently fecal incontinence and OAB have been studied in a pilot trial exploring outcomes [14^{¶¶}]. In this open label OAB study, patients were randomized between once daily or once weekly treatment sessions of 30 min. The area of stimulation was 5 cm cephalad to the medial malleolus. The parameters during treatment were set at an amplitude of 27 mA and a frequency of 1 Hz. The pulse width was increased between 70 and 560 μ s (seven settings) [14^{¶¶}].

Seth *et al.* reported a responders rate of 53% based on global response assessment (GRA) and International Consultations on Incontinence Questionnaires (ICIQ-OAB and ICIQ-LUTS). In their 3-day voiding diary outcomes, they did not show any significant difference between their groups (weekly treatment vs. daily). Number of leakages in their combined group decreased to 1.3/24 h after 12 weeks of treatment versus 2.5/24 h at baseline.

The advantage of the system is the noninvasive nature and high rates of patient satisfaction in usability terms [14^{¶¶}]. Disadvantages of this modality may be the fixed parameter settings and the loss

of efficacy because of higher impedance of the skin. In addition, patients have to attach the device by themselves which can lead to suboptimal positioning and less effective treatment.

Further investigation of this system's efficacy in the field of OAB is warranted to compare the GEKO system to other published treatment modalities and controls.

TIBIAL NERVE IMPLANTS FOR TREATMENT OF OVERACTIVE BLADDER SYNDROME

Bluewind RENOVA system

The Bluewind RENOVA system is a wireless battery-free tibial nerve stimulation system. The system consists of three components: implant, external control unit (ECU), and clinician programmer. Patients are provided with the stimulator, a 25 mm implant with small fixating wings to prevent migration of the implant. The implant is fixated near the tibial nerve, in an open surgical procedure under local anesthesia. Following recovery, the clinician programmer is used to program the ECU for treatment. Patient-specific treatment set-up can be selected by the clinician based on motor and/or sensory response to optimize therapeutic outcome. Treatment set-up can be set with a pulse width of between 50 and 800 ms, a frequency of up to 40 Hz, and an amplitude range of 0 to 9 mA. Patients wear the ECU only during treatment sessions. The ECU provides the implant with the energy needed (closed-loop system) for treatment and allows the patient to adjust the amplitude in a range between the minimum and maximum tolerable level set by the clinician [15¹¹,16].

In a first study, a response rate of 71% during 6 months follow up (FU) period was described. One procedure related serious adverse event occurred that lead to explantation of the device. Recently, 3-year results were published. Seventy-five percentage of the patients who continued in an extended study were still responders after 36-months post-system activation [17].

Advantage of the Bluewind RENOVA system is the closed loop system. As far as we know it is the only system which uses a closed-loop which ensures the transferred energy from ECU to implant is stable during treatment sessions. Another advantage of the system is a decreased risk of migrations is less because of the suture holes near the implant and its size.

Disadvantage of the system is the open surgery procedure. Compared to other percutaneous or injectable implants the open procedure, although minimally invasive, is more invasive than its counterparts.

Bioness Stimrouter

The Bioness Stimrouter neuromodulation system was initially intended for use in chronic pain patients. This device can be easily implanted under local anesthesia near the desired peripheral nerve [18,19]. The Bioness Stimrouter consists of a specially crafted lead that is transcutaneous powered by an external pulse transmitter (EPG). The implanted lead contains a receiver, electrodes and anchoring system [19]. During implantation ultrasound or fluoroscopic imaging may be used to assist lead placement of the stimulation probe which is used to perform a test stimulation in order to insure correct targeting of the peripheral nerve. After placement confirmation, the introducer set is placed over the stimulation probe and the probe is replaced with the stimulation lead. Finally, the proximal end of the lead is buried subcutaneously 2 cm from to the desired site of the EPG [18,20].

Patients wear the EPG on the skin during stimulation of the tibial nerve. A patient programmer can be used to change parameter settings and tracks usage [19]. Parameters which were used during the chronic pain study varied with phase duration 7–500 μ s, pulse rate 1–200 Hz and treatment time 10 min up to 12 h [18]. During the chronic pain study no device related SAE were found, however five patients had the device explanted because of dissatisfaction with the efficacy, one because of development of chronic dermatitis/sensitivity to the electrode patch, and one lead rejection [18].

Advantage of the Stimrouter is the minimally invasive surgery to implant the lead designed with anchors to prevent migration. Patients do have only two small incisions in their lower leg. Another advantage of this system is the possibility to add up to eight different treatment/stimulation programs in the patient programmer. Because of this the treatment is patient specific and based on patient's preferences.

Disadvantage of the system is the loss of energy because of the use of surface electrodes for energy transfer. The lead simply transfers the energy from the superficial end (close to EPT) to the electrodes, passively. Therefore, it is likely that the optimal amplitude will have a 5–10 times higher value in daily practice comparing to test stimulation during implantation.

At present, no studies of this neuromodulation system have been published in the field of OAB. A prospective, multicenter, randomized, double-blinded study is ongoing.

eCoin

One of the new implantable neuromodulation devices is the eCoin (Valencia Technologies Corp., Valencia, California). The implantation of the eCoin

is a minimal invasive open procedure, whereby a leadless and battery powered device is implanted under local anesthesia to the medial aspect of the lower leg. The device is nickel sized in a 23 mm titanium case (diameter), thickness 2.4 mm.

After implantation, the device provides automatically 30-min treatment sessions every 2 days for 12 weeks. Afterwards, the intensity of treatment is lowered to every 15 days. There is no action from the patient necessary to start a treatment session, the device starts the treatment automatically. During the treatment sessions patients can adjust the amplitude from 0.5 to 15 mA with an external controller. Other parameters are fixed: 0.2 ms pulse width and 20 pulses per second [21¹¹]. Recently first 6 months results (N=46) were published by MacDiarmid *et al.* During 6 months FU, 67% of the patients were defined as responders based on their 3-day voiding diary. Eleven of these patients reported during the 6 months FU that they did not experience any UUI episodes anymore. Patients reported an improvement of three folds of the minimal important

difference base on the I-QOL and PGI-I at baseline and 6 months FU [21¹¹]. Regarding safety issues, Macdiarmid *et al.* reported two cases of explantation of the device. One patient wished to undergo explantation following cellulitis and the second because the patient noted device migration 1 cm posterior which led to lack of stimulation [21¹¹].

Advantage of this device is the relative short and easy implantation procedure compared to SNM or other devices. The battery powered system could be an advantage because it does not need patient involvement to be powered, which theoretically means 100% compliance. On the other hand, battery powered means it has to be replaced, which requires additional surgeries for patients – much like sacral neuromodulators, only more frequently because of the small size of the battery.

A disadvantage of the system is the fixed treatment session. Patients cannot increase the number of treatment sessions based on their own preferences/worsening of symptoms. The treatment session starts automatically (during maintenance treatment) every

Table 1. Summary of technical aspects new implantable tibial nerve stimulators

	GEKO [14¹²]	Stimrouter [18,19]	eCoin [21¹¹]	Bluewind RENOVA [15¹³,16]	Stimguard [22,23,24]
Size	15 cm	15 cm	2.3 cm	2.5 cm	12 cm
Duration of stimulation	Daily or weekly	Up to 12 h/day	30 min/2–15 days,	30 min t.i.d.	8 h/day
Pulse width (μs)	70–560	7–500		50–800	50–500
Pulse amplitude (mA)	27		0.5–15	0–9	0–15
Pulse rate (Hz)	1	1–200		0–40	2–1500
External component	TENS – External pulse generator with adhesive surface electrodes	Adhesive external pulse transmitter Patient programmer	No external component.	Wearable unit with leg band	External device in a sleeve at the ankle
Energy transfer	Transcutaneous	Electrical field through surface electrodes.	Battery powered.	Magnetic resonance 6.78 MHz ISM band Closed-loop	Magnetic resonance 915 MHz ISM band Open-loop
Advantage	1. No surgery	1. Eight treatment programs 2. Computerized feedback on use 3. No implanted battery	1. Operates automatically 2. Leadless	1. Tailored settings 2. No migration 3. Computerized feedback on use 4. Leadless 5. No implanted battery	1. Treatment overnight 2. Tailored settings 3. No implanted battery
Disadvantage	1. Fixed amplitude and frequency 2. High impedance 3. No computerized feedback	1. Loss of energy because of use of surface gel pads 2. Long lead requiring tunneling	1. Nonrechargeable battery 2. Fixed stimulation parameters 3. Requires replacement surgeries 4. No computerized feedback on use	1. Open-procedure	1. No anchoring system 2. Long lead requiring tunneling

15 days, which could also be during a moment the patient is not in the position to undergo treatment. Another disadvantage is the possibility of migration, which could lead to decreased stimulation of the tibial nerve. This could be as well a challenge for the future. However long-term results are necessary to confirm efficacy and safety.

Stimguard

Another implantable device is the minimally invasive chronic device of StimGuard LLC. Patients receive an implanted stimulator with embedded receiver through a 5 mm skin incision. The energy source is a small, external, rechargeable transmitter, which is worn by the patient. The external energy source is connected to an external antennae and is worn near the internal antenna of the implant [22]. The system uses an open-loop system which implies the energy which is given from the wearable to the electrode is stable but not secondarily monitored by the external unit [23]. Patients are asked to use the implant during the night, with a maximum treatment durability of 8 h [24].

First published results were obtained from two groups of patients. Group 1 (2014) consisted of two male patients with neurogenic lower urinary tract dysfunction. The second group (2016) consisted of one male patient with spina bifida and five female patients with OAB. Both patients of the first group were completely dry 2 months postoperation. However, both of them quitted because of deterioration of their comorbidity. In one of the patients, the electrode migrated. In the second group ($N = 6$), five patients reported improvement, UUI episodes decreased from 2.1/day at baseline to 2.5/month at 3 months postoperation. One male patient was a nonresponder and as result, was excluded because of lack of improvement [24].

The main benefit of this device is the possibility for patients to have their treatment overnight. However, migration could be a major problem, as noted in this small-scale reporting. Momentarily a study comparing StimGuard CAN-stim versus Medtronic Interstim is conducted.

CONCLUSION

In conclusion, new technologies are on their way in the field of tibial nerve stimulation for the treatment of OAB. Table 1 summarizes all devices with their technical specifications, advantages and disadvantages. The new developments focus on small, battery free devices that are easy to operate and can be positioned in the least invasive or noninvasive ways. The activation software should be flexible in fine-

tuning and should also be able to give feedback on the use and optimization of the stimulation specifications. Based on our idea of ideal tibial nerve stimulation, we can conclude the ideal implant is not yet found. However, close to ideal based on advantages and disadvantages of the implant are the Bluewind RENOVA system and the Stimguard. Demonstration of the safety and efficacy on the long-term and in larger scale trials is needed to confirm our conclusion; and the benefit of computerized feedback and the possibility to have multiple changeable treatment programs.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

All authors are participating in the OASIS-trial, regarding the RENOVA implantable stimulation device for Tibial Nerve Stimulation.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Irwin DE, Abrams P, Milsom I, *et al.* Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol* 2006; 50:1306–1314discussion 1314-5.
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. Haylen BT, de Ridder D, Freeman RM, *et al.* An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol J* 2010; 21:5–26.
4. Wazir J, Ullah R, Li S, *et al.* Efficacy of acupuncture in the treatment of chronic prostatitis-chronic pelvic pain syndrome: a review of the literature. *Int Urol Nephrol* 2019; 51:2093–2106.
5. White A, Ernst E. A brief history of acupuncture. *Rheumatology* 2004; 43:662–663.
6. Langevin HM, Yandow JA. Relationship of acupuncture points and meridians to connective tissue planes. *Anat Rec* 2002; 269:257–265.
7. Minni B, Capozza N, Creti G, *et al.* Bladder instability and enuresis treated by acupuncture and electro-therapeutics: early urodynamic observations. *Acupunct Electrother Res* 1990; 15:19–25.
8. van Balken MR. Percutaneous tibial nerve stimulation: the Urgent PC device. *Expert Rev Med Devices* 2007; 4:693–698.
9. Kobashi K, Nitti V, Margolis E, *et al.* A prospective study to evaluate efficacy using the nuro percutaneous tibial neuromodulation system in drug-naive patients with overactive bladder syndrome. *Urology* 2019; 131:77–82.
10. 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.
11. Hashim H, Beusterien K, Bridges JF, *et al.* Patient preferences for treating refractory overactive bladder in the UK. *Int Urol Nephrol* 2015; 47:1619–1627.
12. Tucker A, Maass A, Bain D, *et al.* Augmentation of venous, arterial and microvascular blood supply in the leg by isometric neuromuscular stimulation via the peroneal nerve. *Int J Angiol* 2010; 19:e31–e37.
13. Summers JA, Clinch J, Radhakrishnan M, *et al.* The geko™ electro-stimulation device for venous thromboembolism prophylaxis: a NICE medical technology guidance. *Appl Health Econ Health Policy* 2015; 13:135–147.

14. Seth JH, Gonzales G, Haslam C, *et al.* Feasibility of using a novel noninvasive ambulatory tibial nerve stimulation device for the home-based treatment of overactive bladder symptoms. *Transl Androl Urol* 2018; 7:912–919.
- First open label OAB study using transcutaneous GEKO system
15. Heesakkers J, Digesu GA, *et al.* A novel leadless, miniature implantable Tibial Nerve Neuromodulation System for the management of overactive bladder complaints. *NeuroUrol Urodyn* 2018; 37:1060–1067.
- Six-month results showing efficacy and safety of the Bluewind RENOVA system.
16. 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: 205–210.
17. Te Dorsthorst M, Digesu GA, Taylor 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; 101097ju0000000000001024.
18. Deer T, Pope J, Benyamin R, *et al.* Prospective, multicenter, randomized, double-blinded, partial crossover study to assess the safety and efficacy of the novel neuromodulation system in the treatment of patients with chronic pain of peripheral nerve origin. *Neuromodulation* 2016; 19:91–100.
19. Guzman-Negron JM, Goldman HB. New devices and technologies for the management of overactive bladder. *Curr Urol Rep* 2017; 18:94.
20. Deer TR, Pope JE, Kaplan M. A novel method of neurostimulation of the peripheral nervous system: the StimRouter implantable device. *Techn Regional Anesth Pain Manag* 2012; 16:113–117.
21. 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; 201:967–972.
- Six-month results of the eCOIN system regarding efficacy and safety.
22. Karl-Dietrich Sievert TK, Stefan DeWachter. Novel chronic tibial neuromodulation treatment option for overactive bladder significantly improves urgency/urge urinary incontinence and normalises sleep patterns: initial results. *EMJ* 2017; 5:58–60.
23. StimGuard Medical Corporation. <https://www.stimguard.com/index.html>, 2019.
24. 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. *Eur Urol* 2017; 16:e994.