Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: Tibial Nerve Stimulation

Description/Background

Percutaneous tibial nerve stimulation (PTNS; also known as posterior tibial nerve stimulation) is a technique of electrical neuromodulation used for treating voiding dysfunction. The tibial nerve is stimulated using a fine-needle electrode inserted slightly above the ankle, and low-voltage electrical current is delivered. The recommended course of treatment is 12 weekly 30-minute sessions followed by an individualized maintenance schedule.

VOIDING DYSFUNCTION

Overactive bladder is a non-neurogenic voiding dysfunction characterized by urinary frequency, urgency, urge incontinence, and nonobstructive retention. Common causes of non-neurogenic voiding dysfunction are pelvic floor neuromuscular changes (e.g., from pregnancy, childbirth, surgery), inflammation, medication (e.g., diuretics, anticholinergics), obesity, and psychogenic factors.

Neurogenic bladder dysfunction is caused by neurologic damage in patients with multiple sclerosis, spinal cord injury, detrusor hyperreflexia, or diabetes with peripheral nerve involvement). The symptoms include overflow incontinence, frequency, urgency, urge incontinence, and retention.

Treatment

Approaches to the treatment of incontinence differentiate between urge incontinence and stress incontinence. Conservative behavioral management such as lifestyle modification (e.g., dietary changes, weight reduction, fluid management, smoking cessation) along with pelvic floor exercises and bladder training are part of the initial treatment of overactive bladder symptoms and both types of incontinence. Pharmacotherapy is another option, and different medications target different symptoms. Some individuals experience mixed incontinence.

If behavioral therapies and pharmacotherapy are unsuccessful, percutaneous tibial nerve stimulation (PTNS), sacral nerve stimulation, or botulinum toxin may be recommended.

Percutaneous Tibial Nerve Stimulation (PTNS)
The current indication cleared by the U.S. Food and Drug Administration (FDA) for PTNS is overactive bladder and associated symptoms of urinary frequency, urinary urgency, and urge incontinence.

Altering the function of the posterior tibial nerve with PTNS is believed to improve voiding function and control. The mechanism of action is believed to be retrograde stimulation of the lumbosacral nerves (L4-S3) via the posterior tibial nerve located near the ankle. The lumbosacral nerves control the bladder detrusor and perineal floor.

Administration of PTNS consists of inserting a needle above the medial malleolus into the posterior tibial nerve followed by the application of low-voltage (10 mA, 1–10 Hz frequency) electrical stimulation that produces sensory and motor responses as evidence by a tickling sensation and plantar flexion or fanning of all toes. Noninvasive PTNS has also been delivered with transcutaneous or surface electrodes. The recommended course of treatment is an initial series of 12 weekly office-based treatments followed by an individualized maintenance treatment schedule.

PTNS is less invasive than traditional sacral nerve neuromodulation, which has been successfully used to treat urinary dysfunction but requires implantation of a permanent device. In sacral root neuromodulation, an implantable pulse generator that delivers controlled electrical impulses is attached to wire leads that connect to the sacral nerves, most commonly the S3 nerve root that modulates the neural pathways controlling bladder function.

PTNS has also been proposed as a treatment for non-neurogenic and neurogenic bladder syndromes and fecal incontinence.

Implantable Devices for Tibial Nerve Stimulation (Subcutaneous and Subfascial)
The current indication approved by the FDA for subcutaneous tibial nerve stimulation and subfascial tibial nerve stimulation is urgency urinary incontinence in individuals who are intolerant or who have had an inadequate response to more conservative treatments or who have undergone a successful trial of PTNS. Subcutaneous tibial nerve stimulation is administered through a coin-sized leadless battery-powered implant, whereas subfascial tibial nerve stimulation is a 3 cm length x 3 mm in diameter device which does not contain a battery. A magnetic wrap is place around the ankle to activate the device and provide impulses to the tibial nerve. The manufacturer advertises that this tibial implant delivers reliable and long-lasting performance in a compact form factor with hopes that future surgery for battery depletion, lead fracture, or lead migration will not be necessary. (see Regulatory section).

Wearable/Non-Implantable Neuromodulation Devices
ZIDA is a home-care neuromodulation system that was designed to deliver non-invasive access to the sacral nerve plexus through transcutaneous electrical stimulation of the posterior tibial nerve. It is intended to treat individuals with an overactive bladder and associated symptoms of urinary urgency, urinary frequency, and urge incontinence. The ZIDA Neuromodulation System is a combination of the battery powered ZIDA control unit and the ZIDA embedded garment (Sock or Tights). Electrodes are imbedded in the fabric of a conventional sock. The control unit

(battery-operated stimulation device) attaches to the sock electrodes and transfers electrical pulses from the control unit to the tibial nerve via the embedded knit electrodes.

Vivally is an FDA cleared closed-loop neuromodulation wearable system with a mobile application. According to Avation Medical, Vivally is designed to optimize therapeutic output in real time for at-home treatment of OAB symptoms, such as urinary urgency and urge urinary incontinence. The CliQ™ stimulator attaches to the smart sense wrap on the foot. The device uses a proprietary EMG analysis algorithm to monitor neuromodulation energy to the tibial nerve via biosensor electrodes strategically placed within the garment (smart sense wrap), detecting muscle contractions of the dorsal foot. The device is programed to confirm activation of the tibial nerve and continuously monitor the EMG response, which are used to adjust neuromodulation energy parameters during therapy.

Regulatory Status

In 2005, the Urgent® PC Neuromodulation System (Uroplasty, Inc.) was the initial PTNS device cleared for marketing by FDA through the 510(k) process to treat patients suffering from urinary urgency, urinary frequency, and urge incontinence. Additional percutaneous tibial nerve stimulators have been cleared for marketing through the 510(k) process. They are listed in Table 1.

The devices are not FDA-cleared for other indications, such as the treatment of fecal incontinence.

Wireless technology is evolving for the treatment of overactive bladder. In March 2022, the eCoin® Peripheral Neurostimulator System (Valencia Technologies Corporation) became the first subcutaneous tibial nerve stimulation implant approved by the FDA through the premarket authorization (PMA) process for individuals with urgency urinary incontinence (P200036; FDA Product Code: QPT)

In August 2023, the FDA authorized marketing for BlueWind Medical's Revi System. The Revi System is a subfascial Tibial Neuromodulation System intended to treat symptoms of urgency incontinence alone or in combination with urinary urgency.

Table 1. FDA-Cleared Percutaneous Tibial Nerve Stimulators (FDA Product Code: NAM)

Device Name	Manufacturer	Cleared	510(k)	Indications
Urgent® PC Neuromodulation System	Uroplasty, now Cogentix Medical	Oct 2005	K052025	Treatment of urinary urgency, urinary frequency, and urge incontinence
Urgent® PC Neuromodulation System	Uroplasty, now Cogentix Medical	Jul 2006	K061333	FDA determined the 70% isopropyl alcohol prep pad contained in the kit is subject to regulation as a drug
Urgent® PC Neuromodulation System	Uroplasty, now Cogentix Medical	Aug 2007	K071822	Labeling update, intended use is unchanged
Urgent® PC Neuromodulation System	Uroplasty, now Cogentix Medical	Oct 2010	K101847	Intended use statement adds the diagnosis of overactive bladder
NURO™ Neuromodulation	Advanced Uro-Solutions, now	Nov 2013	K132561	Treatment of patients with overactive bladder and associated symptoms of urinary urgency,

System	Medtronic			urinary frequency, and urge incontinence
ZIDA Wearable Neuromodulation System	Exodus Innovations	Mar 2021	K192731	Treatment of patients with an overactive bladder and associated symptoms of urinary urgency, urinary frequency, and urge incontinence
Vivally System Wearable, Non-Invasive Neuromodulation System and Mobile Application	Avation Medical, Inc.	Apr 2023	K220454	Treatment of patients with bladder conditions of urinary incontinence and urinary urgency.

FDA: Food and Drug Administration

Medical Policy Statement

The safety and effectiveness of percutaneous posterior tibial nerve stimulation (TNS) for non-neurogenic urinary dysfunction have been established when criteria are met. It may be considered a useful therapeutic option when indicated.

Implantable TNS devices (e.g., eCoin, Revi) are considered experimental and investigational. Evidence is insufficient and has not been shown to improve clinical health outcomes.

Non-invasive/wearable neuromodulation devices (e.g., Vivally, Zida Control Sock) are considered experimental and investigational. Evidence is insufficient and has not been shown to improve clinical health outcomes.

Inclusionary and Exclusionary Guidelines

Inclusions:

Initial 12-week course of percutaneous tibial nerve stimulation (PTNS) for non-neurogenic urinary dysfunction including overactive bladder when the following are met:

- **BOTH** of the following have been attempted and have failed to yield adequate relief:
  - Behavioral therapy (i.e., biofeedback, fluid management, pelvic floor exercises) following an appropriate duration of 8 to 12 weeks of treatment.
  - Pharmacologic therapy (i.e., anti-cholinergic drugs or a combination of an anti-cholinergic and a tricyclic anti-depressant) following 4 to 8 weeks of treatment.

Maintenance[a] therapy at a frequency of 1 per month, following a 12-week initial course of percutaneous tibial nerve stimulation up to a total of 2 years. The 2-year time period begins with the induction of the initial course.

[a] *For continuation of treatment, evidence of improvement of symptoms (e.g., urinary frequency, nocturia, and/or urinary urgency) should be obtained within the initial course of the PTNS treatment.*

Exclusions:

- Percutaneous tibial nerve stimulation for all other indications including but not limited to:
  - Neurogenic bladder dysfunction
  - Fecal incontinence

    - Stress incontinence
- PTNS treatment beyond 2 years
- Implantable tibial nerve stimulation devices for all indications, including individuals with non-neurogenic urinary dysfunction (e.g., overactive bladder).
    - Subcutaneous peripheral neurostimulator system (e.g., eCoin)
    - Subfascial peripheral neurostimulator system (e.g., Revi)
- The use of non-invasive/wearable neuromodulation systems (e.g., Vivally, Zida Control Sock)

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

64566	97014	97032	0587T	0588T	0589T
0590T					

Other codes (investigational, not medically necessary, etc.):

64999	0816T	0817T	0818T	0819T	A4545
E0736	E0737				

Rationale

PERCUTANEOUS TIBIAL NERVE STIMULATION FOR NON-NEUROGENIC URINARY INCONTINENCE INCLUDING OVERACTIVE BLADDER

Clinical Context and Therapy Purpose
The purpose of percutaneous tibial nerve stimulation (PTNS) in individuals who have non-neurogenic urinary dysfunction including overactive bladder (OAB) and have failed behavioral and pharmacologic therapy or those with OAB who have responded to an initial course of PTNS, is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO were used to select literature to inform this review.

Populations
The relevant populations of interest are:
- Individuals who have non-neurogenic urinary dysfunction including OAB who have failed behavioral and pharmacologic therapy and
- Individuals with OAB responsive to an initial course of PTNS.

Interventions
The therapy being considered is PTNS as an initial or maintenance therapy. During PTNS, a needle is inserted above the medial malleolus into the posterior tibial nerve followed by the application of low-voltage (10 mA, 1-10 Hz frequency) electrical stimulation. Noninvasive

PTNS may be delivered with transcutaneous or surface electrodes. The recommended course of treatment is an initial series of 12 weekly office-based treatments followed by an individualized maintenance treatment schedule.

Comparators

The following therapies are currently being used to make decisions about non-neurogenic urinary dysfunction: botulinum toxin and sacral nerve stimulation (SNS).

Botulinum toxin is injected into the detrusor muscle. However, the toxin increases the risk of urinary retention and is not recommended for patients with a history of urinary retention or recurrent urinary tract infections.

SNS may be conducted in an outpatient clinical setting using temporary wire leads. Due to the incidence of lead migration, a 2-step process in a surgical setting is recommended. In the initial test phase, wire leads are inserted under the skin and if 50% improvement is reported, the patient may elect permanent implantation with a pacemaker-like stimulator. If the test phase is unsuccessful, the leads are then removed.

Outcomes

The general outcomes of interest are reductions in symptoms (e.g., self-reported assessment of symptoms, decrease in number of voids per day) and improved quality of life. Outcomes are measured following the 12-week treatment regimen.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Wang et al (2020) evaluated PTNS for patients with OAB in a systematic review and meta-analysis that included 28 studies (N=2,461).(1) The efficacy of PTNS was compared to baseline information before treatment or other treatments (not specified). Reviewers included several trials discussed in the sections below: the Overactive Bladder Innovative Therapy (OrBIT) trial (Peters et al [2009]), the Sham Effectiveness in Treatment of Overactive Bladder Symptoms (SUmiT) trial (Peters et al [2010]), and the Finazzi-Agro et al (2010), Vecchioli-Scaldazza et al (2013), and Preyer et al (2015) trials. Results demonstrated that PTNS reduced the daily frequency of the following symptoms: voiding (mean difference [MD], −2.48; 95% confidence interval [CI], −3.19 to −1.76), nocturia (MD, −1.57; 95% CI, –2.16 to −0.99), urgency episodes (MD, −2.20; 95% CI, –3.77 to −0.62), and incontinence episodes (MD, −1.37; 95% CI, –1.71 to −1.02). Percutaneous tibial nerve stimulation also improved maximum cystometric capacity (MD, 63.76; 95% CI, 31.90 to 95.61) and compliance (MD,

7.62; 95% CI, 0.61 to 14.63). The pooled success rate was 68% (95% CI, 59% to 78%). The most common complication following PTNS was pain at the puncture site.

Xiong et al (2021) performed a systematic review with meta-analysis of 6 RCTs (N=291) evaluating the efficacy of tibial nerve stimulation (either PTNS or transcutaneous tibial nerve stimulation [TTNS]) versus anticholinergic medications for OAB.(2) The SUmIT trial and trials by Vecchioli-Scaldazza et al (2013) and Preyer et al (2015) were among those included. There was a significant reduction in urge incontinence episodes with tibial nerve stimulation versus anticholinergic medications (MD, -1.11; 95% CI, -1.66 to -0.55). However, tibial nerve stimulation and anticholinergic medications had comparable effects on micturition, nocturia, urgency, and voided volume. Discontinuation due to adverse events was lower with tibial nerve stimulation than with anticholinergic medications (odds ratio [OR], 0.13; 95% CI, 0.03 to 0.51).

Two systematic reviews that did not include a quantitative analysis evaluated PTNS for nonobstructive urinary retention. Coolen et al (2020) evaluated 8 studies, 5 of which reported the efficacy of PTNS and 2 of transcutaneous electrical nerve stimulation (TENS).(3) The objective success rate for PTNS (defined as a decrease of at least 50% in the frequency or volume of catheterization per 24 hr) was 25% to 41%. The subjective success rate (defined as the patient's request for continued chronic treatment with PTNS) ranged from 25% to 41%. A subjective success rate of 80% was reported in 1 study of women who received transvaginal TENS. Ho et al (2021) evaluated 16 studies, 5 of which reported on the efficacy of PTNS and 11 that of sacral neuromodulation (also referred to as SNM).(4) The success rate for PTNS (defined as at least a 50% reduction in symptoms) ranged from 50% to 60%, while the success rates for SNM (which had variable definitions across trials) ranged between 42.5% and 100% (median, 79.2%) for the test stimulation phase and 65.5% to 100% (median, 89.1%) in the long term (median follow, 42 months).

Tutulo et al (2018) searched the literature through December 2017 and identified 21 studies using either SNS or PTNS to treat lower urinary tract dysfunction and chronic pelvic pain not responding to standard therapies.(5) Reviewers concluded that both SNS and PTNS were effective therapies. Percutaneous tibial nerve stimulation demonstrated higher success rates (≥50% reduction in leakage episodes) and fewer side effects compared with SNS; however, longer follow-up studies with PTNS are needed. Another systematic review by Tutulo et al (2018) conducted a literature search through December 2017 of RCTs evaluating SNS and PTNS for the treatment of OAB unresponsive to standard medical therapy.(6) Five RCTs were identified. Reviewers concluded that both SNS and PTNS, with success rates ranging from 61% to 90% and 54% to 79%, respectively, could be considered effective.

A Cochrane review by Stewart et al (2016) evaluated electrical stimulation with nonimplanted electrodes for OAB in adults.(7) The literature search was current up to December 2015. The objective of the review was to determine whether electrical stimulation (including vaginal and rectal electrical stimulation, and PTNS) was better than no treatment or better than any other treatment available for OAB. Studies reviewed were RCTs or quasi-RCTs of electrical stimulation that included adults with OAB with or without urgency and urge urinary incontinence. Trials whose participants had stress urinary incontinence were excluded. Sixty-three eligible trials were identified (N=4424 randomized participants). Reviewers included several trials discussed below: the OrBIT (Peters et al [2009]) and OrBIT follow-up trials (MacDiarmid et al [2010]), the SUmiT trial (Peters et al [2010]), the Sustained Therapeutic Effects of Percutaneous Tibial Nerve Stimulation (STEP) trial (Peters et al [2013]), and the

Finazzi-Agro et al (2010), Schreiner et al (2010), Vecchioli-Scaldazza et al (2013), and Preyer et al (2015) trials.

Data were obtained from the end of treatment and the longest available follow-up period. The primary outcomes identified were the perception of cure, the perception of improvement, and condition-related quality of life measures as defined by the original authors or by any validated measurement scales such as the International Consultation on Incontinence Questionnaire. Secondary outcomes pertinent to the evidence review were a quantification of symptoms, procedure outcome measures, and adverse events.

The key findings from the Cochrane review (2016) of evidence are summarized in Table 2. Percutaneous tibial nerve stimulation results were combined for vaginal and rectal electrical stimulation.

Table 2. Summary of Cochrane Systematic Review Outcomes

Comparators to Electrical Stimulation[a]	Electrical Stimulation Effect[a]	QOE
No active treatment, placebo, or sham		
Reduction in OAB symptoms	More effective	Moderate
Reduction in urge urinary incontinence	More effective	Moderate
Improvement in OAB-related quality of life	More effective	Moderate
Pelvic floor muscle training		
Reduction in OAB symptoms	More effective	Moderate
Reduction in urge urinary incontinence	Effect uncertain	No evidence
Improvement in OAB-related quality of life	Effect uncertain	Low
Drug therapy		
Reduction in OAB symptoms	More effective	Moderate
Reduction in urge urinary incontinence	Effect uncertain	No evidence
Improvement in OAB-related quality of life	Effect uncertain	No evidence
Oxybutynin or tolterodine		
Adverse events	Lower risk	Low
Placebo/sham		
Adverse events	Lower risk	Moderate

Adapted from Stewart et al (2016).(7)
OAB: overactive bladder; QOE: quality of evidence.
[a]Electrical stimulation includes percutaneous tibial nerve stimulation.

Forty-four trials did not report the primary outcomes of perception of cure or improvement in OAB. The majority of trials were deemed to be at low or unclear risk of selection and attrition bias and unclear risk of performance and detection bias. Lack of clarity regarding the risk of bias was largely due to poor reporting. Many studies did not report whether electrical stimulation was safer than other treatments or if one type of electrical stimulation was safer than others.

This review was informed by a TEC Assessment (2013) evaluating PTNS as a treatment for voiding dysfunction.(8) It concluded that PTNS as a treatment for voiding dysfunction met TEC criteria and showed that PTNS improves the net health outcome. Specifically, PTNS ameliorated symptoms of chronic OAB or urinary voiding dysfunction, simultaneously improving quality of life parameters among patients who have failed behavioral and pharmacologic therapies.

In this assessment of 6 RCTs, TEC reviewers drew the following conclusion about the evidence:

"Evidence from randomized placebo-controlled trials supports the clinical efficacy of PTNS applied in the standard 12-week regimen. No concurrently controlled evidence exists from a trial over longer periods of time in maintenance therapy. Although the lack of controlled evidence on maintenance PTNS raises concern about whether short-term efficacy is maintained over the long term, the available 12- to 36-month evidence appears consistent with maintained efficacy in relieving symptoms of OAB and urinary voiding dysfunction. Adverse event rates, assuming accurate ascertainment, appear limited."

In 2012 and 2013, several other systematic reviews of the literature on PTNS for treating OAB were published.(9-12) Only one conducted pooled analyses of study results.(9) This review, by Burton et al (2012), conducted a pooled analysis of data from 4 trials (2 of which were abstracts) comparing PTNS with sham treatment. Reviewers found a significantly higher risk of successful treatment with PTNS (relative risk [RR], 7.02; 95% CI, 1.69 to 29.17) compared with a control intervention. The CI was wide, indicating a lack of precision in the pooled estimate. The patient samples in these studies were homogenous by sex, severity and duration of symptoms, and previous treatment history. The definition of successful treatment also varied among studies. The SUmiT trial (discussed below) contributed 220 (76%) of 289 patients in the pooled analysis.

Also, Shamliyan et al (2012) conducted a comparative effectiveness review for the Agency for Healthcare Research and Quality on the broader topic of nonsurgical treatments for urinary incontinence in adult women.(13) Reviewers identified 4 RCTs comparing PTNS with no active treatment in patients with OAB. Two of the 4 RCTs reported 12-week results of the sham-controlled SUmiT trial; 1 of them included a subgroup of SUmiT participants and was only published as an abstract. The Shamliyan report included a pooled analysis of data from 3 studies that found a statistically significant improvement in urinary incontinence in the PTNS group compared with the control group (relative risk, 1.9; 95% CI, 1.1 to 3.2). This pooled analysis included 405 patients: 220 in the SUmiT trial, 150 in the SUmiT trial subgroup analysis, and 35 in a trial by Finazzi-Agro et al (2010).(14) A limit of the Shamliyan et al (2012) analysis was that the 150 patients in the SUmiT subgroup analysis were included twice. The Shamliyan review did not discuss evidence on the efficacy of PTNS beyond 12 weeks.

Sham-Controlled Randomized Trials

The SUmiT trial, reported by Peters et al (2010), was a sham-controlled randomized trial.(15) Before conducting the trial, investigators performed a pilot study in healthy volunteers to determine the adequacy of a sham PTNS intervention.(16) The sham procedure was correctly identified by 10 (33%) of 30 volunteers. This percentage is below the 50% that could be expected by chance; so, investigators concluded that the procedure was a feasible sham. Eligibility criteria included: a score of 4 or more on the Overactive Bladder Questionnaire short form for urgency, self-reported bladder symptoms lasting at least three months, and having failed conservative care for these symptoms or a diagnosis of OAB. OAB and quality of life questionnaires, as well as 3-day voiding diaries, were completed at baseline and 13 weeks.

Both the randomized sham and active intervention groups received 12 weekly 30-minute intervention sessions. In the sham group, a blunt (placebo) instrument was used to simulate the location and sensation of needle electrode insertion in active treatment. One inactive PTNS surface electrode and 2 active transcutaneous electrical nerve stimulation surface electrodes were used. The transcutaneous electrical nerve stimulation unit (Urgent PC system) delivered

low-level stimulation to mimic the PTNS intervention. The 12-week course of treatment was completed by 103 (94%) of 110 in the PTNS group and 105 (95%) of 110 in the sham group.

The primary trial end point was an efficacy assessment measured by a 7-level global response assessment (GRA) tool, in which patients reported change in symptoms as markedly worse, moderately worse, mildly worse, the same, slightly improved, moderately improved, or markedly improved. A responder was defined as one who reported symptoms as moderately or markedly improved at week 13. The rate of responders was 54.5% (60/110) of PTNS subjects compared with 20.9% (23 of 110) of sham subjects. There was a statistically significant benefit reported with PTNS compared with sham treatment in voiding diary variables as well.

Six PTNS subjects reported nine mild or moderate treatment-related adverse events consisting of ankle bruising, discomfort at the site of needle insertion, bleeding at the site, and tingling in the leg. No local treatment-related adverse events were reported in the sham group, and no systemic adverse events occurred in either group.

The Sustained Therapeutic Effects of Percutaneous Tibial Nerve Stimulation (STEP) trial, an extension of the SUmiT study, included only responders from the PTNS group.(17) The purpose was to determine the threshold for maintenance therapy. Of the 60 PTNS group 13-week responders, 50 entered the extension study. Patients underwent a 14-week transitional protocol consisting of two treatments with a 14-day interval, two treatments with a 21-day interval, and then one treatment after another 28 days. Following this 14-week period, a personal treatment plan was developed for each patient. PTNS was delivered when patients reported that their symptoms increased. Between 6 and 36 months, patients received a median of 1.1 monthly PTNS treatments after the 14-week tapering period. Data were available on 34 patients at 24 months and on 29 patients at 36 months. In a per-protocol analysis, compared with baseline, 28 (97%) of 29 patients who completed the 36-month follow-up met the primary efficacy endpoint of moderate or marked improvement in overall bladder symptoms on the GRA. Also, compared with baseline, all voiding diary measures were significantly improved in this group of patients at every six-month follow-up.

Adverse events noted in the STEP study included 1 report of restricted vaginal opening with unknown relation to treatment and 2 mild bleeding events at the needle site in the same participant. Nine patients reported 11 mild adverse events with an unknown relation to treatment including vaginal bleeding, mild depression, shoulder pain, diarrhea, leg pain, stomachache, pelvic pain, urinary tract infection, a pulling sensation in both feet, bladder pressure, and pinched nerve pain.

A limitation of the SUmiT trial was that the primary outcome (the GRA) is a single-item subjective measure. An additional limitation was that only short-term comparative data were available. And unlike medication that can be taken in the same manner on an ongoing basis, PTNS involves an initial 12-week course of treatment followed by maintenance therapy, which varies from the initial treatment course. To date, maintenance therapy has not been well defined.

Table 3 and 4 summarize the SUmiT RCT and STEP extension studies.

Table 3. Summary of SUmiT RCT and STEP Extension Characteristics

Study; Trial	Countries	Sites	Dates	Randomized or Enrolled/ Completed Trial		Outcome
				PTNS	Sham	
Peters et al (2010); SUmiT	U.S.	23	2008-2009	110/103	110/105	GRA at 13 wk
Peters et al (2013); STEP	U.S.	23	2009-2012	50/29[a]	None	GRA at 36 mo

GRA: global response assessment; PTNS: percutaneous tibial nerve stimulation; RCT: randomized controlled trial; STEP: Sustained Therapeutic Effects of Percutaneous Tibial Nerve Stimulation; SUmiT: Sham Effectiveness in Treatment of Overactive Bladder Symptoms.
[a] Extension study of 50 PTNS responders in SUmiT trial.

Table 4. Summary of SUmiT RCT and STEP Extension Results

Study	Primary Outcome: Moderately or Markedly Improved GRA			
	PTNS, n/N (%)	Sham, n/N (%)	Confidence Intervals	p
SUmiT (2010)[1]				
GRA (13 wk)	60/110 (54.5)	23/110 (20.9)	NR	<0.001
STEP (2013)[3]				
GRA (36 mo)	28/29 (97)	None	None	None

GRA: Global response assessment; NR: not reported; PTNS: percutaneous tibial nerve stimulation; RCT: randomized controlled trial; STEP: Sustained Therapeutic Effects of Percutaneous Tibial Nerve Stimulation: SUmiT: Sham Effectiveness in Treatment of Overactive Bladder Symptoms.

An RCT by Finazzi-Agro et al (2010) evaluated 35 women who had urge incontinence and detrusor overactivity on urodynamic testing.(14) Patients were randomized to 30-minute PTNS sessions, three times per week for four weeks (n=18) or sham treatment (n=17). One patient dropped out of the PTNS group, and two dropped out of the sham group; analysis was not intention-to-treat. The primary outcome, percent responders at 4 weeks (defined as at least 50% reduction in incontinent episodes), was attained by 12 (71%) of 17 in the PTNS group and 0 (0%) of 15 in the sham group.

Other RCTs

An RCT comparing PTNS with medication for the treatment of OAB was published by Vecchioli-Scaldazza et al (2018).(18) This three-arm trial compared solifenacin (n=27), PTNS (n=34), and a combination of solifenacin plus PTNS (n=33) and followed patients through 10 months posttreatment. Patients in all three arms experienced significant reductions from baseline in daytime frequency, night-time frequency, and urgency. PTNS was more effective than solifenacin alone, and the combination of PTNS plus solifenacin was more effective than PTNS alone. The combination therapy also showed the longest effect.

A group of RCTs has compared PTNS with an alternative treatment, medication, conservative therapy or electrical stimulation.(14, 18-23) The trials reported inconsistent findings on short-term efficacy, and only one reported on the efficacy of PTNS beyond 12 weeks.

Three studies used medication as the comparison intervention. Preyer et al (2015) published a non-blinded study comparing 12 weeks of PTNS with tolderodine in 36 women who had OAB.(21) There were no significant differences between groups on the reduction of incontinence episodes in 24 hours (p=0.89) or quality of life (p=0.07).

Another RCT comparing PTNS with solifenacin, was a crossover trial published by Vecchioli-Scaldazza et al (2013).(22) Forty women with OAB received PTNS (twice weekly for 6 weeks) or medication, given in random order, with a 6-week wash-out period between treatments. Group A received medication first and group B received PTNS first. The primary efficacy outcome was reduction in the number of voids in a 24-hour period. Thirty (75%) of the 40

patients completed the trial. The number of daily voids (the primary outcome) significantly decreased after each treatment compared with before treatment. Also, secondary outcomes, including nocturia urge incontinence, and voided volume significantly improved after each treatment compared with pretreatment values. The authors did not directly compare the efficacy of medication and PTNS.

An RCT compared PTNS to conservative therapy. Schreiner et al (2010) assessed 51 women older than 60 years of age who complained of urge urinary incontinence.(23) Women were randomized to 12 weeks of conservative treatment (Kegel exercises and bladder training) alone (n=26) or conservative treatment plus 12 weekly sessions of PTNS (n=25). Blinding was not discussed. The response rate at 12 weeks, defined as a reduction of at least 50% in the number of incontinence episodes reported by the patient in a bladder diary, was 76% in the PTNS group and 27% in the conservative treatment only group (p=0.001).

Gungor Ugurlucan et al (2013) in Turkey, compared transvaginal electrical stimulation (n=38) with PTNS (n=21) in women who had OAB.(20) The electrical stimulation protocol consisted of 20-minute treatments, 3 times a week for 6 to 8 weeks. PTNS was performed with an Urgent PC device used for twelve weekly, 30-minute sessions. Fifty-two (88%) of 59 patients completed the trial. The authors assessed numerous outcome variables and did not specify primary outcomes or adjust p values for multiple comparisons. Four bladder diary variables were reported. From baseline to the end of the treatment period, the groups did not differ significantly in mean change in urgency episodes, nocturia or incontinence episodes. The mean number of urgency episodes was 2.9 at baseline and 1.6 after treatment in the electrical stimulation group, and 2.0 at baseline and 1.3 after treatment in the PTNS group (p=0.54). The mean daytime frequency was 7.8 at baseline and 5.8 after treatment in the electrical stimulation group and 7.6 at baseline and 7.4 in the PTNS group (p=0.03). The authors reported that a significantly higher proportion of patients in the electrical stimulation group described themselves as cured, but they did not provide proportions or p values.

The Overactive Bladder Innovative Therapy (OrBIT) trial is the largest randomized trial that was not sham-controlled. This trial was a non-blinded comparison of PTNS and extended-release tolterodine (Detrol LA) in women with OAB.(24) Eligibility included symptoms of OAB, with at least 8 voids per 24 hours; the mean daily voids for those entering the study were 12.3. The primary outcome was the non-inferiority of PTNS in the mean reduction in the number of voids per 24 hours after 12 weeks of treatment. Non-inferiority was defined as no more than a 20% difference in the mean void reduction. As expected, the mean reduction in voids of 1.8 for tolterodine and 3.6 for PTNS was based on previously published efficacy data. Study findings showed the noninferiority of PTNS based on results for 84 participants.

The trial also reported on secondary outcomes. There were no statistically significant differences between the PTNS and tolterodine groups for other symptoms recorded in the voiding diary. Improvement in all OAB symptom episodes was statistically significant within each group from baseline to 12 weeks, but not between groups.

The OrBIT trial lacked blinding of patients and providers and lacked comparative data beyond the end of the initial 12-week treatment period. There was no sham or placebo group to mitigate the potential bias due to subjective outcomes. Also, the trialists did not clearly define criteria for “improvement” or “cure,” (a key secondary outcome), and did not report the extent

of compliance with medical therapy. Finally, different data collection methods were used in the two groups (eg, for adverse event outcomes and possibly for other self-report outcomes).

MacDiarmid et al (2010) reported on one-year follow-up data for patients from the OrBIT trial who had been assigned to the PTNS group and had reported symptom improvement at 12 weeks.(25) Of the 35 responders, 33 were included. They received a mean of 12.1 additional treatments between the 12-week and 12-month visits, and there was a median of 17 days between treatments. Data were available for 32 (97%) of the 33 participants at six months and 25 (76%) of the 33 participants at 12 months.

As noted, this analysis lacked data from the tolterodine group to assess long-term outcomes. Additionally, not all patients in the PTNS group were included in the follow-up analysis; rather only PTNS responders were eligible. A potential bias is that the initial subjective outcome measure might have been subject to the placebo effect. Moreover, patients in the PTNS group who responded to initial treatment might have been particularly susceptible to a placebo response and/or might represent those with the best treatment response. Thus, these individuals might also have been susceptible to a placebo response during maintenance treatments, especially treatments offered on an as-needed basis.

Tables 5 and 6 summarize the OrBIT and OrBIT 1-year follow-up studies.

Table 5. Summary of OrBIT RCT Characteristics

Study	Countries	Sites	Dates	Randomized/Completed		Outcome[a]
				PTNS	***Tolterodine***	
Peters et al (2009)[24,]	U.S.	11	2006-2008	50/41	50/43	Reported
MacDiarmid et al (2010)[25,] 1-y follow-up	U.S.	11	2008-2009	33/32[b]		Reported

OrBIT: Overactive Bladder Innovative Therapy, PTNS: percutaneous tibial nerve stimulation; RCT: randomized controlled trial.
[a] Mean reduction in the number of voids per 24 hours after 12 weeks of treatment.
[b]Eligible responders from 12-week study.

Table 6. Summary of OrBIT RCT Results

Study	Primary Outcome: Mean Reduction in Voids per Day (SD)			
OrBIT (2009)	***PTNS (n=41)***		***Tolterodine (n=43)***	
	Baseline	**12 Weeks**	**Baseline**	**12 Weeks**
Voids per day	12.1 (3.1)	-2.4 (4.0)	12.5 (3.7)	-2.5 (3.9)
p		<0.001		<0.001
Confidence interval		NR		NR
OrBIT 1-y follow-up (2010)	***PTNS (n=25)***			
	Baseline	***12 Months***		
Voids per day	12.4 (3.5)	-2.8 (3.7)	Not applicable	Not applicable
p		<0.001		
Confidence interval		NR		

NR: not reported; OrBIT: Overactive Bladder Innovative Therapy, PTNS: percutaneous tibial nerve stimulation; RCT: randomized controlled trial.

Section Summary: Percutaneous Tibial Nerve Stimulation for Non-Neurogenic Urinary Dysfunction Including Overactive Bladder

Initial Course of Percutaneous Tibial Nerve Stimulation

For individuals who have non-neurogenic urinary dysfunction including OAB who have failed behavioral and pharmacologic therapy and received an initial course of PTNS, a number of RCTs of PTNS have been published, including two key industry-sponsored RCTs, the OrBIT and SUmiT trials. Systematic reviews of the evidence have found short-term improvements with PTNS. The largest, highest quality study was the blinded sham-controlled SUmiT trial. This trial reported a statistically significant benefit of PTNS vs sham at 12 weeks. In another small sham-controlled trial, a 50% reduction in urge incontinent episodes was attained in 71% of the PTNS group compared with 0% in the sham group. The nonblinded OrBIT trial found that PTNS was noninferior to medication treatment at 12 weeks.

Maintenance Course of Percutaneous Tibial Nerve Stimulation

For individuals who have OAB syndrome who have failed behavioral and pharmacologic therapy, respond to an initial course of PTNS, and then receive maintenance PTNS therapy, there are up to 36 months of observational data that suggest there is a durable effect for some of these patients. The SUmiT and OrBIT trials each included extension studies, which followed individuals who responded to the initial course of PTNS and continued to receive periodic maintenance therapy. There is variability in the interval between and frequency of maintenance treatments, and an optimal maintenance regimen remains unclear. While comparative data are not available after the initial 12-week treatment period, the observational data support a clinically meaningful benefit for use in individuals who have already failed behavioral and pharmacologic therapy and respond to the initial course of PTNS. PTNS may allow such individuals to avoid more invasive interventions. Adverse events appear to be limited to local irritation for both short- and long-term PTNS use. Typical regimens schedule maintenance treatments every 4-6 weeks.

IMPLANTABLE TIBIAL NERVE STIMULATION FOR NON-NEUROGENIC URINARY DYSFUNCTION INCLUDING OVERACTIVE BLADDER

Subcutaneous Tibial Nerve Stimulation

Clinical Context and Therapy Purpose

The purpose of subcutaneous tibial nerve stimulation (STNS) in individuals who have non-neurogenic urinary dysfunction including overactive bladder (OAB) with episodes of urgency urinary incontinence and have failed behavioral and pharmacologic therapy or who have responded to an initial course of PTNS, is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are:

- Individuals who have non-neurogenic urinary dysfunction including OAB with episodes of urgency urinary incontinence who have failed behavioral and pharmacologic therapy, and
- Individuals with OAB with episodes of urgency urinary incontinence responsive to an initial course of PTNS.

Interventions

The therapy being considered is STNS. The eCoin Peripheral Neurostimulator System is an FDA-approved coin-sized leadless battery-powered implant that delivers electrical stimulation

to the tibial nerve (0.5-15 mA, 20 Hz frequency). The recommended treatment duration is 30 minutes every 3 days for the first 18 weeks (42 session) and every 4 days thereafter and is programmed by the clinician. A patient controller can be leveraged to inhibit an automatic session in the event of undesired or painful stimulation. The battery life is estimated at up to 3 years (range, 1-8 years).

Comparators
The following therapies are currently being used to make decisions about non-neurogenic urinary dysfunction: botulinum toxin and sacral nerve stimulation (SNS).

Botulinum toxin is injected into the detrusor muscle. However, the toxin increases the risk of urinary retention and is not recommended for patients with a history of urinary retention or recurrent urinary tract infection (UTI).

Sacral nerve stimulation may be conducted in an outpatient clinical setting using temporary wire leads. Due to the incidence of lead migration, a 2-step process in a surgical setting is recommended. In the initial test phase, wire leads are inserted under the skin and if 50% improvement is reported, the patient may elect permanent implantation with a pacemaker-like stimulator. If the test phase is unsuccessful, the leads are then removed.

Outcomes
The general outcomes of interest are reductions in symptoms (e.g., self-reported assessment of symptoms, decrease in the number of voids per day) and improved quality of life.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Nonrandomized Studies
Rogers et al (2021) evaluated the safety and efficacy of the wireless eCoin device in a single-arm, open-label trial at 15 sites in the US.(26) A total of 132 patients with refractory (failed ≥1 second or third-line therapy) OAB received the eCoin device and were included in the intention-to-treat analysis. The majority of patients were female (98%) and 26% had received prior PTNS therapy. At 24-week follow-up, 69% (CI, 61% to 77%) of patients had a 50% reduction in urge urinary incontinence symptoms based on 3-day voiding diaries and were considered "responders". Results were similar at weeks 36 and 48 with 70% (CI, 62% to 78%) and 68% (CI, 60% to 76%) of patients responding, respectively. Fewer patients reported 100% reduction in symptoms with only 21% of patients reporting 100% response at 48 weeks. By 48 weeks there was a mean decrease in urge urinary incontinence episodes (-2.61), urinary voids (-2.12), urgency episodes (-1.49), and nocturia episodes (-0.51). Outcomes were not stratified by prior treatments received. Outcomes were impacted by the COVID-19 pandemic. Pre-

pandemic and in-person responder rates were 75% and 74%, respectively, whereas the responder rate during the pandemic was 60% (n=25) and the responder rate of remote visits was 57% (n=14). Adverse events related to the device or procedure were reported in 20% of patients and most were mild (11%) to moderate (6%). There were 3 severe adverse events, including 1 post-operative wound infection, 1 implant site infection, and 1 device stimulation issue. While the study met its primary performance goal of at least a 40% response rate after 48 weeks of therapy, the certainty of this data is limited by the lack of blinding and a control group and the fact that a performance goal was identified after patients had already been implanted.(27) Thus, the FDA has required the manufacturer of the eCoin system to conduct a post-approval study to provide greater certainty of the potential benefit of the device. It is also intended to address safety concerns regarding device explantation and reimplantation following battery depletion given that the study observed the need to re-implant the device after only 1 year. Possible reasons for the negative impact of COVID-19 on the 48-week response rate were not explored.

A feasibility study conducted by MacDiarmid et al (2019) for the eCoin device conducted in the US and New Zealand initially enrolled 46 patients at 7 sites and found reduced urge urinary incontinence episodes at 3 months follow-up (from 4.2 to 1.7 daily episodes; p=.001).(28) Subsequent long-term data published in 2021 indicate continued safety and efficacy of eCoin with 65% of patients considered responders and 26% of responders having complete continence at 12 months and only 1 serious infection-related adverse event.(29) A follow-up study of 23 patients who were reimplanted with an eCoin device after 1 year with a second-generation device found reimplantation to be successful with 74% and 82% of patients having at least 50% reduction in episodes of urge urinary incontinence at 12 and 24 weeks, respectively.(30) No serious device-related adverse events were reported.

Section Summary: Implantable Subcutaneous Tibial Nerve Stimulation for Non-Neurogenic Urinary Dysfunction Including Overactive Bladder
An open-label, single-arm study evaluating the first FDA-approved wireless subcutaneous tibial nerve stimulation device (eCoin) demonstrated a 68% response rate at 48 weeks of follow-up. However, the certainty of the evidence is limited by the lack of comparator group and a lower response rate during the COVID-19 pandemic. An ongoing post-approval study may elucidate the certainty of benefit, including safety of reimplantation given battery lifespan concerns.

Implantable Subfascial Tibial Nerve Stimulation
The BlueWind Revi Implant is a small, battery-free device that is implanted near the ankle under local anesthesia. To activate the device, a lightweight wireless wearable is placed around the ankle once to twice daily to provide stimulation. Since the implant has no battery, the wearable unit transmits energy via magnetic coupling to the implant, which consequently generates electrical pulses stimulating the tibial nerve. These electrical pulses stimulate the nerve along the leg, reaching the sacral plexus and entering the spinal cord, with the intent to relieve symptoms of urinary incontinence alone or in combination with urinary urgency.

Tipton et al (2020) discussed 2 new small implantable devices designed to stimulate the tibial nerve, BlueWind RENOVA and eCoin.(56) Although promising clinical results were shown, both devices were currently undergoing U.S. Food and Drug Administration approval and 1-year follow-up data was needed. Authors concluded that more clinical data with larger patient cohorts and multicenter studies are necessary to verify the therapeutic efficacy of these new small implantable devices.

NEUROGENIC BLADDER DYSFUNCTION

Clinical Context and Therapy Purpose

The purpose of PTNS in individuals who have neurogenic bladder dysfunction is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with neurogenic bladder dysfunction. Symptoms may include urinating small amounts often, problems starting urination, problems emptying the bladder, inability to detect a full bladder, and losing bladder control.

Interventions

The therapy being considered is PTNS. During PTNS, a needle is inserted above the medial malleolus into the posterior tibial nerve followed by the application of low-voltage (10 mA, 1-10 Hz frequency) electrical stimulation. Noninvasive PTNS may be delivered with transcutaneous or surface electrodes. The recommended course of treatment is an initial series of 12 weekly office-based treatments followed by an individualized maintenance treatment schedule.

Comparators

The following therapies are currently being used to make decisions about neurogenic bladder dysfunction: conservative treatments (eg, medication to relax the bladder or to activate pelvic muscles, catheterization to empty the bladder, pelvic floor muscle training), botulinum toxin and SNS.

Botulinum toxin is injected into the detrusor muscle. However, the toxin increases the risk of urinary retention and is not recommended for patients with a history of urinary retention or recurrent urinary tract infections.

SNS may be conducted in an outpatient clinical setting using temporary wire leads. Due to the incidences of lead migration, a two-step process in a surgical setting is recommended. In the initial test phase, wire leads are inserted under the skin and if 50% improvement is reported, the patient may elect permanent implantation with a pacemaker-like stimulator. If the test phase is unsuccessful, the leads are then removed.

Outcomes

The general outcomes of interest are reduced symptoms and improved quality of life. Outcomes are measured following the 12-week treatment regimen.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systemic Reviews
Schneider et al (2015) published a systematic review on tibial nerve stimulation (transcutaneous and percutaneous) for treating neurogenic lower urinary tract dysfunction.(31) In a literature search through January 2015, 16 studies were identified - four RCTs, nine prospective cohort studies, two retrospective case series and one case report. Sample sizes of the included studies were small; most included fewer than 50 patients and none had a sample size larger than 100 patients. Three of the four RCTs used transcutaneous tibial nerve stimulation (TTNS) and the fourth study, which was conducted in Iran, stated that PTNS was used but did not specify the device. The four RCTs included different study populations; women with neurogenic bladder (n=1), men with neurogenic overactive bladder (n=1), multiple sclerosis patients (n=1) and Parkinson disease patients (n=1). Comparison interventions were tolterodine, pelvic floor muscle training, lower limb stretching and sham (one study each). Pooled analyses were not conducted, and the systematic review mainly discussed intermediate outcomes (eg, maximum cystometric capacity and maximum detrusor pressure). None of the RCTs reported statistically significant between-group differences in clinical outcome variables (eg, number of episodes of urgency, frequency or nocturia).(32-35)

Randomized Controlled Trials
Zonic-Imamovic and coworkers (2019) published the results of a RCT evaluating treatment with oxybutynin compared to transcutaneous tibial nerve stimulation (TTNS) in multiple sclerosis patients with OAB.**(**36) Patients were allocated to two groups of 30 patients each. Patients treated with anticholinergic therapy received 5 mg oxybutynin twice daily for three months. Patients treated with TTNS were treated at home daily for 30 minutes for three months. The Overactive Bladder Questionnaire (OAB-q SF) was utilized to assess the frequency of OAB symptoms and the quality of life of patients. For those treated with oxybutynin, the mean symptom subscale score improved from 61.9±6.0 to 32.4±14.8 ($P<0.001$) and the mean quality of life subscale score improved from 27.8±13.7 to 56.1±17.3 ($P<0.001$) after treatment. For those treated with TTNS, the mean symptom subscale score improved from 61.2±14.6 to 50.8±12.3 ($P=0.004$) and the mean quality of life subscale score improved from 28.5±12.6 to 38.3±11.4 ($P=0.003$). Final differences in symptoms and quality of life were found to be statistically significant between groups ($P<0.001$) and favored treatment with oxybutynin.

A sham-controlled, double-blind RCT of TTNS in patients with neurogenic OAB and women with non-neurogenic OAB was conducted by Welk et al (2020) from January 2016 to March 2019.(37) Fifty patients were recruited (OAB=20;neurogenic=30) and 24 were allocated to the sham group while 26 were allocated to active TTNS therapy. Baseline group characteristics were not specified but were noted to be similar. The majority of neurogenic OAB study participants had multiple sclerosis (22/30; 73%). The primary outcome measure was improvement of patient perception of bladder condition (PPBC). Active responders did not significantly differ between groups, numbering 3/24 (13%) in the sham group and 4/26 (15%) in the active group ($P=0.77$). No significant differences in secondary outcome measures (24-hour pad weight, voiding diary parameters, condition-specific patient-reported outcomes) were noted. The end-of-study marginal mean PPBC score was 3.3 (95% CI, 2.8 to 3.7) vs 2.9 (95% CI, 2.5 to 3.4) in the sham vs active groups, respectively. Findings were not stratified according

to neurogenic or non-neurogenic disease. The authors concluded that TTNS does not appear to be effective for treating symptoms in individuals with neurogenic or non-neurogenic OAB.

Sham-controlled trials of TTNS in individuals with acute spinal cord injury (TASCI; NCT 03965299) and Parkinson's disease (UROPARKTENS; NCT02190851) are ongoing.

Section Summary: Neurogenic Bladder Dysfunction
Few RCTs evaluating tibial nerve stimulation for treating neurogenic bladder have been published to date and all but one performed transcutaneous stimulation rather than PTNS. Studies varied widely in study population and comparator intervention. Study findings have not suggested that tibial nerve stimulation significantly reduces incontinence symptoms and other outcomes.

WEARABLE/NON-IMPLANTABLE NEUROMODULATION DEVICES
ZIDA usability testing was conducted in a simulated home use environment. Fifteen (15) participants were provided the ZIDA control unit, a ZIDA embedded sock, the instruction manual and quick start guide. Users had no prior training or exposure to the ZIDA device. The study results support the device labeling contains appropriate information for home use. Two clinical investigations of the ZIDA wearable neuromodulation system were conducted in the United States at a single center to obtain clinical information to demonstrate whether the device is substantially equivalent to the predicate device, the Urgent PC Neuromodulation System. The initial investigation enrolled 23 out of a planned 50 patient study but was stopped to amend the clinical protocol to obtain effectiveness information. After the protocol was amended, the second trial was launched enrolling 40 subjects. In total, 63 subjects, were randomized 1:1 to treatment with the device or sham-treatment with the device not activated.

Cava et al (2022) reviewed the home-based transcutaneous tibial nerve stimulation for overactive bladder syndrome. Forty patients diagnosed with OAB were recruited from a single site. There were 2 groups: a treatment group (21 patients, mean age 64), which used an active ZIDA® activation device (ZIDA) and a sham control group (SCG, 19 patients, mean age 72) randomized in a 1:1 ratio. After individual fitting of the sock and face-to-face instruction in the use of the device, subjects in both groups self-administered the treatment once weekly for 30 min at home for a duration of 12 weeks. Prior to randomization and in week 12, subjects completed 2, 3-day bladder diaries and a quality-of-life (QOL) survey. Treatment success was defined as at least a 50% reduction in urgency voids with or without incontinence or at least a 30% reduction in 24-h frequency from baseline to week 12. The key secondary endpoint was change in QOL from baseline to week 12. The success rate for the primary endpoint in the ZIDA group was reported at 80% (n = 16/20) versus 39% (n = 7/18) in the SCG (p = 0.02). For QOL, the least squares mean difference in change from baseline to week 12 between the ZIDA and sham control arms total score was - 12.7 (95% CI - 20.2 to - 5.1). No significant adverse effects were observed.

Peer reviewed literature regarding wearable/non-implantable neuromodulation devices is lacking.

FECAL INCONTINENCE

Clinical Context and Therapy Purpose

The purpose of PTNS in individuals who have fecal incontinence is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with fecal incontinence.

Interventions
The therapy being considered is PTNS. During PTNS, a needle is inserted above the medial malleolus into the posterior tibial nerve followed by the application of low-voltage (10 mA, 1-10 Hz frequency) electrical stimulation. Noninvasive PTNS may be delivered with transcutaneous or surface electrodes. The recommended course of treatment is an initial series of 12 weekly office-based treatments followed by an individualized maintenance treatment schedule.

Devices are not FDA cleared for the treatment of fecal incontinence.

Comparators
The following therapies are currently being used to make decisions about with fecal incontinence: conservative therapies (eg, medical management, retraining of pelvic floor and abdominal wall musculature, dietary changes), medications, and SNS.

Sacral nerve stimulation may be conducted in an outpatient clinical setting using temporary wire leads. Due to the incidence of lead migration, a 2-step process in a surgical setting is recommended. In the initial test phase, wire leads are inserted under the skin and if improvement is reported after 2 weeks, the patient may elect permanent implantation with a pacemaker-like stimulator. If the test phase is unsuccessful, the leads are then removed.

Outcomes
The general outcomes of interest are reduced symptoms (eg, self-reported assessment of symptoms, a decrease in number of voids per day) and improved quality of life. Outcomes are measured following the 6- to 12-week treatment regimen.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews
Luo et al (2024) published a meta-analysis evaluating PTNS versus sham electrical stimulation for treatment of fecal incontinence in adults.(38) The literature search was done through May 2022 and identified 4 RCTs (N=439). The analysis concluded that when compared to the

control group, PTNS showed greater efficacy in lowering weekly episodes of fecal incontinence (MD, −1.6; 95% CI −2.94 to −0.26; p=.02; I2=30%). A greater number of patients in the PTNS group also reported a weekly decrease in fecal incontinence episodes of more than 50% compared to the control group (RR, 0.73; 95% CI, 0.57 to 0.94; p=.02; I2=6%). None of the fecal incontinence quality of life or St Mark's incontinence scores showed any significant differences between groups.

Sarveazad et al (2019) conducted a systematic review and meta-analysis investigating the role of tibial nerve stimulation vs sham in the control of fecal incontinence.(39) A literature search conducted through December 2016 identified five studies including 249 patients treated with PTNS and 239 treated with sham. Studies utilizing transcutaneous stimulation were also eligible. A significant decrease in the number of fecal incontinence episodes was found in the PTNS group(standardized mean difference [SMD], -0.38; 95% CI, -0.67 to 0.10; I^2=32.8%; *P*=0.009). However, no significant effect on incontinence scores (SMD, 0.13; 95% CI, -0.49 to 0.75; I^2=88.0%; *P*=0.68), resting pressure (SMD, 0.12; 95% CI, -0.14 to 0.37; I^2=28.8%; *P*=0.67), squeezing pressure (SMD, -0.27; 95% CI, -1.03 to 0.50; I^2=85.5%; *P*=0.50), or maximum tolerable volume (SMD, -0.10; 95% CI, -0.40 to 0.20; I^2=0.0%; *P*=0.52) was reported.

Tan et al (2019) published a systematic review and meta-analysis reporting placebo response rates in electrical nerve stimulation trials for fecal incontinence and constipation.(40) A literature search was conducted through April 2017 identifying 10 randomized sham-controlled trials. Sham stimulation resulted in significant improvements in fecal incontinence episodes by 1.3 episodes per week (95% CI, -2.53 to -0.01; *P*=0.05) and Cleveland Clinic Severity Scoresby 2.2 points (95% CI, 1.01 to 3.36; *P*=0.0003). The authors note that these findings highlight the importance of sham controls in nerve stimulation trials.

Simillis et al (2018) conducted a systematic review and meta-analysis comparing PTNS with SNS for the treatment of fecal incontinence.(41) The literature search identified four studies (one RCT, three nonrandomized prospective studies) including 302 patients (109 undergoing SNS, 193 undergoing PTNS). The Cochrane Collaboration’s risk of bias tool was used to assess study quality. Because none of the studies blinded participants and personnel, the risk of performance and detection biases were high. Attrition and publication biases were not detected. Meta-analysis showed that patients undergoing SNS experienced significant improvements compared with patients undergoing PTNS as measured on the Wexner Fecal Incontinence Score (weighted mean difference [WMD], 2.3; 95% CI, 1.1 to 3.4) and fecal incontinence episodes per week (WMD, 8.1; 95% CI, 4.1 to 12.1).

Edenfeld et al (2015) conducted a literature search through November 2013 and identified 17 studies (four RCTs, 13 case series) for the use of tibial nerve stimulation (percutaneous and transcutaneous) for the treatment of fecal incontinence.(42) Three of the RCTs evaluated TENS stimulation and the other PTNS. The one RCT and 4 case series using PTNS reported significant decreases in weekly fecal incontinence episodes following 12 weeks of treatment. The quality-of-life domain scores (eg, depression, embarrassment, coping, lifestyle) showing significant improvements differed across the PTNS studies.

Horrocks et al (2014) conducted a literature search through February 2013 and identified 12 articles, six related to PTNS, five related to transcutaneous nerve stimulation, and one comparing both methods.(43) One RCT, by George et al 2013,(44) discussed below, was

included in the Horrocks et al (2014) and the Edenfield et al (2015) reviews. Horrocks et al (2014) identified five case series and an RCT that reported the outcome, 50% or greater reduction in the number of fecal incontinence episodes per week immediately after PTNS treatment. In these studies, a median of 71% of patients (range, 63%-82%) reported at least a 50% reduction in episodes. The Horrocks (2014) analysis did not report on control groups.

Randomized Controlled Trials

George et al (2013) published the first sham-controlled trial.(44) Thirty patients (28 women) who had failed conservative therapy for fecal incontinence were randomized to PTNS (n=11), TTNS ((n=11), or sham transcutaneous stimulation (n=8). Patients in all groups received a total of 12 treatments given twice-weekly for six weeks. (This differed from the PTNS manufacturer's recommended course of 12 weekly treatments.) The primary study end point was at least a 50% reduction in the mean number of incontinence episodes per week at the end of the 6-week treatment period. Only 1 patient failed to complete the trial, and data were analyzed on an ITT basis. Nine of 11 patients in the PTNS group, five of 11 in the TTNS group, and one of eight in the sham group attained the primary end point (p=0.035). The mean number of incontinence episodes per week (standard deviation) at the end of the study was 1.8 (0.8), 5.1 (4.2), and 4.7 (3.5) in the PTNS, transcutaneous nerve stimulation, and sham groups, respectively (p=0.04). The study is limited by the small sample size and short-term follow-up.

A large sham-controlled randomized trial, known as CONFIDeNT, was by Knowles et al (2015).(45) The trial was double-blind and multicenter. A total of 227 patients with fecal incontinence sufficiently severe to warrant intervention (according to the principal investigator at each site) were randomized to PTNS (n=115) or sham stimulation (n=112). Both groups received 12 weekly, 30-minute sessions. The primary outcome was at least a 50% reduction in the mean number of episodes of fecal incontinence per week compared with baseline. The mean number of episodes was calculated from 2-week bowel diaries. Twelve patients withdrew from the study. After treatment, 39 (38%) of 103 in the PTNS group and 32 (31%) of 102 in the sham group had at least a 50% reduction in the number of fecal incontinence episodes per week. The difference between groups was not statistically significant (adjusted OR, 1.28; 95% CI, 0.72 to 2.28; p=0.396). There was also no significant difference between the PTNS and sham groups in the proportion of patients achieving more than 25%, more than 75%, or 100% reduction in mean weekly episodes. There was, however, a significantly greater reduction in the absolute mean number of weekly fecal incontinence episodes in the PTNS group. The mean number of weekly fecal incontinence episodes in the PTNS group was 6.0 at baseline and 3.5 after treatment compared with 6.9 and 4.8, respectively, in the sham group (mean difference between, -2.26; 95% CI, -4.18 to -0.35; p=0.021).

Horrocks et al (2017) conducted a post hoc analysis of data from the CONFIDeNT trial, to evaluate factors associated with the efficacy of PTNS for fecal incontinence.(46) Results from the multivariable logistic regression on the outcome of 50% improvement in weekly fecal incontinence episodes found that age, fecal urgency, stool consistency, and severity of fecal incontinence did not affect response to PTNS. Presence of obstructive defecation was the only variable that negatively affected response to PTNS (odds ratio, 0.4; 95% CI, 0.2 to 0.9). Excluding patients with obstructive defecation (n=112) resulted in a significant effect of PTNS compared with sham (49% vs 18%, p=0.002).

Thin et al (2015) published data on PTNS versus sacral nerve stimulation (SNS) for fecal incontinence.(47) Forty women were randomized, 17 to PTNS and 23 to SNS. Patients in the PTNS group had an initial course of 12 weekly sessions and received three maintenance treatments during the following two months. SNS was provided using a two-stage approach: a test stimulation was conducted first, followed by permanent stimulation if they achieved a decrease in fecal incontinence episodes of at least 50% over the 2-week test period. The primary outcome was a reduction of at least 50% in fecal incontinence episodes per week (as determined by two-week bowel diaries). Fifteen women passed temporary SNS and underwent permanent implantation. The proportion of patients who achieve the primary outcome at six months was 11 (61%) of 18 in the SNS group and 7 (47%) of 15 in the PTNS group. Rates at three months were 9 (47%) of 19 in the SNS group and 6 (38%) of 16 in the PTNS group. The authors did not conduct a direct statistical comparison of SNS and PTNS because the study was a pilot.

A single-center, investigator-blinded RCT compared PTNS (n=25) to anal inserts (n=25) in patients with fecal incontinence.(48) At 3 months, a 50% reduction in weekly episodes of fecal incontinence, as calculated by a prospectively completed 2-week bowel diary, was found in 76% (19/25) of patients in the anal insert group and 48% (12/25) of patients in the PTNS group (p=.04). Both groups had similar improvements in St Mark's fecal incontinence scores and the International Consultation on Incontinence Questionnaire.

Zyczynski et al (2022) conducted the Neuromodulation for Accidental Bowel Leakage (NOTABLe) sham-controlled trial of PTNS in women with fecal incontinence (N=166).(49) Women with greater than or equal to 3 months of moderate-to-severe fecal incontinence were randomized to PTNS (n=111) or sham stimulation (n=55). Stimulation was delivered in 12 weekly 30-minute sessions to a single lower extremity. The primary outcome was change from baseline in St. Mark score (a 7-item, validated patient-reported outcome) measured after 12 weekly treatments. Secondary outcomes included stool consistency, bowel movement, and stool leakage episodes per week. There was no significant difference between the PTNS group (-5.3 points) and the sham group (-3.9 points) in terms of improvement from baseline in St. Mark scores (adjusted difference -1.3; 95% CI, -2.8 to 0.2). There also was no significant difference in reduction in weekly fecal incontinence episodes from baseline between the PTNS group (-2.1 episodes) and sham group (-1.9 episodes) (adjusted difference -0.26; 95% CI, -1.85 to 1.33).

Nonrandomized Studies

Sanagapalli et al (2018) conducted a retrospective chart review of consecutive patients with multiple sclerosis-related fecal incontinence who had failed conservative therapy and who were subsequently treated with PTNS.(50) Patients (N=33) received eight weekly treatments of PTNS, with responders receiving an additional four weeks of treatment. Subjects were classified as responders based on the Wexner Fecal Incontinence Score if scores at the end of treatment were either half of the baseline score or if the score was less than ten. Twenty-six (79%) of the patients were classified as responders. Responders tended to be more symptomatic at baseline and had greater improvements in quality-of-life scores.

Section Summary: Fecal Incontinence

Few RCTs evaluating PTNS for treating fecal incontinence have been published to date. The available RCTs have not found a clear benefit of PTNS. None of the sham-controlled trial found that active stimulation was superior to sham for achieving the primary outcome of at

least a 50% reduction in mean incontinence episodes. The sham-controlled randomized trial by Knowles et al found a significantly greater decrease in absolute number of weekly incontinence episodes in the active treatment group, but the overall trial findings did not suggest superiority of PTNS over sham treatment. The sham-controlled randomized trial by Zyczynski et al did not indicate a benefit of PTNS over sham stimulation either. A meta-analysis of one RCT and several observational studies reported that patients receiving SNS experienced significant benefits compared with patients receiving PTNS. A post hoc analysis of the larger trial suggested a subset of patients with fecal incontinence, those without concomitant obstructive defecation, might benefit from PTNS.

Summary of Evidence

For individuals who have non-neurogenic urinary dysfunction including overactive bladder and have failed behavioral and pharmacologic therapy who receive an initial course of PTNS, the evidence includes randomized sham-controlled trials, RCTs with an active comparator, and systematic reviews. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life and treatment-related morbidity. The Sham Effectiveness in Treatment of Overactive Bladder Symptoms (SUmiT) and the Overactive Bladder Innovative Therapy (OrBIT) trials are 2 key industry-sponsored RCTs. Systematic reviews that included these and other published trials have found short-term reductions in voiding dysfunction with PTNS. The largest, highest quality study was the double-blinded, sham-controlled SUmiT trial, which reported a statistically significant benefit of PTNS versus sham at 12 weeks. In an additional, small sham-controlled trial, a 50% reduction in urge incontinent episodes was attained in 71% of PTNS group compared with 0% in the sham group. The nonblinded OrBIT trial found that PTNS was noninferior to medication therapy at 12 weeks. Adverse events were limited to local irritation effects. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have overactive bladder syndrome that have failed behavioral and pharmacologic therapy who respond to an initial course of PTNS who receive maintenance PTNS, the evidence includes observational studies and systematic reviews. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The SUmiT and the OrBIT trials each included extension studies that followed individuals who responded to the initial course of PTNS and continued to receive periodic maintenance therapy. There is variability in the interval between and frequency of maintenance treatments, and an optimal maintenance regimen remains unclear. There are up to 36 months of observational data available, reporting that there is a durable effect for some of these patients. While comparative data are not available after the initial 12-week treatment period, the observational data support a clinically meaningful benefit for use in individuals who have already failed behavioral and pharmacologic therapy and who respond to the initial course of PTNS. PTNS may allow such individuals to avoid more invasive interventions. Adverse events appear to be limited to local irritation for both short- and long-term PTNS use. Typical regimens schedule maintenance treatments every 4-6 weeks. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have non-neurogenic urinary dysfunction including overactive bladder and who have failed behavioral and pharmacologic therapy or who have responded to an initial course of PTNS and then receive subcutaneous tibial nerve stimulation (STNS), the evidence includes single-arm studies. Relevant outcomes are symptoms, change in disease status,

functional outcomes, quality of life, and treatment-related morbidity. The pivotal open-label, single-arm study leading to FDA-approval of the subcutaneously-implanted, wireless eCoin tibial nerve stimulation system demonstrated a 68% response rate at 48 weeks of follow-up which surpassed a performance goal of 40%. However, the certainty of the evidence is limited by the lack of comparator group and a lower response rate observed during the COVID-19 pandemic. Additionally, the FDA noted that the performance goal was identified after patients had already been implanted. An ongoing post-approval study may elucidate the certainty of benefit, including safety of reimplantation given battery lifespan concerns. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have neurogenic bladder dysfunction who receive PTNS, the evidence includes several RCTs and a systematic review of RCTs and observational data. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Only a few RCTs evaluating tibial nerve stimulation for treating neurogenic bladder have been published to date, and all but one performed transcutaneous stimulation rather than PTNS. Studies varied widely in factors such as study populations and comparator interventions. Study findings have not reported that tibial nerve stimulation significantly reduced incontinence symptoms and improved other outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have an overactive bladder and associated symptoms of urinary urgency, urinary frequency, and urge incontinence and receive tibial nerve stimulation with a wearable non-implantable device, the evidence is lacking. FDA approvals are based on small studies and there is insufficient evidence in the peer-reviewed medical literature to establish the role of wearable/non -implantable neuromodulation devices. Well-designed clinical trials supporting the efficacy of wearable non-implantable neuromodulation devices for the use in urinary urgency, urinary frequency, and urge incontinence are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have fecal incontinence who receive PTNS, the evidence includes several RCTs and systematic reviews. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The available RCTs have not found a clear benefit of PTNS. Neither of the sham-controlled trials found that active stimulation was superior to sham for achieving a reduction in mean weekly fecal incontinence episodes. The larger sham-controlled randomized trial did find a significantly greater decrease in the absolute number of weekly incontinence episodes in the active treatment group, but the overall trial findings did not suggest the superiority of PTNS over sham treatment. An additional sham-controlled randomized trial did not identify a benefit of PTNS over sham stimulation. A meta-analysis of a single RCT and several observational studies reported that patients receiving sacral nerve simulation experienced significant benefits compared with patients receiving PTNS. A post hoc analysis of the larger trial suggested a subset of patients with fecal incontinence (those without concomitant obstructive defecation) may benefit from PTNS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

In 2018, the Blue Cross Blue Shield Association received clinical input on the use of maintenance percutaneous tibial nerve stimulation and its effect on net health outcome, for individuals with non-neurogenic urinary dysfunction including overactive bladder who have failed behavioral and pharmacologic therapy and responded to an initial course of percutaneous tibial nerve stimulation. Questions also included whether the use is consistent with generally accepted medical practice.

For individuals with non-neurogenic urinary dysfunction including overactive bladder who have failed behavioral and pharmacologic therapy and respond to an initial course of PTNS, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice.

RESPONDENTS

Clinical input was provided by the following physician members identified by a specialty society:

- David A. Ginsberg,[a] MD, Urology, Female pelvic medicine & reconstructive surgery (FPMRS), University of Southern California identified by American Urological Association (AUA)
- Howard B. Goldman,[a] MD, Urology, Female pelvic medicine & reconstructive surgery (FPMRS) Cleveland Clinic identified by AUA
- Matthew P. Rutman, MD, Association Professor of Urology, Columbia University identified by Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU).

[a] Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Clinical Input Responses

Figure 1:

Clinical Indication	Respondent	Identified by	Confidence Level That Clinical Use Expected to Provide Clinically Meaningful Improvement in Net Health Outcome										Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice									
			Yes or No	NO: 5 (High)	4	3 (Intermediate)	2	1 (Low)	YES: 1 (Low)	2	3 (Intermediate)	4	5 (High)	Yes or No	NO: 5 (High)	4	3 (Intermediate)	2	1 (Low)	YES: 1 (Low)	2	3 (Intermediate)	4	5 (High)
Maintenance PTNS in individuals with non-neurogenic urinary dysfunction including overactive bladder who have failed behavioral and pharmacologic therapy and who respond to an initial course of PTNS	Dr. Ginsberg**	AUA	YES								■			YES									■
	Dr. Goldman**	AUA	YES										■	YES									■
	Dr. Rutman	SUFU	YES										■	YES									■

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent

Additional Comments

- “In regard to duration we maintain patients on a monthly treatment. We do not give them leeway in regard to symptoms such that they might be stimulated more often.” (Dr. Ginsberg identified by AUA)

- “Patients typically have it done once a week for 12 weeks and then, if successful, every 4-6 weeks after that. They are seen in office by MD on a yearly basis to ensure efficacy is continuing.” (Dr. Goldman identified by AUA)
- “Management criteria would be once a week for 12 weeks and monthly afterward for maintenance.” (Dr. Rutman identified by SUFU)

Based on the evidence and independent clinical input, the clinical input supports that the following indication provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice:

- Use of monthly maintenance PTNS for individuals with non-neurogenic urinary dysfunction including overactive bladder who have failed behavioral and pharmacologic therapy and respond to an initial course of PTNS.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Urological Association et al

In 2019, the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) published guidelines on the diagnosis and treatment of non-neurogenic overactive bladder in adults.(51) The guidelines included a statement that clinicians may offer PTNS as a third-line treatment option in carefully selected individuals. The statement carried as Grade C, indicating that the balance of benefits and risks/burdens are uncertain. In 2024, the AUA/SUFU published a guideline on the diagnosis and treatment of idiopathic overactive bladder.(52) In the unabridged version of the guideline, PTNS is mentioned as a minimally invasive therapy option. The guideline states that:

- "Clinicians may offer minimally invasive procedures to patients who are unable or unwilling to undergo behavioral, non-invasive, or pharmacologic therapies (Clinical Principle)"
- "Clinicians may offer patients with OAB, in the context of shared decision making, minimally invasive therapies without requiring trials of behavioral, non-invasive, or pharmacologic management (Expert Opinion)".
- “In patients with OAB who have an inadequate response to or have experienced intolerable side effects from pharmacotherapy or behavioral therapy, clinicians should offer…percutaneous tibial nerve stimulation….” (Moderate Recommendation; Evidence Level: Grade A)

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2015) practice bulletin on treatment of urinary incontinence in women did not address PTNS or other types of nerve stimulation.(53)

American Gastroenterological Association

The American Gastroenterological Association (2017) issued an expert review and clinical practice update on surgical interventions and device-aided therapy for the treatment of fecal incontinence.(54) The update stated that “until further evidence is available, percutaneous tibial nerve stimulation should not be used for managing FI [fecal incontinence] in clinical practice.”

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 7.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05685433[a]	A Real World Study of eCoin for Urgency Urinary Incontinence: Post Approval Evaluation (RECIPE)	200	Dec 2030 (recruiting)
NCT05882318[a]	Evaluating Effectiveness of Sensory and Subsensory Stimulation Amplitudes With eCoin® Tibial Nerve Stimulation in Urgency Urinary InContinence Episodes and Quality of Life (ESSENCE)	50	Jul 2024 (unknown)
NCT05422625	PTNS for Female Patients Suffering From Multiple Sclerosis (PTNS-MS)	34	Oct 2023
Unpublished			
NCT02190851	Evaluation of Treatment by Transcutaneous Electrical Nerve Stimulation (TENS) of the Posterior Tibial Nerve for Lower Urinary Tract Disorders in Parkinson's Syndrome (UROPARKTENS)	220	Oct 2020 (completed)

NCT: national clinical trial.

Government Regulations

National:

No national coverage determination noted.

Local:

No local coverage determination noted.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Biofeedback
- Fecal Incontinence – Investigational Treatments
- Magnetic Pelvic Floor Stimulation as a Treatment of Urinary Incontinence
- Percutaneous Electrical Nerve Stimulation and Percutaneous Neuromodulation Therapy
- Sacral Nerve Neuromodulation/Stimulation

References

1. Wang M, Jian Z, Ma Y, et al. Percutaneous tibial nerve stimulation for overactive bladder syndrome: a systematic review and meta-analysis. Int Urogynecol J. Dec 2020; 31(12): 2457-2471. PMID 32681345

2. Xiong SC, Peng L, Hu X, et al. Effectiveness and safety of tibial nerve stimulation versus anticholinergic drugs for the treatment of overactive bladder syndrome: a meta-analysis. Ann Palliat Med. Jun 09 2021. PMID 34118839
3. Coolen RL, Groen J, Scheepe JR, et al. Transcutaneous Electrical Nerve Stimulation and Percutaneous Tibial Nerve Stimulation to Treat Idiopathic Nonobstructive Urinary Retention: A Systematic Review. Eur Urol Focus. Oct 22 2020. PMID 33268327
4. Ho FCS, He C, Yao HH, et al. Efficacy of sacral neuromodulation and percutaneous tibial nerve stimulation in the treatment of chronic nonobstructive urinary retention: A systematic review. Neurourol Urodyn. Jun 2021; 40(5): 1078-1088. PMID 33973670
5. Tutolo M, Ammirati E, Heesakkers J, et al. Efficacy and Safety of Sacral and Percutaneous Tibial Neuromodulation in Non-neurogenic Lower Urinary Tract Dysfunction and Chronic Pelvic Pain: A Systematic Review of the Literature. Eur Urol. Mar 2018; 73(3): 406-418. PMID 29336927
6. Tutolo M, Ammirati E, Van der Aa F. What Is New in Neuromodulation for Overactive Bladder?. Eur Urol Focus. Jan 2018; 4(1): 49-53. PMID 29773501
7. Stewart F, Gameiro LF, El Dib R, et al. Electrical stimulation with non-implanted electrodes for overactive bladder in adults. Cochrane Database Syst Rev. Dec 09 2016; 12: CD010098. PMID 27935011
8. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Percutaneous tibial nerve stimulation for the treatment of voiding dysfunction. TEC Assessments. 2013;Volume 28:Tab 10.
9. Burton C, Sajja A, Latthe PM. Effectiveness of percutaneous posterior tibial nerve stimulation for overactive bladder: a systematic review and meta-analysis. Neurourol Urodyn. Nov 2012; 31(8): 1206-16. PMID 22581511
10. Levin PJ, Wu JM, Kawasaki A, et al. The efficacy of posterior tibial nerve stimulation for the treatment of overactive bladder in women: a systematic review. Int Urogynecol J. Nov 2012; 23(11): 1591-7. PMID 22411208
11. Moossdorff-Steinhauser HF, Berghmans B. Effects of percutaneous tibial nerve stimulation on adult patients with overactive bladder syndrome: a systematic review. Neurourol Urodyn. Mar 2013; 32(3): 206-14. PMID 22907807
12. Gaziev G, Topazio L, Iacovelli V, et al. Percutaneous Tibial Nerve Stimulation (PTNS) efficacy in the treatment of lower urinary tract dysfunctions: a systematic review. BMC Urol. Nov 25 2013; 13: 61. PMID 24274173
13. Shamliyan T, Wyman J, Kane RL. Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness (Comparative Effectiveness Review No. 36). Rockville, MD: Agency for Healthcare Research and Quality; 2012.
14. Finazzi-Agro E, Petta F, Sciobica F, et al. Percutaneous tibial nerve stimulation effects on detrusor overactivity incontinence are not due to a placebo effect: a randomized, double-blind, placebo-controlled trial. J Urol. Nov 2010; 184(5): 2001-6. PMID 20850833
15. Peters KM, Carrico DJ, Perez-Marrero P, et al. Randomized trial of percutaneous tibial nerve stimulation versus sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial. J Urol. 2010;183(4):1438-1443. PMID 20171677
16. Peters K, Carrico D, Burks F. Validation of a sham for percutaneous tibial nerve stimulation (PTNS). Neurourol Urodyn. 2009;28(1):58-61. PMID 18671297
17. 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. Dec 3, 2012. PMID 23219541
18. Vecchioli-Scaldazza C, Morosetti C. Effectiveness and durability of solifenacin versus percutaneous tibial nerve stimulation versus their combination for the treatment of women

with overactive bladder syndrome: a randomized controlled study with a follow-up of ten months. *Int Braz J Urol.* Jan-Feb 2018;44(1):102-108. PMID 29064651
19. Boudaoud N, Binet A, Line A, et al. Management of refractory overactive bladder in children by transcutaneous posterior tibial nerve stimulation: A controlled study. *J Pediatr Urol.* Jun 2015;11(3):138 e131-110. PMID 25979217
20. Gungor Ugurlucan F, Onal M, Aslan E, et al. Comparison of the effects of electrical stimulation and posterior tibial nerve stimulation in the treatment of overactive bladder syndrome. Gynecol Obstet Invest. 2013;75(1):46- 52. PMID 23171636
21. Preyer O, Umek W, Laml T, et al. Percutaneous tibial nerve stimulation versus tolterodine for overactive bladder in women: a randomised controlled trial. Eur J Obstet Gynecol Reprod Biol. Aug 2015;191:51-56. PMID 26073262
22. Vecchioli-Scaldazza C, Morosetti C, Berouz A, et al. Solifenacin Succinate versus Percutaneous Tibial Nerve Stimulation in Women with Overactive Bladder Syndrome: Results of a Randomized Controlled Crossover Study. Gynecol Obstet Invest. Mar 28 2013. PMID 23548260
23. Schreiner L, dos Santos TG, Knorst MR, et al. Randomized trial of transcutaneous tibial nerve stimulation to treat urge urinary incontinence in older women. Int Urogynecol J. Sep 2010;21(9):1065-1070. PMID 20458465
24. Peters K, MacDiarmid SA, Wooldridge LS, et al. Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results from the overactive bladder innovative therapy trial. J Urol. 2009;182(3-Jan): 1055-1061. PMID 19616802
25. MacDiarmid SA, Peters KM, Shobeiri SA, et al. Long-term durability of percutaneous tibial nerve stimulation for the treatment of overactive bladder. J Urol. 2010;183(1):234-240. PMID 19913821
26. Rogers A, Bragg S, Ferrante K, et al. Pivotal Study of Leadless Tibial Nerve Stimulation with eCoin® for Urgency Urinary Incontinence: An Open-Label, Single Arm Trial. J Urol. Aug 2021; 206(2): 399-408.PMID 33797291
27. U.S. Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED): eCoin Peripheral Neurostimulator System (P200036). March 1, 2022;https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200036B.pdf. Accessed June 28, 2023.
28. 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 UrinaryIncontinence. J Urol. May 2019; 201(5): 967-972. PMID 31009968
29. Gilling P, Meffan P, Kaaki B, et al. Twelve-month Durability of a Fully-implanted, Nickel-sized and Shaped Tibial Nerve Stimulator for the Treatment of Overactive Bladder Syndrome with Urgency UrinaryIncontinence: A Single-Arm, Prospective Study. Urology. Nov 2021; 157: 71-78. PMID 34048826
30. Kaaki B, English S, Gilling P, et al. Six-Month Outcomes of Reimplantation of a Coin-Sized Tibial Nerve Stimulator for the Treatment of Overactive Bladder Syndrome With Urgency Urinary Incontinence. Female Pelvic Med Reconstr Surg. May 01 2022; 28(5): 287-292. PMID 35536667
31. Schneider MP, Gross T, Bachmann LM, et al. Tibial Nerve Stimulation for Treating Neurogenic Lower Urinary Tract Dysfunction: A Systematic Review. *Eur Urol.* Nov 2015;68(5):859-867. PMID 26194043
32. Monteiro ES, de Carvalho LB, Fukujima MM, et al. Electrical stimulation of the posterior tibialis nerve improves symptoms of poststroke neurogenic overactive bladder in men: a randomized controlled trial. Urology. Sep 2014;84(3):509-514. PMID 25168524

33. Perissinotto MC, D'Ancona CA, Lucio A, et al. Transcutaneous tibial nerve stimulation in the treatment of lower urinary tract symptoms and its impact on health-related quality of life in patients with Parkinson disease: a randomized controlled trial. *J Wound Ostomy Continence Nurs.* Jan-Feb 2015;42(1):94-99. PMID 25549314
34. Gaspard L, Tombal B, Opsomer RJ, et al. [Physiotherapy and neurogenic lower urinary tract dysfunction in multiple sclerosis patients: a randomized controlled trial]. *Prog Urol.* Sep 2014;24(11):697-707. PMID 25214451
35. Eftekhar T, Teimoory N, Miri E, et al. Posterior tibial nerve stimulation for treating neurologic bladder in women: a randomized clinical trial. *Acta Med Iran.* 2014;52(11):816-821. PMID 25415813
36. Zonic-Imamovic M, Imamovic S, Cickusic A, et al. Effects of Treating an Overactive Urinary Bladder in Patients with Multiple Sclerosis. Acta Med Acad. Dec 2019; 48(3): 271-277. PMID 32124625
37. Welk B, McKibbon M. A randomized, controlled trial of transcutaneous tibial nerve stimulation to treat overactive bladder and neurogenic bladder patients. Can Urol Assoc J. Jul 2020; 14(7): E297-E303. PMID 32017693
38. Luo C, Wei D, Pang K, et al. Is percutaneous tibial nerve stimulation (PTNS) effective for fecal incontinence (FI) in adults compared with sham electrical stimulation? A meta-analysis. Tech Coloproctol. Feb 24 2024; 28(1): 37. PMID 38401006.
39. Sarveazad A, Babahajian A, Amini N, et al. Posterior Tibial Nerve Stimulation in Fecal Incontinence: A Systematic Review and Meta-Analysis. Basic Clin Neurosci. Sep-Oct 2019; 10(5): 419-431. PMID 32284831
40. Tan K, Wells CI, Dinning P, et al. Placebo Response Rates in Electrical Nerve Stimulation Trials for Fecal Incontinence and Constipation: A Systematic Review and Meta-Analysis. Neuromodulation. Dec 30 2019. PMID31889364
41. Simillis C, Lal N, Qiu S, et al. Sacral nerve stimulation versus percutaneous tibial nerve stimulation for faecal incontinence: a systematic review and meta-analysis. Int J Colorectal Dis. May 2018;33(5):645-648. PMID 29470730
42. Edenfield AL, Amundsen CL, Wu JM, et al. Posterior tibial nerve stimulation for the treatment of fecal incontinence: a systematic evidence review. *Obstet Gynecol Surv.* May 2015;70(5):329-341. PMID 25974730
43. Horrocks EJ, Thin N, Thaha MA, et al. Systematic review of tibial nerve stimulation to treat faecal incontinence. Br J Surg. Apr 2014;101(5):457-468. PMID 24446127
44. George AT, Kalmar K, Sala S, et al. Randomized controlled trial of percutaneous versus transcutaneous posterior tibial nerve stimulation in faecal incontinence. Br J Surg. Feb 2013;100(3):330-338. PMID 23300071
45. Knowles CH, Horrocks EJ, Bremner SA, et al. Percutaneous tibial nerve stimulation versus sham electrical stimulation for the treatment of faecal incontinence in adults (CONFIDeNT): a double-blind, multicentre, pragmatic, parallel-group, randomised controlled trial. Lancet. Oct 24, 2015;386(10004):1640-1648. PMID 26293315
46. Horrocks EJ, Chadi SA, Stevens NJ, et al. Factors associated with efficacy of percutaneous tibial nerve stimulation for fecal incontinence, based on post-hoc analysis of data from a randomized trial. Clin Gastroenterol Hepatol. Dec 2017;15(12):1915-1921 e1912. PMID 28647458
47. Thin NN, Taylor SJ, Bremner SA, et al. Randomized clinical trial of sacral versus percutaneous tibial nerve stimulation in patients with faecal incontinence. *Br J Surg.* Mar 2015;102(4):349-358. PMID 25644291

48. Leo CA, Thomas GP, Hodgkinson JD, et al. Randomized Pilot Study: Anal Inserts Versus Percutaneous Tibial Nerve Stimulation in Patients With Fecal Incontinence. Dis Colon Rectum. Apr 01 2021; 64(4): 466-474. PMID 33399411
49. Zyczynski HM, Richter HE, Sung VW, et al. Percutaneous Tibial Nerve Stimulation vs Sham Stimulation for Fecal Incontinence in Women: NeurOmodulaTion for Accidental Bowel Leakage Randomized Clinical Trial. *Am J Gastroenterol*. Apr 01 2022; 117(4): 654-667. PMID 35354778
50. Sanagapalli S, Neilan L, Lo JYT, et al. Efficacy of percutaneous posterior tibial nerve stimulation for the management of fecal incontinence in multiple sclerosis: a pilot study. Neuromodulation. Mar 25, 2018. PMID 29575432
51. Lightner, DD, Gomelsky, AA, Souter, LL, Vasavada, SS. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. J. Urol., 2019 May 1;101097 PMID 31039103
52. Cameron AP, Chung DE, Dielubanza EJ, et al. The AUA/SUFU guideline on the diagnosis and treatment of idiopathic overactive bladder. J Urol. Published online April 23, 2024. doi:10.1097/JU.0000000000003985. https://www.auajournals.org/doi/10.1097/JU.0000000000003985.
53. ACOG Practice Bulletin No. 155: Urinary Incontinence in Women. *Obstet Gynecol.* Nov 2015;126(5):e66-81. PMID 26488524
54. Bharucha AE, Rao SSC, Shin AS. Surgical interventions and the use of device-aided therapy for the treatment of fecal incontinence and defecatory disorders. Clin Gastroenterol Hepatol. Dec 2017;15(12):1844-1854. PMID 28838787
55. Wisconsin Physicians Service Insurance Corporation, Local Coverage Determination: Posterior Tibial Nerve Stimulation (PTNS) (L34436). Retired Effective Date 04/14/2019.
56. Tipton, WA, de Riese, WTW, and de Riese, CS. "Review of New Implantable Tibial Nerve Stimulators in Comparison to Established Third Line Treatment Modalities for Nonneurogenic Overactive Bladder." *Uro Prac.* 2020; 7(6):530-537.
57. Zida. "Clinical Data." 2023. https://livezida.com/clinical-data/. Accessed December 20, 2024.
58. U.S. Food & Drug Administration. "ZIDA Wearable Neuromodulation System 510(k). K192731. 2021. https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192731.pdf. Accessed December 20, 2024.
59. Cava R, Orlin Y. "Home-based transcutaneous tibial nerve stimulation for overactive bladder syndrome: a randomized, controlled study." *Int Urol Nephrol*. 2022 Aug;54(8):1825-1835. doi: 10.1007/s11255-022-03235-z. Epub 2022 May 27. PMID: 35622269.
60. Goudelocke, C. Sobol, J. et al. "A Multicenter Study Evaluating the FREquency of Use and Efficacy of a Novel Closed-Loop Wearable Tibia Neuromodulation System for Overactive Bladder and Urgency Urinary Incontinence (FREEOAB)." *Female Urology*. 2023. 183:1-7. https://avation.com/closed-loop-neuromodulation. Accessed December 20, 2024.
61. U.S. Food & Drug Administration. "Vivally System Wearable, Non-Invasive Neuromodulation System and Mobile Application. 510(k). K220454. 2023. https://www.accessdata.fda.gov/cdrh_docs/pdf22/K220454.pdf. Accessed December 20, 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/15/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/08	9/15/08	8/19/08	Joint policy established
1/1/11	10/12/10	10/27/10	Code update: added CPT code 64566; removed NOC code 64999 No change to policy status Changed the word “voiding” to “urinary” in policy title
1/1/13	10/16/12	10/16/12	Routine maintenance; title changed from “Posterior Tibial Nerve Stimulation for Urinary Dysfunction” to current title.
5/1/14	2/18/14	2/28/14	Policy position changed to “established;” supporting literature updated. CMS information updated to reflect coverage of PTNS.
7/1/15	4/21/15	5/8/15	Routine review; title changed from “Posterior Tibial Nerve Stimulation for Voiding Dysfunction” to current title; added fecal incontinence as an exclusion.
7/1/16	4/19/16	4/19/16	Routine maintenance
1/1/17	10/11/16	10/11/16	Routine maintenance
1/1/18	10/19/17	10/19/17	Routine maintenance
1/1/19	10/16/18	10/16/18	Routine maintenance
5/1/19	2/19/19		Routine maintenance
5/1/20	2/18/20		Routine maintenance; 0587T-0590T added per code update
5/1/21	2/16/21		Routine maintenance
5/1/22	2/15/22		Routine maintenance
5/1/23	2/21/23		Routine maintenance (slp) Vendor Managed: N/A
5/1/24	2/28/24		• Routine maintenance (slp) • Vendor Managed: EviCore manages 97014 and 97032 • Exclusion added for implantable TNS products (e.g., eCoin [subcut], Revi [subfascial]) • Title updated from: Percutaneous Tibial Nerve Stimulation

			• MPS statement added for implantables - EI • Maximum timeframes added for treatment regimens
5/1/25	2/18/25		• Routine maintenance (slp) • Vendor managed: Evicore manages 97014 and 97032 • A4545, E0736 and E0737 added to policy as EI (Vivally and Zida) • Title change from Percutaneous and Implantable Tibial Nerve Stimulation

Next Review Date: 1st Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: TIBIAL NERVE STIMULATION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.