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Medical Policy Manual

Topic: Posterior Tibial Nerve Stimulation for Voiding Dysfunction

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Posterior tibial nerve stimulation (PTNS) is a technique of electrical neuromodulation for the treatment of voiding dysfunction in patients who have failed behavioral and/or pharmacologic therapies. The posterior tibial nerve is derived from the lumbar-sacral nerves (L4-S3) which control the bladder detrusor and perineal floor. The goal of PTNS is to alter the function of the posterior tibial nerve to improve voiding function and control. Voiding dysfunction includes urinary frequency, urgency, incontinence, and nonobstructive retention. Urgency symptoms and/or urge incontinence may also be referred to as overactive bladder (OAB). Common causes of voiding dysfunction are pelvic floor dysfunction (from pregnancy, childbirth, surgery, etc.), inflammation, interstitial cystitis, medication (e.g., diuretics and anticholinergics), obesity, psychogenic factors and disease (e.g., multiple sclerosis, spinal cord injury, detrusor hyperreflexia, diabetes with peripheral nerve involvement).

PTNS was developed as a less-invasive treatment alternative to traditional sacral root neuromodulation which has been successfully used in the treatment of urinary dysfunction, but requires implantation of a permanent device. The procedure for PTNS consists of the insertion of a needle above the medial malleolus into the posterior tibial nerve followed by the application of low voltage (10mA, 1-10 Hz frequency) electrical stimulation which produces sensory and motor responses (i.e., a tickling sensation and plantar flexion or fanning of all toes). Noninvasive PTNS has also been delivered with surface electrodes. PTNS studies have been designed as 30-minute sessions given weekly for 10-12 weeks. Recently, consideration has been given to increasing the frequency of treatments to 3 times per week to

speed achievement of desired outcomes. Also being studied is whether a shorter initial weekly treatment period might be as effective as the 12 week regimen. However, an optimal treatment protocol has not been established.

PTNS must be distinguished from acupuncture with electrical stimulation. In electrical acupuncture, needles are also inserted just below the skin, but the placement of needles is based on specific theories regarding energy flow throughout the human body. Thus in PTNS, the location of stimulation is directly in the posterior tibial nerve rather than using the theories of energy flow that guide placement of stimulation for acupuncture.

Regulatory Status

The Urgent® PC Neuromodulation System (Uroplasty, Inc.) – Formerly called the Stoller Afferent Nerve Stimulator (PerQ SANS System), received U.S. Food and Drug Administration (FDA) 510(k) approval for the treatment of urinary urgency, urinary frequency, and urge incontinence.

Note: Stimulation of the sacral nerve as a treatment of incontinence is discussed separately in Surgery Policy No. 134. Pelvic floor stimulation as a treatment of urinary incontinence refers to electrical stimulation of the pudendal nerve and is addressed separately in Allied Health, Policy No. 4.

MEDICAL POLICY CRITERIA

Posterior tibial nerve stimulation for urinary dysfunction, including but not limited to overactive bladder syndrome, neurogenic bladder, urinary frequency, urgency, incontinence and retention, is considered **investigational**.

SCIENTIFIC EVIDENCE

Literature Appraisal

In order to isolate the specific therapeutic effects of posterior tibial nerve stimulation (PTNS) and adequately control for placebo effects and individual patient differences (clinical and demographic, known and unknown), well-designed randomized clinical trials (RCTs) that compare PTNS with the current standard of care and sham treatment are necessary. The RCT is the most rigorous and reliable study design for demonstrating a causal relationship between the therapy under investigation and the health outcomes of interest. This form of study is necessary in order to understand whether an intervention such as PTNS can positively impact the health outcomes of patients with voiding dysfunction. Although informative, evidence from observational studies describing experiences of PTNS-treated patients is of limited utility in establishing causal relationships; therefore, the focus of the literature appraisal below is on RCTs investigating PTNS for voiding dysfunction.

Technology Assessments

The 2010 BlueCross BlueShield Association (BCBSA) Technology Evaluation Center (TEC) assessment for treatment of voiding dysfunction offered the following parameters for the study of

posterior tibial nerve stimulation (PTNS) for voiding dysfunction:[1]

- To establish the safety and effectiveness of posterior tibial nerve stimulation (PTNS), both the initial 12-week treatment phase and the subsequent maintenance phase must be considered.
- Because of the differences in treatment protocol, efficacy in the initial treatment phase cannot automatically be extrapolated as demonstrating efficacy in the maintenance phase.
- Overactive bladder (OAB) is a chronic condition and, as such, it is important to establish efficacy over a period of time longer than several months.
- A sham control is feasible, as validated by Peters and colleagues in a blinded pilot study in which 10 of the 30 healthy volunteers (33%) correctly identified the sham procedure.[2] This percentage is below the 50% that could be expected by chance, so the authors concluded that the procedure was a feasible sham.

The TEC Assessment summarized the articles described below and offered the following conclusions:

- The scientific evidence is sufficient to establish a short-term treatment benefit for PTNS.

  Three randomized, controlled trials (2 with placebo control group, 1 with medication control group) reported short-term benefit for the 12-week initial treatment period.

- The scientific evidence is not sufficient to permit conclusions on the long-term efficacy of PTNS treatment
  - Longer-term durability of treatment response has not been demonstrated.
  - Only one trial reports on outcomes past the initial 12-week treatment period; however, the data from this trial is unreliable due to significant study design flaws.
  - The ideal study design to answer the question of durability would be a longer-term randomized, controlled trial that maintained masked group assignment.

In 2014, BCBSA published an updated TEC assessment which concluded that PTNS met the TEC criteria for treatment of voiding dysfunction.[3] The Assessment included 6 randomized controlled trials (RCTs) which are assessed in further detail in the RCT section of this policy. The 2014 assessment reached the following conclusions:

- RCT evidence supports short-term efficacy of PTNS compared with a placebo applied in the standard 12-week regimen.

  This conclusion was based upon two short-term sham controlled trials[4,5] and four RCTs[2,6-8] which compared PTNS to active intervention, which included antimuscarinics, ES, or Kegel exercises. Only one of these trials[4] was noted as being of "high" quality by the U.S. Preventative Services Task Force (USPSTF), while four were noted of being of "poor" quality due to various limitations which included the following:

  - Lack of blinding to PTNS and sham controls
  - Substantial dropout rates
  - Failure to use sham control group
  - Suboptimal administration of comparison medication

In addition, four of the six RCTs were small in nature with less than 60 subjects total enrolled.

- Evidence is still lacking regarding the efficacy of PTNS past a 12-week regimen; however, 12- to 36- month evidence appears consistent in direction with 12- week data outcomes.

  This conclusion is based upon data provided by two extension studies[9,10] regarding PTNS maintenance effects. Responders were followed for 12 months in one study and 36 months in another; however, patients in the control groups were not followed past 12 weeks, limiting comparison between groups. In addition, there was a high drop-out rate in both extension studies which limited the ability to control for placebo affects or draw conclusions about the long-term efficacy of PTNS treatment.

Randomized Controlled Trials (RCTs)

The following is a summary of the six clinical trials analyzed in the 2010 and 2014 TEC assessments above.

- In 2009, Peters and colleagues published an industry-sponsored non-blinded comparison of PTNS and extended-release tolterodine (Detrol LA) for treatment of overactive bladder syndrome (the OrBIT trial).[11] The study included 100 patients, over 90% women, with at least eight voids per 24 hours (mean 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.

  A total of 87 of the 100 (87%) patients completed the study and voiding diary data were available for only 84 patients, 41 of 50 (82%) in the PTNS group and 43 of 50 (86%) in the tolterodine group. Study findings showed non-inferiority of PTNS, with a decrease in voids per day of 2.4 in the PTNS group and 2.5 in the tolterodine group. The study reported mixed findings for a number of secondary outcomes, some of which were based on patient reports. There were no statistically significant differences in the PTNS and tolterodine groups for other symptoms recorded in the voiding diary. This finding includes episodes of nocturia (-0.7 and -0.6, respectively) and episodes of moderate to severe urgency per day (-2.2 and -2.9, respectively), and episodes of urge incontinence per day (-1.0 and -1.7, respectively). There was a statistically significant difference in the proportion of patients reporting improvement or cure in symptoms in favor of the PTNS group (79.5 vs. 54.8%).

  Limitations of this study include the following:

  - Lack of blinding of patient and providers
  - Lack of comparative data beyond the end of the initial 12-week treatment period
  - Lack of a sham/placebo group both to mitigate the potential bias due to subjective outcomes and to evaluate whether either treatment is better than placebo
  - The results for 16% of the original 100 patients is not reported
  - Data were not reported for compliance with medication therapy
  - The authors did not clearly define criteria for “improvement” or “cure”, a key secondary outcome
  - Different methods of data collection in the 2 groups for adverse event outcomes and possibly also for other self-report outcomes; specifically, The PTNS group was assessed in person while the medication group was assess by telephone

  In 2010, MacDiarmid and colleagues reported 1-year follow-up data for patients from the OrBIT trial who had been assigned to the PTNS group and had responded to the initial course of treatment,

defined as reporting symptom improvement at 12 weeks.[9] Thirty-three of the 35 responders were included. They received a mean of 12.1 (SD=4.9) treatments between the 12-week and 12-month visits, and there was a median of 17 days between treatments. Data were available for 32 of the 33 (97%) participants at 6 months and 25 of the 33 (76%) participants at 12 months. The mean reduction in number of voids per day from baseline (the original primary outcome of the study) was 3.2 (SD=3.7) at 6 months and 2.8 (SD=3.7) at 12 months. Other voiding diary outcomes at 12 months, based on 25 responses, were mean changes in nocturia episodes of -0.8, in episodes of moderate to severe urgency per day of -3.7, and in episodes of urge incontinence per day of -1.6. As noted above, this analysis was limited in that no data from the tolterodine group were available to compare long-term outcomes. Additionally, not all patients in the PTNS group were included in the follow-up analysis; only PTNS responders were eligible. Therefore, a potential bias is that the initial subjective outcome measure may be subject to the placebo effect. Patients in the PTNS group who responded to initial treatment may be particularly susceptible to a placebo response and/or may represent those with the best treatment response. Thus, these individuals may also be susceptible to a placebo response during maintenance treatments, especially treatments offered on an as-needed basis. It is important that long-term response data from RCTs reflect the patient population at the beginning of the study. In addition, since subjects were not counseled on fluid management, it is unknown if subject fluid management habits influenced results. The authors note that, "with an average overactive bladder (OAB) symptom duration of more than 10 years, subjects may have already learned fluid management as a means to mediate OAB symptoms." Due to these significant study design flaws, the data in this study are unreliable and do not permit conclusion about long-term efficacy.

- The SUmiT trial was a randomized, sham-controlled trial that included 220 OAB patients with a score of at least 4 on the overactive bladder questionnaire (OAB-q) short form for urgency, self-report bladder symptoms lasting at least 3 months, and having failed conservative care.[4] Patients were randomized at a 1:1 ratio to either active or sham PTNS. Both 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. An inactive PTNS surface electrode was used and also 2 active TENS surface electrodes. The TENS unit was used to deliver low-level sensation to simulate the PTNS intervention. The 12-week course of treatment was completed by 103 of 110 (94%) in the PTNS group and 105 of 110 (95%) in the sham group.

  The primary study outcome was response to treatment based on a single-item global response assessment (GRA) variable at 13 weeks. Possible responses were that symptoms were markedly worse, moderately worse, mildly worse, the same, slightly improved, moderately improved, or markedly improved. The proportion of patients who responded to treatment based on the GRA (i.e., answered that symptoms were moderately or markedly improved) was 60 of 110 (54.5%) in the PTNS group and 23 of 110 (20.9%) in the sham group ($p<0.001$). Intention-to-treat analysis was used for the primary endpoint only. Several secondary outcomes also favored the PTNS group. The mean reduction in a symptom severity score (a lower score indicates less severity) was 36.7 (SD=21.5) in the PTNS group and 29.2 (SD=20.0) in the sham group ($p=0.01$). Similarly, the mean reduction in a quality of life scale, the SF-36 (a higher score indicates higher quality of life), was 34.2 (SD=21.3) in the PTNS group and 20.6 (SD=20.6) in the sham group ($p=0.006$).

  For the 4 voiding diary variables used, there was a statistically significant difference between groups favoring PTNS. The mean change from baseline in the number of voids per day was -2.4 (SD=2.5) in the PTNS group and -1.5 (SD=2.4) in the sham group (difference between groups 0.9 voids per day, $p=0.01$). The mean change in nocturia episodes was -0.7 (SD=1.2) in the PTNS group and -0.3

(SD=1.4) in the sham group (difference between groups 0.4 nighttime voids, p=0.04). The mean change in moderate to severe urgency per day was -3.7 in the PTNS group and -2.0 in the sham group (difference between groups 1.7 episodes, p less than 0.001). Finally, the mean change in urge incontinence episodes was -1.3 in the PTNS group and -0.3 in the sham group (difference between groups 1 episode per day, p less than 0.002). (Standard deviations were not reported for the latter 2 outcomes.)

Advantages of the SUmiT trial were that it included a sham comparison and the primary endpoint analysis was intention to treat. A limitation was that the primary outcome, the GRA, was a single-item subjective measure. For the more objective measures, the voiding diary variables, there was statistically significantly greater benefit with PTNS compared to sham treatment; however, the clinical significance of the difference between the PTNS and sham groups was unclear e.g., on average, there was 1 fewer episode of urge incontinence a day in the PTNS group. In addition, as in the OrBIT trial, the SUmiT trial only reported comparative data immediately following the initial course of treatment; the study did not evaluate the long-term effectiveness of PTNS. Unlike medication which can be taken on an ongoing basis, PTNS involves an initial 12-week course of treatment followed by maintenance therapy, which to date has not been well-defined. Therefore, the assumption cannot be made that short-term treatment effects will be maintained.

Results from a long-term extension of the SUmiT study were published in 2012.[10] Fifty patients were included and were prescribed a fixed schedule 14 week tapering protocol followed by a personal treatment plan. Only 29 patients (58%) completed the study and of those who did, 77% showed a moderate or marked improvement in OAB symptoms. Like the OrBIT trial extension, the STEP (Sustained Therapeutic Effects of Percutaneous Tibial Nerve Stimulation) study only included patients assigned to the PTNS group who responded to treatment and did not include additional follow-up of initial non-responders or comparative data from patients assigned to the sham-control group. Given this design, it is unlikely that the study results adequately resolve outstanding issues. It is critically important that long-term response rates reflect the patient population at the beginning of the study, not just those considered successes at 12 weeks. Other methodological limitations include the addition of an external intervention in the form of a personalized treatment plan which may have biased outcomes. In addition, the high loss-to-follow-up rate severely limited the reliability of any conclusion regarding the long-term utility of PTNS treatment for patients with OAB.

- Finazzi-Agro and colleagues studied the effect of more frequent treatment sessions for a reduced initial period.[5] Patients, who had urge incontinence and detrusor overactivity on urodynamic testing, were randomized to 30-minute PTNS (n=18) or sham treatment (n=17) sessions 3 times a week for 4 weeks. One patient dropped out of the PTNS group and 2 dropped out of the sham group. The primary outcome, percent responders at 4 weeks (defined as at least 50% reduction in incontinent episodes), was attained by 12/17 (71%) in the PTNS group and 0/15 (0%) in the sham group. The study did not conduct intention-to-treat analysis, was not double-blind, and did not report follow-up data beyond 4 weeks.

- Schreiner and colleagues randomized 51 women above 60 years old who complained of urge urinary incontinence 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).[6] 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. Blinding was not discussed and this study was also limited by small sample size.

- In 2013, Gungor Ugurlucan and colleagues published findings of an RCT comparing transvaginal electrical stimulation (ES) (n=38) and PTNS (n=21) in women with OAB.[7] The ES 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 12 30-minute weekly sessions. A total of 52 of 59 (88%) patients completed the study. 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 at the $p<0.05$ level in mean change in urgency episodes, nocturia or incontinence episodes. For example, the mean number of urgency episodes was 2.9 (SD: 4.1) at baseline and 1.6 (SD: 0.5) after treatment in the ES group and 2.0 (SD: 3.1) at baseline and 1.3 (SD: 0.5) after treatment in the PTNS group, p=0.54. There was a statistically significant difference in daytime frequency. The mean daytime frequency was 7.8 (SD: 2.7) at baseline and 5.8 (SD: 1.9) after treatment in the ES group and 7.6 (SD: 2.6) at baseline and 7.4 (SD: 2.9) in the PTNS group (p=0.03). The authors reported that a significantly higher proportion of patients in the ES group described themselves as cured, but they did not provide proportions or p-values.

- Vecchioli-Scaldazza and colleagues studied 40 women with OAB in a randomized controlled crossover study to evaluate the effectiveness of solifenacin succinate (SS) versus PTNS.[8] Group A received SS and then PTNS and group B received PTNS and then SS. The primary efficacy outcome was reduction in the number of voids in a 24-hour period and outcomes were measured through voiding diaries, quality of life surveys and perception of urgency ratings both before and after each treatment. In addition, a global impression score was completed at the end of the study. Only 30 of the 40 subjects (75%) completed the study. Improved outcomes were observed in both groups, however greater improvement in voided volume and greater effectiveness overall was found in PTNS compared to SS. However, much of the reported improvements were based upon subjective data, which limit conclusions regarding the superiority of PTNS over SS. In addition, authors did not compare the efficacy of PTNS to medication. Other study limitations include a lack of blinding and uncertainty regarding the clinical significance of these findings.

Other Systematic Reviews

In addition to the two TEC assessments, several systematic reviews and meta-analysis have been published regarding the use of PTNS as a treatment for OAB, reporting a positive success rate of 37-82%[12], 54-93%[13], 37-100%[14] and 36.7-80%[15], when compared to placebo or medication. Some of the trials included in these reviews are RCTs addressed separately within this policy or were non-randomized, observational studies. All studies used in each of the reviews were limited by short-term follow-up of 12 weeks and relatively small sample size[12,16,17] between 16 and 32 patients. Although the authors reported promising results for use of PTNS in patients with OAB, many called for larger, long-term, randomized trials to better evaluate the effects of PTNS treatment over time.[13-17]

Also in 2012, the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program published a comparative effectiveness review on the broader topic of nonsurgical treatments for urinary incontinence in adult women.[18] The review identified 4 reports of RCTs comparing PTNS and no active treatment in patients with OAB. Two of the 4 articles reported 12 week results of the sham-controlled SUmiT trial; one of these included a subgroup of SUmiT participants and was only published as an abstract. The other 2 studies consisted of the Finazzo-Agro et al. RCT[5] which reported outcomes at 4 weeks and the Schriner and colleagues et al. RCT[6] which reported outcomes at 12 weeks. The AHRQ report included a pooled analysis of data from 3 studies that found statistically significantly greater improvement in urinary incontinence in the PTNS compared to control group (RR: 1.9, 95% CI:

1.1 to 3.2). This pooled analysis included a total of 405 patients; 220 in the SUmiT trial, 150 in the SUmiT trial sub-analysis and 35 in the Finazzo-Agro trial. A limitation of the analysis was that the 150 patients in the SUmiT sub-analysis were included twice. The AHRQ report did not discuss evidence on the efficacy of PTNS beyond 12 weeks.

Other Randomized Controlled Trials

Several other RCTs have been published which were not included in the 2010 and 2014 TEC assessments; however, both are limited by short-term follow-up as none reported on the efficacy of PTNS beyond 12 weeks.

- Raheem and colleagues reported on 28 patients with refractory monosymptomatic nocturnal enuresis in a randomized control study comparing PTNS treatment to placebo.[19] The treatment group received a weekly session of PTNS for 12 weeks and a follow-up assessment was also made at 3 months post-treatment. Consistent with the 2010 TEC assessment conclusions, short-term treatment effects were observed in patients who received PTNS compared to the placebo group, however response rates decreased from 78.6% to 42.9% at the 3 month follow-up. The decrease in response rates also support the TEC assessment conclusion that efficacy of long-term treatment effect of PTNS has not been established.

- Sancaktar and colleagues evaluated 40 women with severe overactive bladder without any prior treatment who were randomized into medication alone and combination treatment groups.[20] All subjects received 4 mgs of tolterodine daily and 20 subjects also received Stoller afferent neuro-stimulation (SANS), a form of PTNS, for 12 weeks. Subjects completed a IIQ-7 questionnaire and a 7-day voiding diary at baseline and after treatment and results were compared. Of the 38 women completing the study, severity of symptoms were reduced in both groups, although a more significant decrease was observed in the combination group. This study is limited by small sample size and relatively short term follow-up.

Clinical Practice Guidelines

American Urological Association (AUA)[21]

In 2014, the AUA updated their guidelines regarding the diagnosis and treatment of overactive bladder in adults. The following recommendation was made as a third-line treatment option:

Clinicians may offer peripheral tibial nerve stimulation (PTNS) (also known as posterior tibial nerve stimulation) as third-line treatment in a carefully selected patient population.
This option was based primarily upon observational studies that are inconsistent, have small sample sizes, lack long-term randomized follow-up, and have varying inclusion criteria. The statement was rated as Grade C, indicating that the balance of benefits and risks/burdens are uncertain.

No evidence-based clinical practice guidelines were identified that recommend PTNS as a treatment of voiding dysfunction. The American Congress of Obstetricians and Gynecologists practice bulletin on treatment of urinary incontinence in women does not address PTNS or other types of nerve stimulation.[22]

American College of Obstetricians and Gynecologists (ACOG)[22]

The 2009 ACOG practice bulletin on treatment of urinary incontinence in women does not address PTNS or other types of nerve stimulation.

Summary

The published randomized controlled trials of posterior tibial nerve stimulation (PTNS) are limited in quantity and have significant methodological shortcomings, which limit the ability to reach conclusions concerning its impact on health outcomes. Until the durability of PTNS has been demonstrated in well-designed, long-term comparative studies and its clinical impact more clearly shown, its efficacy for treating urinary dysfunction, a chronic condition, remains uncertain. Therefore, PTNS for urinary dysfunction, including but not limited to overactive bladder syndrome, urinary frequency, neurogenic bladder, urgency, incontinence and retention, is considered investigational.

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CROSS REFERENCES

Pelvic Floor Stimulation as a Treatment of Urinary Incontinence, Allied Health, Policy No. 4

Biofeedback, Allied Health, Policy No. 32

Sacral Nerve Modulation/Stimulation for Pelvic Floor Dysfunction, Surgery, Policy No. 134

CODES	NUMBER	DESCRIPTION
CPT codes for percutaneous implantation of neurostimulator electrodes (i.e., 64553, 64555, 64561, 64565, 64590) are not appropriate since PTNS uses percutaneously temporarily inserted needles and wires rather than percutaneously implanted electrodes that are left in place.		
CPT	64566	Posterior tibial neurostimulation, percutaneous needle electrode, single treatment, includes programming
HCPCS	L8680	Implantable neurostimulator electrode, each