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REVIEW

New Implantable Tibial Nerve Stimulation Devices: Review of Published Clinical Results in Comparison to Established Neuromodulation Devices

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Purpose: The purpose of this review is to offer an update for medical providers practicing general urology and urogynecology in evolving and new promising technologies for neuromodulation in patients with OAB.

Patients and Methods: A focused literature search for the years 2015 through 2019 was conducted on PubMed/Medline for the terms: "new techniques" AND "neuromodulation" AND "tibial nerve stimulation" AND "overactive bladder". We limited our search to publications in English, for the last five years and with patient follow-up of at least 3 months.

Results: Clinical success, safety based on adverse events, and quality of life improvement criteria were evaluated and compared to sacral nerve stimulation (SNS) devices and older, non-implantable percutaneous tibial nerve stimulation (PTNS) treatment devices. Considering the limited number of participants with up to 6 months follow-up data currently available, overall the clinical response rates suggest that the new implantable devices stimulating the tibial nerve have a promising clinical outlook, are less invasive upon implantation than SNS, less expensive, and less of a burden on patients compared to the older non-implantable PTNS devices.

Conclusion: Practicing urologists should be aware of this new treatment option when counseling their patients regarding treatment for OAB.

Keywords: overactive bladder, urgency, incontinence, frequency

Introduction

Patients with overactive bladder (OAB) symptoms complain about debilitating urgency and frequency with or without urinary incontinence, often associated with nocturia but in the absence of urinary tract infection or other obvious pathological conditions. OAB is highly prevalent in women, decreases quality of life, and affects millions of people worldwide.[1] Although therapeutic advances for OAB have been accomplished over the recent decades, the pathophysiology of this syndrome still remains not well understood and presents a significant management challenge for medical providers.[2] A range of therapeutic options is now available for clinicians managing these patients. After failing conservative treatment alternatives such as behavioral modification and pharmaceutical management, sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS) are well-established third-line treatment options: SNS received FDA approval in 1997 and PTNS in 2005.[3,4] Both techniques, SNS and PTNS, have not seen any significant improvement of the devices over the last decade or since FDA approval.

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PTNS is a low-risk, non-surgical treatment option. A needle electrode is placed near the tibial nerve at the ankle of the foot. A stimulator device is connected to the electrode and sends mild electrical pulses to the tibial nerve (Figure 1). These impulses travel to the sacral nerve plexus including S2-S4 containing the efferent and afferent nerve fibers serving the bladder and responsible for bladder function. It is our current understanding that by stimulating these nerves through gentle electrical impulses (neuromodulation), pathological detrusor overactivity can be beneficially modified.[3] Based on clinical experience this improvement happens gradually, and patients usually receive a series of 12-weekly treatment sessions, 30 mins each. In responding patients regular further sessions are needed to sustain symptom improvement thereafter.[4]

The purpose of this review is to offer an update for medical providers practicing general urology and urogynecology in evolving and new promising technologies for neuromodulation in patients with OAB.

Materials and Methods

A focused literature search for the years 2015 through 2019 was conducted on PubMed/Medline for the terms: "new techniques" AND "neuromodulation" AND "tibial nerve stimulation" AND "overactive bladder". We limited our search to publications in English, for the last five years and with patient follow-up of at least 3 months.

Results

The results of the literature search are listed in Tables 1, 2 and 3. Our review revealed two emerging technologies in the field of implantable neuromodulation. These new two implantable devices are the BlueWind RENOVA^{TM} (BlueWind Medical, Herzliya, Israel) and eCoin^{TM} (Valencia, California, USA). BlueWind RENOVA^{TM} is a small cylinder-shaped implantable device measuring 25 mm with a diameter of 3.4 mm. This small device is implanted adjacent to the distal peripheral tibial nerve above the ankle. The implantation is performed in the office under local, or general anesthesia in the operating room per surgeon's discretion. This cylinder acts as an electrical receiver (antenna) powered by an outside cuff (Figure 2). The electric stimulation controlled by the outside cuff generator can be modified with a pulse width between 50 and 800 microseconds, frequency of 5, 10, 20 and 40 Hz, and an amplitude in the range of 0–9 mA. Patients can adjust the amplitude only between a patient-specific minimum and maximum safety range.

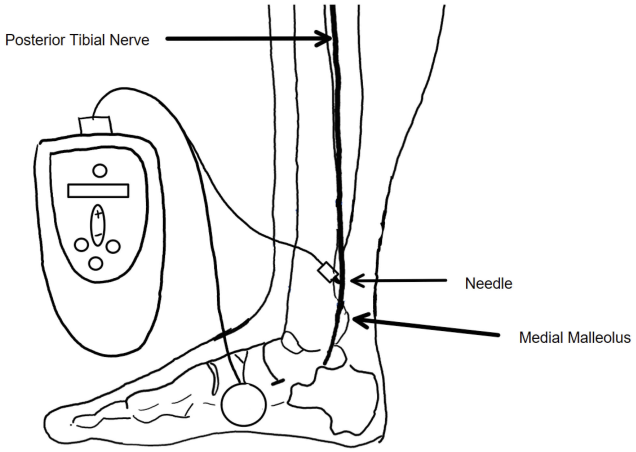

Figure 1 Percutaneous Tibial Nerve Stimulation (PTNS).

A clinical study of 15 patients using the BlueWind RENOVA^{TM} device was performed in the Netherlands, the results were reported in 2017.[5] Study inclusion criteria were: a) adult patients between 18 and 80 years of age with OAB symptoms with or without urinary urgency incontinence, b) medication-refractory urinary frequency and/or urinary urgency incontinence, c) no clinical evidence for neurological deficits, d) no previous botulinum toxin injections within the last 6 months, e) no kind of nerve stimulation therapy for OAB except for successful PTNS. The main exclusion criteria were: a) pelvic pain disorder, b) any kind of neuropathy diagnosis, c) current urinary tract infection and d) uncontrolled diabetes mellitus.

Thirteen females and two males were enrolled in this study (Table 1). Mean age was 54 years, 5 of the 15 patients were previously treated with PTNS and 12 patients experienced urgency urinary incontinence prior to the study. The implant procedure was done under general anesthesia, median skin to skin operation time was around 30 mins. Postoperatively 3 patients received extended antibiotic treatment for 1 week and 3 patients received prolonged pain medication for 1 week. One patient had the implant explanted due to pain and swelling suspicious for infection. Of the 14 patients, 13 demonstrated greater than 50% improvement in the number of severe urinary incontinence episodes, 2 of the 11 patients were completely dry at 3-month follow-up. Eight of the 14 patients demonstrated greater than 50% improvement in the bother score. Statistical analysis was done by the Wilcoxon signed-rank test where $p<0.05$ was considered significant.

Table 1 Study Results for OAB Treatment with BlueWind RENOVA™

Criteria	Baseline n=15	Results After 3 Months n=14	p-Value Compared to Baseline[c]	Number of Patients with >50% Improvement of Symptoms
Number of Voids	11.8±3.5	8.1±2.0 (31.4%)[b]	0.002	8/14 (57%)
Mean Micturition Vol (mL)	158.5±58.7	176.5±59.2 (11.4%)[b]	0.041	–
Severe Urinary Urgency[a]	6.5±5.1	2.0±2.1 (69.2%)[b]	0.003	13/14 (93%)
Urinary Incontinence[a]	7.2±5.0	3.72±3.7 (48.3%)[b]	0.091	4/11 (36%)
Severe Incontinence[a]	2.8±5.2	0.3±0.4 (89.3%)[b]	0.017	5/7 (71%)
Mean Urine Loss (g)	243.1±388.2	38.9±55.4 (84%)[b]	0.038	5/9 (56%)
ICIQ-FLUTS[d]	18.9±6.9	12.3±5.5 (34.9%)[b]	0.001	4/14 (29%)
UDI[e]	112.5±43.6	64.4±48.3 (42.8%)[b]	0.004	5/14 (36%)
PPBC[f]	5.0±1.1	3.7±1.3 (26%)[b]	0.002	3/14 (21%)

Notes: [a]Assessed by number of episodes/day. [b]Percent of improvement from baseline in respective criteria. [c]Statistical analysis performed with Wilcoxon sign ranked test. [d]ICIQ-FLUTS consists of 12 questions on bladder filling, voiding, and incontinence. [e]UDI is a 19-question survey on symptoms associated with lower urinary tract dysfunction, obstructive/discomfort symptoms, irritative symptoms and stress symptoms. [f]PPBC is a global measure for patients with OAB. Data from van Breda et al.[5]

Another study published in 2018 also evaluated the BlueWind RENOVA™ implant device at four clinical sites, 2 in the United Kingdom and 2 in the Netherlands.[6] Inclusion criteria were adult patients between 18 and 80 years of age with OAB symptoms, urinary frequency and/or urinary urgency leaks, and who had failed at least 6 months of conservative treatment and experienced no neurological deficits. The exclusion criteria were essentially the same as in the above-mentioned study from 2017.

The study population consisted of 5 men and 31 women. Overall 36 patients were implanted with BlueWind RENOVA™ but one withdrew, and another was excluded due to serious adverse effects. Mean age was 54.1 years, 15 patients had successful PTNS treatment before entering the study, 29 patients suffered from urge incontinence, and 30 suffered from urgency and frequency. The implant procedure was done under local or general anesthesia upon surgeon's discretion. Only one patient experienced procedure-related adverse effects while 17 patients experienced adverse events during the study mainly related to implant site pain or suspected infection which all resolved within 1–2 weeks with antibiotics. After a 6-month follow up, 25 (70.6%) patients demonstrated clinical success of their OAB symptoms (Table 2). Patients suffering from urgency and frequency had a significant decrease in average number of voids per day and increase in voided volume. Those with urge incontinence also had a decrease in number of leaks and severity (Table 2). Statistical significance was determined by a paired *t*-test where $p \leq 0.05$ was considered statistically significant.

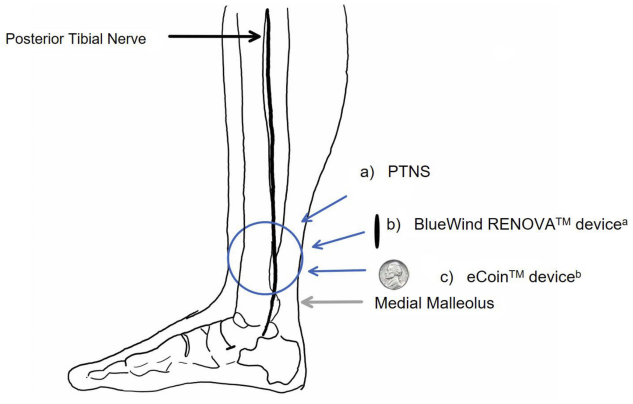

Figure 2 Anatomy of the posterior tibial nerve and a) positioning of the PTNS needle; b) the BlueWind RENOVA™ device; c) the eCoin™ device.
Notes: b)For details see http://www.bluewindmedical.com/bluewind-renova; c) For details see http://valenciatechnologies.com/.

eCoin™ is the other device stimulating the tibial nerve which is fully implanted, leadless, nickel sized with an intrinsic/inside battery (Figure 2). The implant procedure is done in the office under local anesthesia and takes about 20–30 mins. This device does not require any outside electric power source as needed for the BlueWind™ implant. An external controller modifies the stimulation pulse amplitude in a range of 0.5 to 15 mA, using the highest comfortable level for the patient. The implant automatically provides 30 mins stimulation sessions every 2 days for 12 weeks and every 15 days thereafter. Amplitude can be adjusted between sessions.

An open-label clinical feasibility trial was published in 2019.[7] This clinical study was performed at 7 sites in the United States and New Zealand, 46 patients participated, 45 patients were female (98%). The mean age of the participants was 63 years; the inclusion and exclusion criteria were similar and comparable with the BlueWind RENOVA™ device. For one participant the device was explanted prior to treatment initiation due to an adverse event unrelated to the device (formation of 1 cm posterior migration thought to be caused by vigorous bicycling

Table 2 Study Results for OAB Treatment with BlueWind RENOVA™

Criteria	Baseline n=34	Results After 6 Months n=34	p-Value Compared to Baseline[c]	Number of Patients (n=34) with >50% Improvement of Symptoms
UF voids[a]	12±0.5	9.4±0.5 (21.7%)[b]	<0.05	–
UF voided volume (mL)	161.7±12.3	179.3±15.1(10.9%)[b]	<0.05	–
UF urgency[a]	7.5±0.8	3.8±0.7 (49.3%)[b]	<0.05	–
UF Clinical Success	–	–	<0.01	23(66.7%)
UI leaks[a]	6.6±0.8	3.9±0.7 (40.9%)[b]	<0.05	–
UI leak severity	1.8±0.1	1.4±0.1 (22.2%)[b]	<0.0.5	–
UI Clinical Success	–	–	<0.001	25 (70.6%)
HRQL	All subscales > suggested MID of 10 points	–	<0.0001	–

Notes: [a]Assessed by number of episodes/day. [b]Percent of improvement from baseline in respective criteria. [c]Statistical analysis performed with paired *t*-test. Data from Heesakkers et al.[6]
Abbreviations: UF, urinary frequency; UI, urinary incontinence; HRQL, health related QoL questions and symptoms severity scores; MID, minimally important difference.

resulting in no benefit from the device). Data on 3 participants were incomplete. This study reported 3-month and 6-month follow-up results which are summarized in Table 3. The eCoin™ investigational device was safe and resulted in reproducible reduction of urinary incontinence episodes in 32 (69.6%) of participants after 3 months. Ten (21.7%) participants were dry with no urgency urinary incontinence episodes and the response was durable to at least 6 months. Patient reported outcomes were consistent with objective findings. Statistical analysis was done using the Wilcoxon signed rank test and the R software (R 3.2, The R Foundation for statistical Computing) was used for descriptive statistics.

Discussion

Millions of people worldwide, in particular women, suffer from overactive bladder (OAB) symptoms significantly affecting their quality of life.[8] Although therapeutic advances for OAB have been accomplished over the last decades, the pathophysiology of this syndrome still remains not well understood and the clinical management is often a challenge for medical providers.[2] A range of therapeutic options have evolved. First-line treatment options include behavioral modification and second-line options involve medications with significant adverse effects and long-term compliance issues.[9]

Table 3 Major Clinical Results of OAB Treatment with eCoin

Criteria	Baseline n=46	Results After 3 Months n=46	Results After 6 Months n=46	p-Value Compared to Baseline[c]	Overall Improvement Rate for 3 Months	Overall Improvement Rate for 6 Months
Urinary Incontinence[b]	4.2	1.7 (59.5%)[a]	1.5 (64.3%)[a]	0.001	71% median reduction 21.7% dry	47.8% with at least 75% reduction 23.9% with complete cessation
Urinary Urgency[b]	6.0	2.8 (53.3%)[a]	3.2 (46.7%)[a]	0.001	49.4% median reduction	43.4% median reduction
I-QOL[d]	45.4±20.4	71.3±20.8 (58.9%)[a]	67.4±23.7 (48.9%)[a]	–	Improved an average of 25.9 points	3 times the MID
PGI-I[e]	–	5.4±1.3	–	–	–	72% indicated improvement with scores ≥5

Notes: [a]Percent of improvement from baseline in respective criteria. [b]Assessed by number of episodes/day. [c]Statistical analysis done with Wilcoxon sign ranked test. [d]I-QOL = A self-reporting incontinence quality of life instrument. [e]PGI-I = Patient global assessment of improvement survey on 7-point Likert scale from 1 (very much worse) to 7 (very much better). Data from MacDiarmid et al.[7]
Abbreviation: MID, minimally important difference.

After failing conservative treatment modalities neuromodulation has evolved as an important alternative in improving the lives of these patients.[10] SNS and PTNS are currently well-established third-line treatment options: SNS received FDA approval in 1997 and PTNS in 2005.[3,4] Both SNS and PTNS have not seen any significant technical modifications over the last decade or since FDA approval.

BlueWind RENOVA™ and eCoin™ are the only modified devices in neuromodulation developed within the last five years which may add significant improvement to the currently established neuromodulation. Both new devices are in ongoing FDA clinical trials and showing promising clinical results as outlined above.[5–7] Compared to the established techniques of SNS and PTNS, these new implantable devices provide comparable clinical response rates (see Table 4) at a lower risk and costs to patients with OAB. Note, however, there are currently only up to 6 months of clinical data available for the new implantable devices stimulating the tibial nerve.

SNS is still considered the gold standard of third-line treatment for patients with OAB, although its technology has shown minimal feasibility improvements since its initial invention decades ago.[11] Many studies have been reported looking at the long-term (>1 year) clinical response rates of SNS for urge incontinence and urgency/frequency ranging around 50% or higher.[3] SNS has proven to achieve good long-term success in many patients, much better than previous treatment methods.[12] The main shortcomings of the SNS technique are still the size of the device, the challenge of placing the lead next to the sacral nerve under fluoroscopy, and often the need for two surgeries: the first as a test phase, or percutaneous nerve evaluation, to verify the desired patient's response to the test electrode connected to an outside stimulator, and then the second OR procedure to implant the permanent device.[13] In studies looking at the short-term complications reported that within 12 months 30% (82/272) of patients had adverse effects with the most common being undesirable change in stimulation, 12% (32/272).[14] Long-term complications of the SNS device showed that within the first 5 years about 30–40% of the devices had to be removed or replaced.[3] The main adverse events were pain at stimulator site, lead migration, infection, malfunctioning including transient electric shock.[3] Compared to drug therapies in OAB patients, SNS is considered more expensive (US$15,743 vs US$4392), but slightly more effective in a two-year period.[3] Another study looked at the cost-effectiveness of SNS versus PTNS showing that PTNS was least costly at $4999 for a 3-year treatment compared to SNS at $26,269 for the same period.[4] Time is also

Table 4 Comparison of Main Clinical Results for Different OAB Therapies

	BlueWind	**eCoin**	**Urgent-SQ**[a]	**InterStim**[b]	**Botox**[c]
Type of Treatment	Implantable PTNS	Implantable PTNS	PTNS	Sacral Neuromodulation	Injection
Timeline	6 Months n=34	6 Months n=46	6 Months n=8	6 Months	6 Months n=60
UF voids/day	9.4±0.5 (21.7%)[f]	–	10.88 (24.3%)[f]	8.2 (49.1%)[f]	32.9±18.1[d] (14.1%)[f]
UI episodes/day	3.9±0.7 (40.9%)[f]	1.5 (64.3%)[f]	3.63 (60.8%)[f]	2.3 (73.9%)[f]	5.0±12.5[d] (39%)[f]
UI severity[e]	1.4±0.1 (22.2%)[f]	–	0.5 (55.6%)[f]	0.7±1.5 (86.3%)[f]	3.1±1.1 (18.4%)[f]
UU episodes/day	3.8±0.7 (49.3%)[f]	3.2 (46.7%)[f]	Rated urgency with either frequency or incontinence	Rated urgency with either frequency or incontinence	21.9±22.1[d] (27%)[f]
I-QoL[g]	Improvement in both ICIQ-FLUTS[h] and HRQL[i] scales	67.4± 23.7 (48.9%)[f]	86.5 (34.9%)[f]	Improvement in both HRQL[i] and OABqol scales	Improvement in both CSQ-8[j] and KHQ[k] scales

Notes: [a]Study taken from outside the time criteria; no new updated clinical results are available.[17] [b]Data taken from review articles presenting meta-analysis data of clinical studies.[3,12] [c]Data taken from review articles presenting meta-analysis data of clinical studies.[18,19] [d]Number of episodes in 72 hrs. [e]Severity based off a categorical scale designed by each study with lower numbers being loss of urine droplets to higher numbers being small amount of urine loss to changing clothes because of urine loss. [f]Percent of improvement from baseline in respective criteria. [g]I-QoL = A self-reporting incontinence quality of life instrument. [h]ICIQ-FLUTS consists of 12 questions on bladder filling, voiding, and incontinence. [i]HRQL = Health-Related QoL questions and symptoms severity scores. [j]CSQ-8 = 8 questions about satisfaction of treatment. [k]KHQ = questionnaire that evaluates quality of life in patients with UI.

a factor when evaluating these treatments since SNS clinic visit intervals are longer than PTNS, which requires a more intensive stimulation schedule of office visits.[12]

The overall subjective success rate for PTNS (defined by quality of life and willingness to continue treatment) has been reported between 55% - 65%.[4] By defining objective success with greater than 50% reduction of OAB symptoms, in clinical studies, the majority of patients responded to this treatment option.[4] When comparing the clinical results, PTNS showed similar success rates as SNS but was less invasive, less costly, and did not have as many adverse effects. Nevertheless, many patients did not keep up with office visits, and had a high relapse rate for OAB symptoms.[4,15] Because patient must come into the doctor's office regularly to get the benefits of PTNS, and most patients are unwilling to do this, the therapy is not well utilized.

The desire to overcome these limitations stimulated the idea to develop implantable devices stimulating the tibial nerve. eCoin™, which is fully implantable with a primary battery, and once implanted does not require office visits or patient's active involvement to induce treatment.[7] BlueWind™ makes it possible for patients to use a wireless device worn over the implanted stimulator to receive treatment in the comfort of home, but this device is still patient-dependent with possible compliance issues. Since the BlueWind RENOVA™ device is battery-free, there is no necessity for follow-up surgeries for battery replacement.[5] Both devices do not require complex surgery and can be performed under local anesthetic in the office, which eliminates the risks associated with general anesthesia. Tables 1 and 3 show both implantable devices having significant ($p<0.05$) decreases in urinary incontinence, urgency, and frequency.[5–7] All studies showed an improvement in the quality of life.

The safety monitoring in the eCoin™ study was very strict and measured any adverse events (AE) that presented as mild, moderate, or severe; serious or not serious; related or unrelated. All related AEs resolved and only 3 of the 46 participants experienced serious adverse events. In one case, the device had to be explanted prior to device activation. One participant experienced cellulitis without involvement of incision or implant site; another presented with a limp and pain related to a previous hip bursitis; and lastly, one participant contracted pneumonia that was determined to be unrelated to the device.[7] The BlueWind RENOVA™ studies similarly monitored AEs and safety. In one study 47% of the patients presented with AEs such as implant site pain, infection, and procedural wound complications. All symptoms completely resolved within 1–2 weeks. All but one participant had AEs related to the implantation procedure.[6]

Table 4 displays clinical results for different OAB therapies. Compared to the older and well-established therapies, the new implantable ones have demonstrated similar success in the different clinical parameters. For the 6-month post-implantation observation period, eCoin™ demonstrated a greater decrease in urinary incontinence episodes per day than InterStim (see Table 4). This is significant for OAB patients because incontinence creates many problems and more pronounced decrease in quality of life.[16]

The new implantable devices also held up to other therapies such as Urgent-SQ, a subcutaneous version of PTNS, and botox injections. Urgent-SQ consisted of an external pulse generator, included an internal electromagnetic pulse receiver, and electrodes.[17] This device allowed for self-treatment, but the subcutaneous portion was larger, with more parts compared to the new implantable devices. This device was only implanted in a few patients and never got FDA approval.[12] This implantable device has been abolished in the meantime and is no longer available.

Onabotulinum toxin A is an antimuscarinic used to target overactive detrusor muscles. This therapy requires the injection of the toxin into the muscle of the bladder with the effects lasting from 6–8 months.[18,19] Studies have shown that onabotulinum toxin A is highly effective in treating OAB symptoms, comparable to other third-line treatments.[20] It is important to acknowledge that comparing these therapies is difficult because there is no clear-cut definition of clinical success or improvement and measuring each parameter is done differently for each study.

Reviewing and comparing the outcomes of the different invasive treatment options for OAB is difficult and cumbersome because investigators have used different definitions of clinical parameters and success. The new implantable devices stimulating the tibial nerve have demonstrated similar or even greater response rates in the 6-month follow-up period with less adverse effects when compared to the well-established therapeutic modalities such as SNS; however, no long-term clinical studies for these new devices are currently available. Both new implantable devices, BlueWind RENOVA™ and eCoin™, are currently undergoing FDA clinical trials with a high probability of approval within 1–2 years. This review may offer additional insight to medical providers when counseling OAB patients who have failed non-invasive treatment options.

Conclusion

Practicing urologists should be aware of the new upcoming treatment options for patients with overactive bladder. The new implantable eCoin™ and BlueWind RENOVA™ devices stimulating the tibial nerve show reproducible and favorable clinical results (≥50% improvement in symptoms) comparable to the older and well-established neuromodulation devices. These new devices come at a lower cost, they are less invasive for implantation, and they are more convenient for patients. Recent trials have demonstrated the efficacy and safety of these devices. Further clinical trials and studies including ongoing FDA trials will evaluate the long-term efficacy of these new implantable neuromodulation devices.

Disclosure

The first author JY reports no conflicts of interest in this work. Authors WdR and CdR report consulting and financial interests in the following companies: Wenco, Valencia, Kiromic.

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