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Systematic review

The Role of Neuromodulation (PTNS/ SNS) in Refractory Overactive Bladder: Long-Term Outcomes

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ABSTRACT

Background: Overactive bladder (OAB) imposes a significant global health and economic burden. While behavioral and pharmacological treatments are standard, many patients become refractory. Neuromodulation, specifically Sacral Nerve Stimulation (SNS) and Percutaneous Tibial Nerve Stimulation (PTNS), offers a third-line alternative, but data on their long-term durability is still varied. **Methods:** Following PRISMA guidelines, a systematic review was conducted in PubMed, Scopus, and Web of Science for studies from 2007 to 2026 reporting clinical outcomes for refractory OAB with a minimum 24-month follow-up. Methodological quality was assessed using the Newcastle Ottawa Scale. **Results:** Nine studies met the inclusion criteria. SNS show high long-term success rates, ranging from 47% at nearly 10 years to 82% at 5 years. SNS was associated with surgical revision rates up to 33% due to lead migration or loss of efficacy. PTNS show a strong durability in responders, with 77% maintaining improvement at three years. Long-term PTNS adherence is a challenge, with one study reporting 25% patient retention at three years. Both modalities improved Qol. **Conclusion:** SNS and PTNS provide effective long-term management for refractory OAB. SNS offers high durability but requires surgical revisions, while PTNS provides a better safety profile and it heavily dependent on patient adherence to maintenance schedules.

Keywords: Overactive bladder; Refractory OAB; Neuromodulation; Sacral Nerve Stimulation; Percutaneous Tibial Nerve Stimulation; Long-term outcomes.

Introduction

Overactive bladder (OAB) is a common clinical syndrome characterized by urinary urgency, usually associated with frequency and nocturia, with or without urgency urinary incontinence (Bhide et al. 2020). Large scale epidemiological data from the EPIC study indicated that OAB affects 11.8% of the population, with prevalence rates increasing with age (Irwin et al. 2006). OAB imposes a good economic burden on healthcare systems; annual direct and indirect costs in Western countries are estimated to reach billions of Euros, driven largely by management of incontinence and loss of productivity (Irwin et al. 2008).

The standard treatment algorithm follows a tiered approach starting with behavioral modifications and progressing to pharmacological agents as outlined by the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) (Cameron et al. 2024). Many patients are considered refractory when they fail to achieve adequate symptom control or cannot tolerate the (Botox), Sacral Neuromodulation (SNS), and Percutaneous Tibial Nerve Stimulation (PTNS) are recommended (Cameron et al. 2024).

Neuromodulation is a vital component of third-line therapy, SNS involves the surgical implantation of a lead at the S3 sacral nerve root to modulate the neural pathways controlling the bladder (Goldman et al. 2018). PTNS provides a less invasive alternative by delivering retrograde electrical stimulation to the sacral plexus via the posterior tibial nerve (Bhide et al. 2020). The efficacy of PTNS validated in the SUmiT trial, which show its superiority over sham treatment in improving OAB symptoms (Peters et al. 2010).

While clinical trials and network meta-analyses confirmed the short-term efficacy of these modalities (Lo et al. 2020; Wang et al. 2020), and randomized trials like ROSETTA have compared SNS directly to Botox (Amundsen et al. 2016), there were a need for a comprehensive synthesis of their long term durability. Given the chronic nature of OAB, understanding the maintenance of therapeutic effects and the rates of long term

adherence is essential for clinical decision making. This systematic review aims to evaluate the long-term functional outcomes and safety profiles of SNS and PTNS in patients with refractory OAB.

Methods

Search Strategy and Information Sources

We conduct this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A literature search was performed in three electronic databases: PubMed/MEDLINE, Scopus, and Web of Science (WOS) from 2007 to 2026.

The search utilized a combination of Medical Subject Headings (MeSH) and free text keywords: "overactive bladder," "OAB," "refractory," "neuromodulation," "sacral nerve stimulation," "SNS," "percutaneous tibial nerve stimulation," "PTNS," "long-term," and "clinical outcomes." Boolean operators (AND, OR) were applied to maximize search sensitivity. The reference lists of all included studies and relevant review articles were manually screened for additional eligible citations.

Eligibility Criteria

Studies were selected based on the following criteria:

Population: Adult patients (≥18 years) with refractory idiopathic overactive bladder (OAB) who failed conservative and pharmacological treatments.

Intervention: Treatment with either SNS or PTNS.

Outcomes: Report of long term clinical efficacy, defined as a minimum follow-up duration of 24 months.

Study Design: Original research including prospective and retrospective cohort studies and clinical trials.

Exclusion criteria: we exclude studies with follow up <24 months, case reports (n <10), review articles, animal models, and studies focusing on neurogenic bladder populations.

Study Selection

The initial database search identified a total of 630 records (PubMed: 185, Scopus: 242, WOS: 203). After removing 215 duplicates, 415 records remained for title and abstract screening. Of these, 381 records were excluded as they did not meet the primary scope of the review. The remaining 34 full-text articles were rigorously assessed for eligibility. Twenty-five articles were excluded with specific reasons: follow up duration <24 months (n=14), review articles or meta-analyses (n=6), ineligible study population (n=3), and overlapping data duplicate cohorts (n=2). 9 original studies were included in the final qualitative synthesis (Fig 1).

Data Extraction and Quality Assessment

Data were extracted by two independent reviewers using a standardized data collection form. Extracted variables were: primary author, year, study design, intervention type (SNS/PTNS), patient demographics, sample size, follow-up duration, definition of success, and specific clinical outcomes, voiding diary parameters, QoL, and complications.

Methodological quality was appraised using the Newcastle-Ottawa Scale (NOS) for non-randomized studies. Each study was evaluated in three domains selection of the study groups, comparability of the groups, and the assessment of outcomes. Studies were assigned a numeric score out of 9, where

scores of 7–9 were classified as high quality, 5 to 6 as fair quality, and <5 as low quality (Table 1 & 2).

Data Synthesis

Due to the heterogeneity in study designs, outcome definitions, and follow-up intervals, a meta-analysis was not performed, and a qualitative synthesis was utilized. Clinical success was reported based on the specific definitions provided in each study. Outcomes were categorized by neuromodulation modality to compare the long-term durability and safety profiles of SNS and PTNS.

Fig 1: PRISMA flow chat

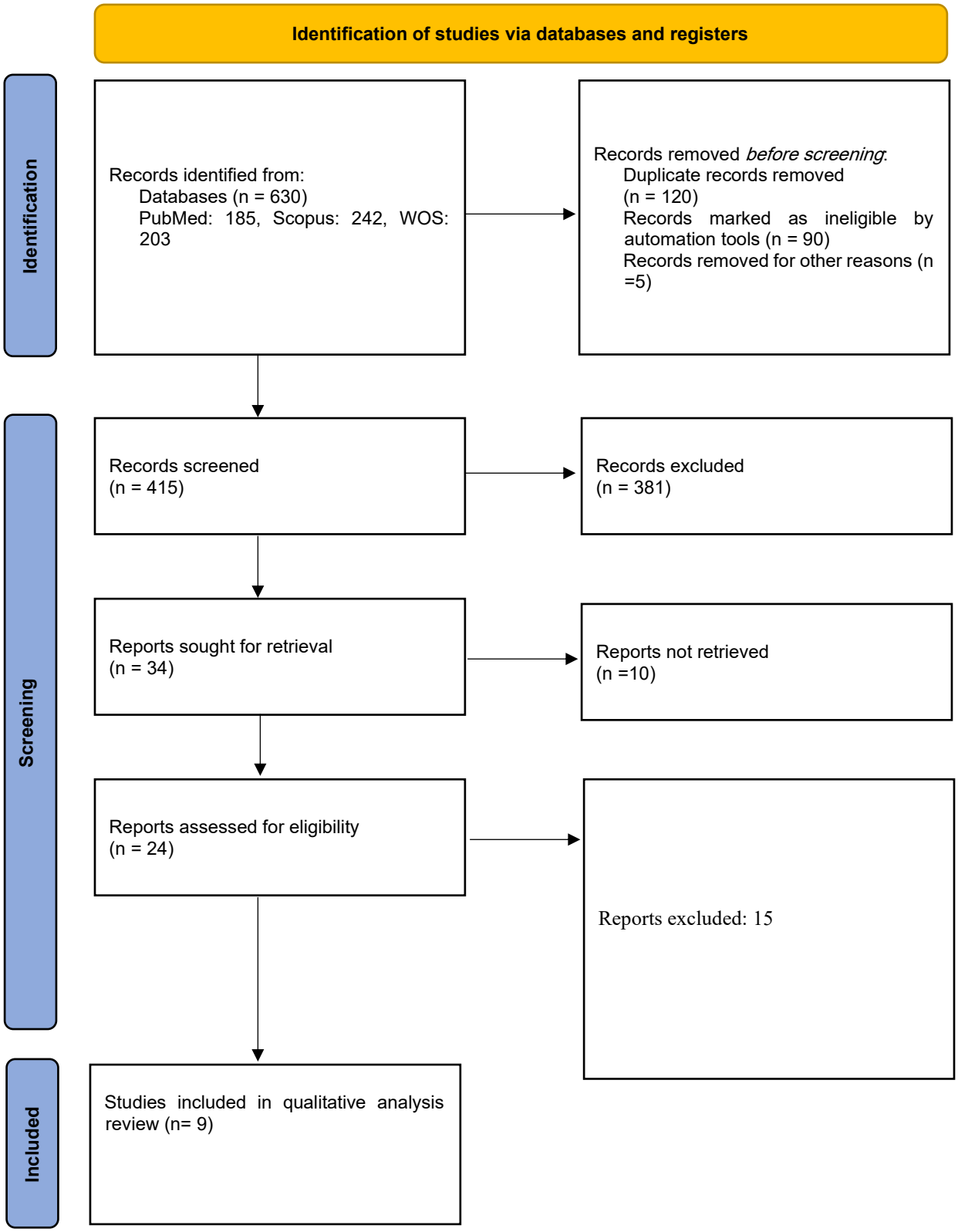

Table 1: quality assessment of included studies (Modified Newcastle-Ottawa Scale)

Study (Year)	Selection (0 to 4)	Comparability (0 to 2)	Outcome (0 to 3)	Total Score	Quality Level
Siegel et al. (2018)	4	1	3	8	High
Van Kerrebroeck et al. (2007)	4	1	3	8	High
Peters et al. (2013)	4	1	3	8	High
Ismail et al. (2017)	3	1	2	6	Fair
Kaaki & Gupta (2020)	3	1	2	6	Fair
te Dorsthorst et al. (2020)	3	1	2	6	Fair
Bianchi et al. (2021)	3	1	2	6	Fair
Marchal et al. (2011)	3	1	2	6	Fair
Yoong et al. (2012)	3	1	2	6	Fair

Table 2: detailed quality assessment

Study	S1	S2	S3	S4	C1	O1	O2	O3	Total
Siegel (2018)	1	1	1	1	1	1	1	1	8
Van Kerrebroeck (2007)	1	1	1	1	1	1	1	1	8

Study	S1	S2	S3	S4	C1	O1	O2	O3	Total
Peters (2013)	1	1	1	1	1	1	1	1	8
Ismail (2017)	1	0	1	1	1	1	1	0	6
Kaaki (2020)	1	0	1	1	1	1	1	0	6
te Dorsthorst (2020)	1	0	1	1	1	1	1	0	6
Bianchi (2021)	1	0	1	1	1	1	1	0	6
Marchal (2011)	1	0	1	1	1	1	1	0	6
Yoong (2012)	1	0	1	1	1	1	1	0	6

Selection (S): S1: Representativeness of the cohort; S2: Selection of the non-exposed cohort; S3: Ascertainment of exposure; S4: Demonstration that outcome of interest was not present at start.

Comparability (C): C1: Comparability of cohorts on the basis of the design or analysis.

Outcome (O): O1: Assessment of outcome; O2: Was follow-up long enough for outcomes to occur; O3: Adequacy of follow-up of cohorts.

Result

We analyzed a total of nine studies to evaluate the long term effectiveness and durability of SNS and PTNS in patients with OAB. SNS show high durability of therapeutic success, and it was associated with surgical revision rates. In a 5 year prospective multicenter study, Siegel et al. reported an 82% therapeutic success rate, with improvements in health related quality of life (HRQoL) and symptom interference. Van Kerrebroeck et al. found a good success in 58% of patients with urge incontinence at five years. In the longest follow-up study (median 9.7 years), Ismail et al. observed that 47% of patients maintained success, and the device removal rate was 23.5%, due to loss of efficacy or pain. Kaaki and Gupta found a 65.4% success rate over a mean follow-up of 32.4 months, with 16.8% of patients requiring surgical revision.

PTNS studies show the need for maintenance therapy to preserve clinical benefits, the STEP study (Peters et al.) showed that 77% of initial responders maintained good improvement in OAB symptoms over three years with a tapered treatment protocol. Bianchi et al. found that 71% of responders continued to benefit at 30 months, requiring a median of eight sessions per year. Adherence is a challenge as te Dorsthorst et al. observed that initial adherence was high, and only 25% of patients remained on therapy after three years, and lack of efficacy being the primary reason for cessation. Marchal et al. found a 62.5% improvement rate at 24 months, indicate a significant increases in bladder capacity. Yoong et al. confirmed these by reporting a 57% reduction in nocturnal frequency at two years among responders.

Both modalities improve Qol in all included studies, and SNS carried a higher risk of adverse events requiring intervention, such as lead migration (18%) and surgical revisions (up to 33%). PTNS characterized by a good safety profile with minor, transient local side effects like pain or skin irritation. Both SNS and PTNS offer effective long-term management for refractory OAB, provided that patients are appropriately selected and, in the case of PTNS, remain adherent to maintenance schedules.

Table 3: Characteristics of the Included Studies

Author	Intervention	Study Design	Patient Population	Sample Size	Follow-up Duration
Ismail et al. (2017)	SNS	Retrospective	Refractory Idiopathic OAB	34	Median 9.7 years
Siegel et al. (2018)	SNS	Prospective, Multicenter	Refractory OAB	340	5 years
Kaaki & Gupta (2020)	SNS	Retrospective	Refractory OAB	107	Mean 32.4 months
Van Kerrebroeck et al. (2007)	SNS	Prospective, Worldwide	Refractory Voiding Dysfunction	163	5 years
Peters et al. (2013)	PTNS	Prospective (STEP Study)	OAB Responders	29	3 years
te Dorsthorst et al. (2020)	PTNS	Retrospective	OAB	402	Median 35 months
Bianchi et al. (2021)	PTNS	Retrospective	OAB Responders	52	Median 30 months
Marchal et al. (2011)	PTNS	Prospective Cohort	Refractory OAB	53	24 months
Yoong et al. (2012)	PTNS	Prospective Cohort	OAB Responders	23	2 years

Table 4: Main Findings and Outcomes

Author	**Success Definition**	**Success Rate**	**Key Findings**	**Adverse Events and revisions**
Ismail (2017)	>50% improvement in clinical parameters	47% of those followed	Sustained long-term efficacy in urgency and frequency	14.7% revision rate; 23.5% removal rate
Siegel (2018)	>50% improvement in symptoms	82% at 5 years	Significant improvement in QoL and symptom interference	Revisions various reasons; high patient satisfaction

Author	Success Definition	Success Rate	Key Findings	Adverse Events and revisions
Kaaki (2020)	>50% improvement in symptoms	65.4% at last follow-up	Success rates: UI (68.9%), U/F (61.5%)	16.8% surgical revision rate
Van Kerrebroeck (2007)	>50% improvement in diary parameters	58% (UI), 56% (U/F)	Durable results at 5 years; significant reduction in leaks	18% lead migration; 33% total surgical revision
Peters (2013)	GRA Moderately Improved	77% at 3 years	Durable results for frequency and nocturia	No serious treatment-related adverse events
te Dorsthorst (2020)	Adherence to therapy	25% adherence at 3 years	Median time to quit was 14 months; primary reason: lack of efficacy	Local pain/discomfort (rare)
Bianchi (2021)	Maintenance of >50% improvement	71% at last follow-up	50% of responders were still on PTNS after 3 years	Mild local side effects
Marchal (2011)	Cure or clinical improvement	62.5% at 24 months	Increased first sensation of bladder filling	No significant complications
Yoong (2012)	Maintenance of clinical response	Sustained at 2 years	57% reduction in median nocturnal frequency	Well-tolerated; no major side effects

Discussion

OAB management is a significant clinical and economic challenge, as highlighted by the EPIC study, OAB affects 11.8% of the population (Irwin et al. 2006), with direct and indirect costs reaching billions of dollars due to healthcare resource utilization and work absenteeism (Irwin et al. 2008). Our systematic review of nine original studies show that neuromodulation, through SNS and PTNS, offers durable and effective long term symptom relief for patients who have failed conservative and second-line therapies.

Our analysis of SNS outcomes confirms high therapeutic durability over extended periods. Siegel et al. (2018) found a remarkable 82% therapeutic success rate at five years, accompanied by improvements in Qol. This is consistent with earlier multicenter data from Van Kerrebroeck et al. (2007), which showed sustained success in 58% of patients with urge incontinence at the five year mark. Ismail et al. (2017) provided the longest follow-up data to date, and found that half of the patients maintained clinical success a decade after implantation. The application of SNS involves surgical burden; Ismail et al. (2017) reported a 14.7% revision rate and a 23.5% device removal

rate, while Van Kerrebroeck et al. (2007) noted that up to 33% of patients required surgical revision over five years. These findings indicate that SNS is highly effective, and patients must be counseled on the potential for future surgical interventions to maintain efficacy (Goldman et al. 2018).

PTNS serves as a less invasive alternative, though its long term success is dependent on patient adherence to maintenance protocols. The efficacy of PTNS established by the SUmiT trial, which show its superiority over sham treatment (Peters et al. 2010). Our review found that for those who adhere to treatment, the benefits are durable; Peters et al. (2013) show a 77% success rate at three years in the STEP study, while Yoong et al. (2012) reported a 57% reduction in nocturnal frequency at two years. Despite these positive outcomes for responders, adherence is a major hurdle. te Dorsthorst et al. (2020) observed that 25% of patients remained on PTNS therapy at three years, with the median time to cessation is 14 months. PTNS is clinically effective (Wang et al. 2020), and the requirement for frequent clinic visits for maintenance sessions unlike the set-and-forget nature of SNS lead to high attrition rates in a non-trial setting.

When comparing these modalities, the choice hinges on the trade-off between invasiveness and convenience. SNS provides a continuous, automated therapy but requires a surgical procedure with a risk of revision. PTNS offers a high safety profile with no serious adverse events (Peters et al. 2013), yet it demands a high level of patient commitment to long-term maintenance. While network meta-analyses suggest that SNS, PTNS, and OnabotulinumtoxinA all provide improvements over placebo (Wang et al. 2020; Lo et al. 2020), the choice between SNS and PTNS should be personalized based on patient comorbidities and lifestyle preferences.

Conclusion

SNS and PTNS are effective long-term strategies for refractory OAB. SNS characterized by higher long-term clinical success rates at the cost of surgical risk, whereas PTNS offers a safe, non-surgical pathway that is limited by patient adherence to maintenance schedules.

List of abbreviations

AUA, American Urological Association; OAB, Overactive bladder; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PTNS, Percutaneous Tibial Nerve Stimulation; Qol, Quality of life; SNS, Sacral Nerve Stimulation; SUFU, Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction.

Conflict of interest

None

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Ethical approval

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References

Amundsen CL, Richter HE, Menefee SA, Komesu YM, Arya LA, Gregory WT, Myers DL, Zyczynski HM, Vasavada S, Nolen TL,

Wallace D, Meikle SF; Pelvic Floor Disorders Network. OnabotulinumtoxinA vs sacral neuromodulation on refractory urgency urinary incontinence in women: a randomized clinical trial. JAMA. 2016 Oct 4;316(13):1366-1374. doi: 10.1001/jama.2016.14617.

Bhide AA, Tailor V, Fernando R, Khullar V, Digesu GA. Posterior tibial nerve stimulation for overactive bladder—techniques and efficacy. Int Urogynecol J. 2020 May;31(5):865-870. doi: 10.1007/s00192-019-04186-3.

Bianchi D, Iacovelli V, Parisi I, Petta F, Gaziev G, Topazio L, Bove P, Vespasiani G, Finazzi Agrò E. Real-life data on long-term follow-up of patients successfully treated with percutaneous tibial nerve stimulation. Minerva Urol Nephrol. 2021 Apr;73(2):260-264. doi: 10.23736/S0393-2249.19.03492-1.

Goldman HB, Lloyd JC, Noblett KL, Carey MP, Castaño-Botero JC, Gajewski JB, Lehur PA, Hassouna MM, Matzel KE, Paquette IM, de Wachter SG, Ehlert MJ, Chartier-Kastler E, Siegel SW. International Continence Society best practice statement for use of sacral neuromodulation. Neurourol Urodyn. 2018 Jun;37(5):1821-1822. doi: 10.1002/nau.23596.

Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, Coyne K, Kelleher C, Hampel C, Artibani W, Abrams P. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol. 2006 Dec;50(6):1306-14. doi: 10.1016/j.eururo.2006.09.019.

Irwin DE, Mungapen L, Milsom I, Kopp Z, Reeves P, Kelleher C. The economic impact of overactive bladder syndrome in six Western countries. BJU Int. 2009 Feb;103(2):202-9. doi: 10.1111/j.1464-410X.2008.08036.x.

Ismail S, Chartier-Kastler E, Perrouin-Verbe MA, Rose-Dite-Modestine J, Denys P, Phé V. Long-term functional outcomes of S3 sacral neuromodulation for the treatment of idiopathic overactive bladder. Neuromodulation. 2018 Oct;21(7):686-692. doi: 10.1111/ner.12696.

Kaaki B, Gupta D. Medium-term outcomes of sacral neuromodulation in patients with refractory overactive bladder: A retrospective single-institution study. PLoS One. 2020 Jul 9;15(7):e0235961. doi: 10.1371/journal.pone.0235961.

Lo CW, Wu MY, Yang SS, Jaw FS, Chang SJ. Comparing the efficacy of OnabotulinumtoxinA, sacral neuromodulation, and peripheral tibial nerve stimulation as third line treatment for the management of overactive bladder symptoms in adults: systematic review and network meta-analysis. Toxins (Basel). 2020 Feb 18;12(2):128. doi: 10.3390/toxins12020128.

Marchal C, Herrera B, Antuña F, Saez F, Perez J, Castillo E, Cantero J, Milla F, Machuca J, Redondo M, Galacho A. Percutaneous tibial nerve stimulation in treatment of overactive bladder: when should retreatment be started? Urology. 2011 Dec;78(6):1254-8. doi: 10.1016/j.urology.2011.08.025.

Peters KM, Carrico DJ, Perez-Marrero RA, Khan AU, Wooldridge LS, Davis GL, MacDiarmid SA. 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 Apr;183(4):1438-43. doi: 10.1016/j.juro.2009.12.036.

Peters KM, Carrico DJ, Wooldridge LS, Miller CJ, MacDiarmid SA. Percutaneous tibial nerve stimulation for the long-term treatment of overactive bladder: 3-year results of the STEP study. J Urol. 2013 Jun;189(6):2194-201. doi: 10.1016/j.juro.2012.11.175.

Siegel S, Noblett K, Mangel J, Bennett J, Griebling TL, Sutherland SE, Bird ET, Comiter C, Culkin D, Zylstra S, Kan F, Berg KC. Five-year follow-up results of a prospective, multicenter study in overactive bladder subjects treated with sacral neuromodulation. J Urol. 2018 Jan;199(1):229-236. doi: 10.1016/j.juro.2017.07.010.

te Dorsthorst MJ, Heesakkers JPFA, van Balken MR. Long-term real-life adherence of percutaneous tibial nerve stimulation in over 400 patients. Neurourol Urodyn. 2020 Feb;39(2):702-708. doi: 10.1002/nau.24254.

The AUA SUFU guideline (2024) Cameron AP, Chung DE, Dielubanza EJ, Enemchukwu E, Ginsberg DA, Helfand BT, Linder BJ, Reynolds WS, Rovner ES, Souter L, Suskind AM, Takacs E, Welk B, Smith AL. The AUA/SUFU guideline on the diagnosis and treatment of idiopathic overactive bladder. Neurourol Urodyn. 2024 Jun;43(5):1048-1059. doi: 10.1002/nau.25532.

van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, Lycklama á Nijholt AA, Siegel S, Jonas U, Fowler CJ, Fall M, Gajewski JB, Hassouna MM, Cappellano F, Elhilali MM, Milam DF, Das AK, Dijkema HE, van den Hombergh U. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. J Urol. 2007 Nov;178(5):2029-34. doi: 10.1016/j.juro.2007.07.016.

Wang M, Jian Z, Ma Y, Jin X, Li H, Wang K. Percutaneous tibial nerve stimulation for overactive bladder syndrome: a systematic review and meta-analysis. Int Urogynecol J. 2020 Nov;31(11):2457-2471. doi: 10.1007/s00192-020-04429-8.

Yoong W, Shah P, Dadswell R, Green L. Sustained effectiveness of percutaneous tibial nerve stimulation for overactive bladder syndrome: 2-year follow-up of positive responders. Int Urogynecol J. 2013 May;24(5):795-9. doi: 10.1007/s00192-012-1936-3.