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REVIEW

Sacral and Implantable Tibial Neuromodulation for the Management of Overactive Bladder: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Implantable tibial neuromodulation (iTNM) systems have recently become commercially available in the US, and offer a new method of neurostimulation for the treatment of overactive bladder (OAB). In the absence of head-to-head studies, the aim of this meta-analysis was to indirectly compare the efficacy and safety of sacral neuromodulation (SNM) and implantable tibial neuromodulation (iTNM) for the treatment of OAB.

Methods: A comprehensive search was performed using terms for OAB and neuromodulation. Primary efficacy measures included a ≥ 50% reduction in urgency urinary incontinence (UUI) episodes, urinary frequency, and/or OAB symptoms. Primary safety measures included the rate of device-related adverse events (AEs).

Results: A total of 20 studies met selection criteria, encompassing 1416 patients treated with SNM and 350 patients treated with iTNM. No comparative or placebo-controlled studies for SNM and iTNM were identified, and therefore the analysis was completed using single-arm results. Weighted averages showed that the UUI responder rate was similar for both SNM and iTNM (71.8% and 71.3%, respectively). Similarly, weighted averages of OAB responder rates were 73.9% for SNM and 79.4% for iTNM. Similar rates of device-related AEs were also observed.

Conclusions: This meta-analysis found similar efficacy and safety of SNM and iTNM for the treatment of OAB and UUI, including UUI and OAB symptom response rates, reduction in UUI episodes, significant improvements in quality-of-life (QoL), and low rates of procedure and device-related adverse events. Notably, this comparable efficacy was seen without the use of a trial phase of neuromodulation in the iTNM studies versus SNM studies.

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Key Summary Points

Why carry out this study?

In the past two years, implantable tibial neuromodulation (iTNM) systems have become available in the US, offering a less invasive implantable neuromodulation treatment option for overactive bladder (OAB) and its significant impact on quality of life.

This analysis indirectly compares the clinical efficacy and safety of iTNM with sacral neuromodulation (SNM), the most common implantable neuromodulation option for OAB treatment, to provide healthcare providers and patients with additional decision-making information.

What was learned from this study?

This analysis demonstrated that iTNM appears to have similar efficacy and safety to SNM, offering patients with OAB a valuable additional treatment choice.

In the future, randomized comparative studies will be important to further establish similarities and differences in efficacy and safety between iTNM and SNM.

INTRODUCTION

Overactive bladder (OAB) affects millions of individuals worldwide, with greater prevalence in older adults [1]; it is estimated that about one in six adults in the United States (US) and Europe suffer from OAB [2, 3]. OAB may be particularly distressing to patients [4, 5], and those with OAB report increased anxiety and depressive symptoms compared to healthy controls [6], likely due to the emotional burden of embarrassment and disruption to normal daily activities of living. Symptoms may arise for a variety of reasons including hormonal changes (associated with menstruation, pregnancy, menopause), postpartum changes, aging, prior bladder or pelvic surgery, pelvic floor muscle disorders, and neurological issues (such as Parkinson's, multiple sclerosis, stroke, and spinal cord injuries) [7]. However, most patients with OAB do not have definable causation and are therefore termed idiopathic.

OAB encompasses a constellation of symptoms that can include urgency, frequency, nocturia, and urgency urinary incontinence (UUI). Given OAB's prevalence and substantial impact on quality-of-life (QoL) [8–10], the need to develop efficacious and safe treatment modalities remains manifest.

In the US, historically, first-, second-, and third-line OAB treatment options have been defined in guidelines provided by the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU) [11], with updates periodically released as new technologies and clinical evidence become available. Most recent updates to the AUA/SUFU guidelines were published this year (2024) [12], and provide additional flexibility to clinicians and patients by removing the traditional "step therapy" approach. These 2024 updated guidelines instead emphasize the importance of shared decision-making between clinicians and patients, and have further organized treatment options according to their perceived level of invasiveness. Additionally, these updated guidelines allow more flexibility in the utilization of OAB treatment options, by no longer requiring a stepwise failure of all conservative and pharmacologic therapies as a pre-requisite of initiating minimally invasive treatment procedures.

Overview of Current Treatment Options for OAB

Non-invasive treatment options for OAB, designated as "first-line" therapies, include dietary and behavioral modifications, bladder re-training techniques, pelvic floor muscle physiotherapy, and transcutaneous and transvaginal

methods of pelvic floor electrical stimulation, with the acknowledgment that combined multimodality therapy regimens prove most successful [12, 29–34]. However, while all have proven to be moderately effective at reducing the symptoms of OAB and UUI in select patients [13, 14], these therapies have noted inconsistent and limited results when compared to pharmacotherapy [15]; thus again, combination therapy to include "first-line" interventions with OAB medications is often recommended [12, 29–34].

Until recently, pharmacotherapy was considered a "second-line" option for treating OAB, commonly in the form of anticholinergic agents and beta-adrenergic agonists [12, 16, 17]. Despite their efficacy for some patients, many OAB medications (i.e., anticholinergics) have bothersome side effects, including dry mouth, dry eyes, headache, and constipation, often resulting in more than 50% of patients discontinuing OAB medication use during their first year of treatment [18–21]. Recently, safety concerns have been raised regarding a potential link between the long-term use of anticholinergics and the risk of developing dementia [22–24], resulting in a hesitancy for continued use.

The current AUA/SUFU guidelines recognize percutaneous tibial nerve stimulation (PTNS), implantable tibial nerve stimulation (iTNM), sacral neuromodulation (SNM), and botulinum toxin injection ("Botox"; BTX) as minimally-invasive procedural therapies with high success rates, durable efficacy, and excellent patient satisfaction [12]. These historically "third-line" therapies have been shown to be the most successful methods of reducing OAB/UUI symptoms, especially for conservative treatment-resistant cases [25]. Their success among the elderly patient population is also promising [26–28]. While acupuncture is also considered a minimally invasive therapy, less evidence regarding efficacy is currently available [29].

Treatment of the bladder with BTX results in successful reduction of OAB and UUI symptoms and has proven similar efficacy to SNM [30, 31]. However, because BTX is metabolized over time, this form of therapy necessitates repeat injections every 3–6 months, resulting in patient inconvenience and accumulative costs. Additionally, AUA/SUFU guidelines recommend post-BTX post-void residual evaluation to ensure adequate voiding and emptying; those with significant difficulty may require temporary catheterization [12]. Other potential complications following BTX injections can include peri-procedural urinary tract infection (UTI) and hematuria [30, 32].

SNM, using electrical stimulation to the S3 sacral nerve root, was FDA-approved in 1997 and is a proven efficacious treatment for OAB and UUI [33–35]. SNM is traditionally performed in a 2-stage manner (i.e., involving 2 separate procedures), requiring first an initial stimulation trial (typically 1–3 weeks) to identify clinical "responders" with adequate efficacy prior to permanent implantable pulse generator (IPG) implantation. This initial trial can be accomplished through an in-office peripheral nerve evaluation (PNE) procedure, or via initial surgical implantation of the permanent tined lead (advanced evaluation). SNM has been shown to have excellent efficacy; however, it may require reprogramming visits and surgical re-intervention for lead revisions or battery replacement. Moreover, a trial of SNM can be a viable option for patients who have previously failed BTX [36, 37].

PTNS—neuromodulation of the pelvic plexus for OAB by accessing a peripheral nerve—was first cleared for commercial use in the US in 2000; PTNS is provided be using a thin "acupuncture-like" needle which is applied in the office setting. Efficacy of PTNS has been established for mild-to-moderate OAB—even against sham controls—with comparative efficacy clinically to tolterodine tartrate (Detrol LA). [38–41]. Primary drawbacks of PTNS include the need for frequent office visits to achieve and then maintain clinical response, and variations in needle placement proficiency among different providers. Indeed, additional options for stimulation of the tibial nerve using transcutaneous tibial nerve stimulation, have also been recently shown to provide benefit in dry-OAB [42], further supporting the usefulness of the tibial nerve as a target for treatment of OAB.

Similar to SNM, iTNM offers a permanent implant, either subcutaneously or sub-fascially implanted in the ankle, which allows for in-home stimulation sessions, alleviating the

hardship of frequent office visits [43–50]. iTNM became commercially available in the US in 2022, with promising results from recent pivotal studies [51, 52] for the treatment of UUI.

For patients refractory to (or with contraindications to) all first-, second-, and third-line therapies, the AUA/SUFU guidelines acknowledge the role of more aggressive treatment options such as bladder augmentation cystoplasty, urinary diversion, and chronic indwelling catheters [12].

Current Analysis

Neuromodulation as a viable treatment option for OAB was first approved in the US nearly 30 years ago (see Supplementary Table S1). Much innovation has occurred over time to improve the therapy, allowing it to be more efficacious with an improved safety profile. In the last few years, two new iTNM systems have emerged and are now commercially available: Revi (BlueWind) and eCoin (Valencia). Although these iTNM options are certainly less invasive than currently available SNM, it is important to understand how they compare to SNM with respect to efficacy and safety; however, randomized comparative studies have not yet had time to be developed and completed. This systematic review and meta-analysis aims to "bridge the gap"; to recognize and quantify both similarities and differences in the outcomes of patients with symptoms of OAB treated with either iTNM or SNM through an indirect comparison of results from studies using iTNM or SNM.

METHODS

This systematic literature review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [53], and was registered prospectively (PROSPERO ID CRD42024549598). Pre-specified methods including objectives, literature-search strategies, eligibility criteria, outcome measures, quality assessment, and methods of statistical analysis were prepared. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Literature-Search Strategy

A systematic literature search was performed in May 2024 without any initial restrictions for languages, regions, or publication types to identify all available randomized controlled trials (RCTs), comparative studies, and single-arm cohort studies that assess efficacy and safety of iTNM and SNM for treatment of OAB and/or UUI. Electronic searches of PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were completed. The PICOS elements used for the search strategy developed have been provided in Supplementary Table S2 (A and B); searches between databases used identical search terms with formatting to match database requirements. Electronic searches were supplemented by nonsystematic manual literature searches using Google Scholar.

Study Selection

Inclusion and exclusion criteria have been summarized in Supplementary Table S3. Key inclusion criteria included permanent implantation of SNM or iTNM, prospective or retrospective clinical study or randomized trial with ≥ 15 patients, adult patient population, and publication after January 1, 2010. Key exclusion criteria included non-human studies, reviews/study protocols/health economics studies, studies enrolling only subjects with previous failure of SNM/iTNM, subjects enrolling only subjects with ongoing use of previously implanted devices, population outside of OAB and/or UUI, concurrent use of multiple minimally invasive therapies, studies that did not report on any meta-analysis primary safety of efficacy endpoints, and articles not available in English.

After deletion of duplicate and retracted records, studies were evaluated for inclusion in a two-phase process. In the first step, two reviewers independently screened article titles and abstracts for inclusion or exclusion. In the

second step, full-text articles were obtained for publications that were identified as potentially meeting inclusion and exclusion criteria. The full-text reviews were completed by two independent reviewers. Discrepancies were resolved through discussion, and disagreements were arbitrated by a third reviewer.

Studies were not restricted by a patient's prior or current use of OAB therapies or traditional second-line medications. To avoid inclusion of multiple studies with overlapping patient populations (for example, clinical studies with available reports at several timepoints), the publication summarizing the longest time of follow-up was selected for inclusion in the analysis.

It was pre-specified that if, after the assessment of bias was completed, the total number of published studies with high risk of bias made up less than 15% of the total study citations selected, these publications would be listed in the risk of bias assessment, but further data extraction from these studies would not be completed.

Data Extraction and Assessment of Bias

Two reviewers independently extracted and summarized data from the selected publications, including study design and demographics. Information including type of study, device, number of patients, mean age, gender, baseline OAB symptoms, length of follow-up, primary efficacy and safety outcomes, secondary outcomes, and QoL measures were extracted. There was no imputation for missing data. Where data for multiple timepoints were presented in the publication, data from the longest length of follow-up were reported. For all studies, patient-level data were not available, and data extraction was based on information presented in publications. No automation tools were used in the data extraction process. Discrepancies were resolved by discussion, and disagreements were arbitrated by a third reviewer.

For the meta-analysis across studies, the following performance measures were extracted as primary outcome measures from voiding diaries, when available: percentage of patients with ≥ 50% improvement of OAB symptoms (study-specific composites of voiding-diary changes), percentage of patients with ≥ 50% improvement of UUI symptoms, and percentage of patients with ≥ 50% improvement of urinary frequency (UF) symptoms.

The following primary safety outcomes were extracted, when available: rate of reported device- or procedure-related adverse events, including specific rates for infection, pain, lead migration, and wound healing issues, as reported. In addition, the rate of surgical revision/removal were extracted and reasons for re-interventions were collected.

Secondary efficacy measures of mean decrease in UUI episodes, mean change in urinary frequency, and short-term (< 6 month) impact on UUI episodes were recorded. Patient-reported outcomes were examined and included QoL measures [Overactive Bladder Questionnaire (OAB-q), etc.] and patient satisfaction, among others.

Data Synthesis and Analysis

Risk of bias ratings were completed to assess quality. Bias assessment measures included study design, number of centers, random assignment, blinding, studies with standardized patient reported measures for primary efficacy measures (e.g., bladder diaries), withdrawal/drop-out rate, length of follow-up, adverse event reporting, and status of industry funding. Low levels of bias were assumed for the following: prospective study designs, multicenter studies, randomized study designs, studies with standardized patient reported measures for primary efficacy measures (e.g., bladder diaries), blinded studies, length of more than 6 months, low drop-out rates (as defined below), adverse event reporting, and studies without industry funding. Studies with high levels of bias were assumed for the following: retrospective studies, single-center studies, single-arm studies, studies with subjective assessments for primary efficacy measures, unblinded studies, 6 months or less of follow-up, high drop-out rates, studies with zero adverse events reported, and studies with industry funding. To assess drop-out rates equally in studies of varied length, studies with less than a 10% rate of

drop-out per year were considered to have low bias (e.g., remaining subjects at 1, 2, or 3 years was 90.0%, 81.0% or 72.9%, respectively). Bias levels were aggregated equally across these nine categories. Studies with an aggregated bias assessment rating of 0–3 were considered to have low bias, 4–6 were considered to have moderate bias, and 7–9 were considered to have high bias.

For the meta-analysis of primary efficacy and safety outcomes across studies, weighted averages were presented for available results for both iTNM and SNM. As studies with multiple designs (RCTs, interventional studies, retrospective data collections, etc.) were allowed in the primary analysis, key primary endpoint data were also analyzed by study design, with data from interventional (RCTs and prospective interventional) and observational (prospective observational and retrospective reviews) presented separately. Descriptive statistics, including weighted averages, were calculated using Microsoft Excel, and graphical figures were produced in GraphPad Prism and Microsoft Excel.

RESULTS

An initial literature search obtained from PubMed and Cochrane CENTRAL yielded a total of 1185 citations. Additionally, one relevant article was identified from additional non-systematic searches in Google Scholar. After removing 105 duplicates and 2 retracted articles, a total of 1079 article abstracts were screened for inclusion. A total of 934 of these articles were excluded at the initial abstract screening, as described in the PRISMA Table (Fig. 1). A total of 145 full-text articles were screened, and 124 additional articles were excluded, as detailed in the PRISMA Table (Fig. 1). After completing the bias assessment, one additional study was excluded as having a high risk of bias for the measures of this meta-analysis [54]. Therefore, a total of 20 studies, summarized by device in Supplementary Table S1, were included in the meta-analysis. Details related to the results of the systematic and nonsystematic literature search are included in Fig. 1.

Bias assessment ratings of the included studies are presented in Fig. 2. A total of nine studies were rated as having a low rate of bias, eleven were considered to have moderate rates of bias, and one was considered to have a high rate of bias for the measures considered in this meta-analysis. Most studies were unblinded; notably, blinded studies for treatment of OAB using neuromodulation are unusual, as sensation perceived by patients during treatment prevents blinding for randomized study designs using different methods of treatment. Of the selected studies, two studies [55, 56] had 3-month windows in which a single-blind was implemented in standard versus delayed activation of implanted neuromodulation systems, following which all subjects continued unblinded with neuromodulation. As data for this meta-analysis used the latest timepoint reported, all data presented in primary endpoints were from unblinded patients aware of the type of treatment being received.

Patient Populations and Risk of Bias Across Studies

Of the 20 studies included in the meta-analysis, three were RCTs [30, 55, 57], ten were prospective interventional studies [51, 52, 56, 58–64], one was a prospective observational study [65], and six were retrospective chart reviews [66–71]. A total of 1766 patients were included in the meta-analysis, where 350 patients in 4 studies were treated with iTNM, and 1416 patients in 16 studies were treated with SNM. For iTNM studies, the weighted average age was 61.2 years old (n = 350), and the weighted average percentage of female patients was 98.0% (n = 350); length of follow-up ranged from 12 months to 3 years, with the weighted average length of follow-up of 13.0 months. For SNM studies, the weighted average age was 57.0 years old (n = 1416), and the weighted average percentage of female patients was 87.5% (n = 1416); length of final follow-up ranged from 6 months to 9.7 years, with the weighted average length of follow-up equaling 39.2 months (Table 1). As expected, the length of follow-up data available did vary between the newer iTNM technology

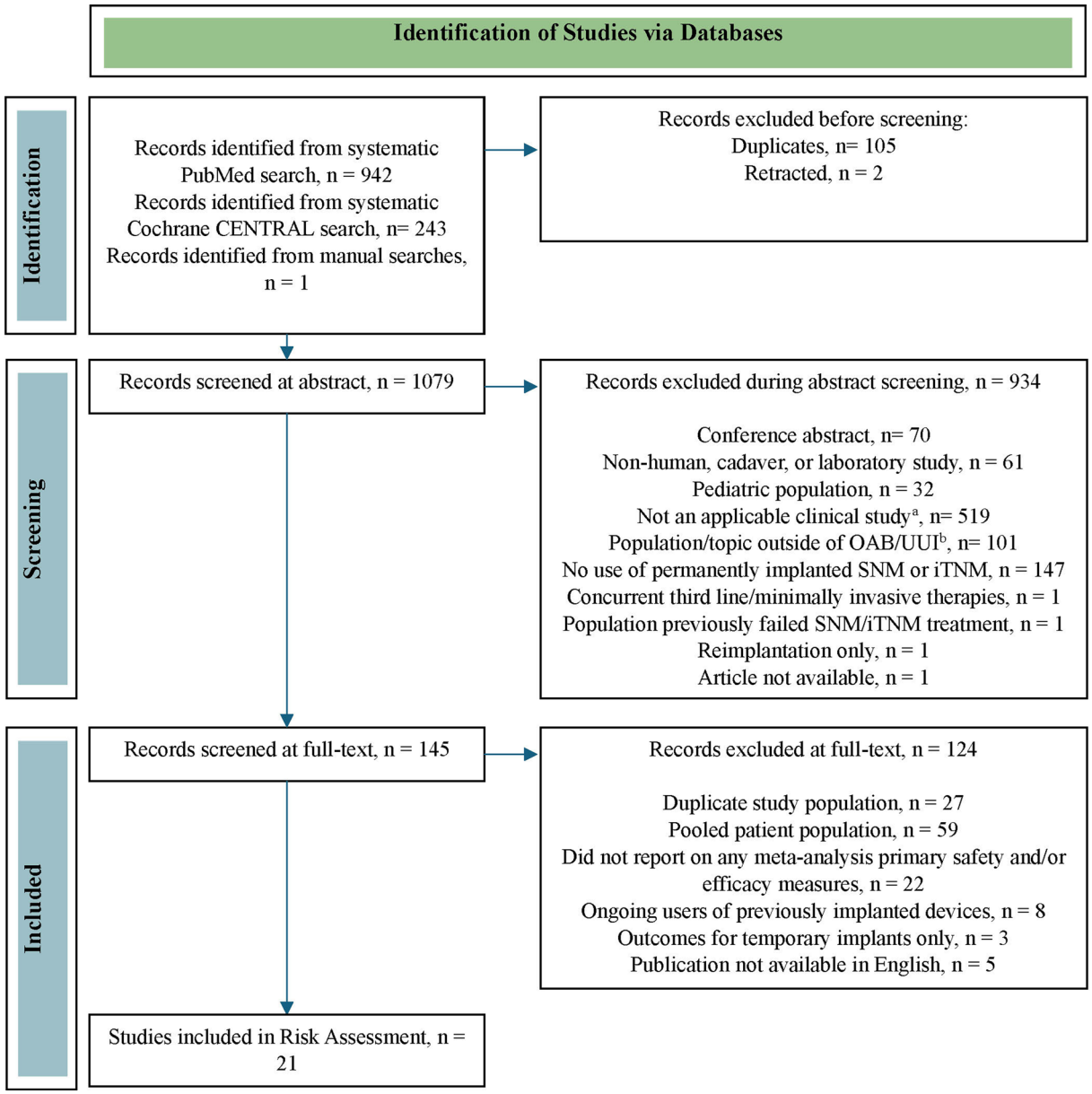


Fig. 1 PRISMA of systematic literature search [a]Includes exclusion of reviews and study protocols without results, as well as other types of studies on topics such as health economics, procedure methods or imaging, and use trends, along with case reports/case series. Studies with < 15 patients were excluded. [b]Population/topic outside of OAB and/or UUI (i.e., neurogenic bladder, urinary retention, interstitial cystitis, pelvic pain, etc.) or pooled population where results for OAB and/or UUI were not separately presented. *CENTRAL* Cochrane Central Register of Controlled Trials, *OAB* overactive bladder, *UUI* urgency urinary incontinence, *SNM* sacral neuromodulation, *iTNM* implantable tibial neuromodulation

(FDA-approved 2022) and traditional SNM (FDA-approved 1996) (also see Supplementary Table S1).

Baseline variables of disease severity were similar across studies (Supplementary Table S4). The majority of patients treated with SNM and iTNM in the selected studies had UUI [weighted

A

	Author	Prospective vs Retrospective	Multicenter vs Single Center	Random Assignment	Blinding	Voiding Diary	Withdrawal/ Drop-out Rate	Length of Follow-up	Adverse Event Reporting	Industry Sponsorship[a]	Total
SNM	Amundsen et al. (30)	+	+	+	-	+	+	+	+	+	Low
	Blok et al. (58)	+	+	-	-	+	+	+	+	-	Low
	Liao et al. (55)	+	+	+	+	+	+	+	+	-	Low
	Pezzella et al. (59)	+	+	-	-	+	+	+	+	-	Low
	Siegel et al. (57)	+	+	+	-	+	+	+	+	-	Low
	Zhang et al. (56)	+	+	-	+	+	-	+	+	+	Low
	Al-Azzawi et al. (60)	+	-	-	-	+	-	-	+	?	Moderate
	Chartier-Kastler et al. (65)	+	+	-	-	+	-	+	+	-	Moderate
	Goudelocke et al. (61)	+	+	-	-	+	+	-	+	-	Moderate
	Groen et al. (71)	-	-	-	-	+	+	+	+	?	Moderate
	Ismail et al. (66)	-	-	-	-	+	+	+	+	+	Moderate
	Kaaki et al. (67)	-	-	-	-	-	+	+	+	+	Moderate
	Meng et al. (68)	-	+	-	-	+	-	+	+	+	Moderate
	Moon et al. (62)	+	+	-	-	+	-	+	+	-	Moderate
	Peeters et al. (69)	-	-	-	-	+	+	+	+	?	Moderate
	Zhang et al. (70)	-	+	-	-	+	+	+	+	-	Moderate
	Singh et al. (54)	-	-	-	-	-	+	-	+	?	High[b]
iTNM	Gilling et al. (63)	+	+	-	-	+	+	+	+	-	Low
	Heesakkers et al. (52)	+	+	-	-	+	+	+	+	-	Low
	Rogers et al. (51)	+	+	-	-	+	+	+	+	-	Low
	Dorsthorst et al. (64)	+	+	-	-	+	-	+	+	-	Moderate

[a] Full or partial funding for the study was provided by industry.
[b] As noted in the methods, further data was not extracted from studies with potential for high bias based on the criteria noted for this bias assessment.
+ = low risk of bias
- = high risk of bias
? = unknown risk of bias

B

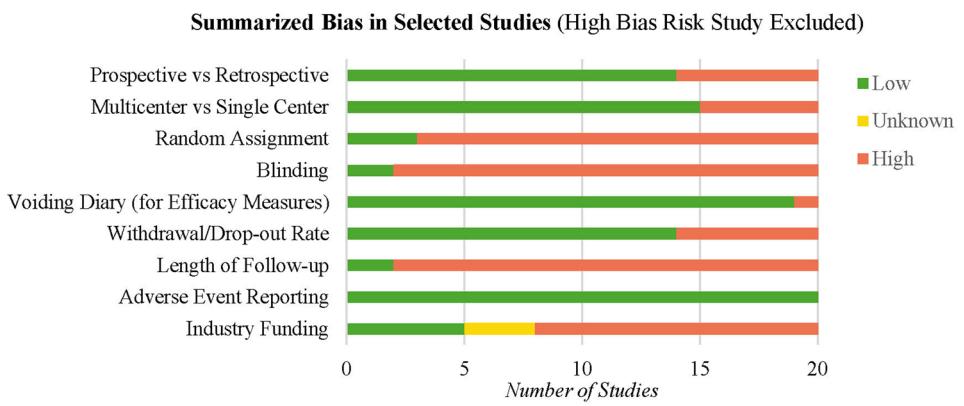


Fig. 2 Bias ratings of included studies. **A** Overview of areas potential bias that were assessed for each selected publication. Studies with 0–2 areas of potential bias were rated as "Low", studies with 3–5 areas of potential bias were rated as "Moderate", and studies with 6 or more areas of potential bias were rated as "High". As prespecified, if less than 15% of the total identified publications had high potential bias, these studies were excluded from further data extraction. **B** Summary of potential bias

Table 1 Study design and demographics of identified clinical studies

	References	Type of study	Device name	No. of patients[a]	Mean age (SD), years	% female	Length of follow-up (months)[b]
SNM	Blok et al. [58]	Prospective interventional	Axonics	51	51.0 (NR)	74.5%	24
	Pezzella et al. [59]	Prospective interventional	Axonics	129	59.3 (NR)	98.0%	24
	Zhang et al. [56]	Prospective interventional	BetterStim	70	52.8 (± 15.6)	72.9%	36
	Amundsen et al. [30] (SNM group)	RCT	InterStim	139	62.7 (± 11.8)	100.0%	24
	Siegel et al. [57]	RCT	InterStim	272	57.0 (± 14.2)	91.2%	60
	Al-Azzawi et al. [60]	Prospective interventional	InterStim	15	37.2 (± 11.1)	100.0%	6
	Goudelocke et al. [61]	Prospective interventional	InterStim	68	62.0 (± 13)	89.7%	6
	Moon et al. [62]	Prospective interventional	InterStim	40	54.2 (± 15.4)	83.9%	12
	Chartier-Kastler et al. [65]	Prospective observational	InterStim	229	60.5 (± 15.1)	85.4%	58
	Ismail et al. [66]	Retrospective review	InterStim	34	57.8 (NR)	91.2%	116
	Kaaki et al. [67]	Retrospective review	InterStim	55	62.7 (NR)	100.0%	32
	Meng et al. [68] (InterStim group)	Retrospective review	InterStim	43	52.4 (± 19.9)	65.1%	22
	Peeters et al. [69] (OAB UUI group)	Retrospective review	InterStim	70	55.0 (NR)	85.7%	27
	(OAB UF group)			34	54.2 (NR)	73.5%	32
	Zhang et al. [70]	Retrospective review	InterStim	34	53.6 (± 18.8)	64.7%	20
	Groen et al. [71]	Retrospective review	NR	60	48 (NR)	100.0%	60
	Liao et al. [55] (Treatment group)	RCT	SacralStim	37	52.5 (± 14.1)	78.4%	11
	(Control group)			36	50.3 (± 13.9)	58.3%	11

Table 1 continued

	References	Type of study	Device name	No. of patients[a]	Mean age (SD), years	% female	Length of follow-up (months)[b]
	Total/weighted averages			**1416**	**57.0**	**87.5%**	**39.2**
iTNM	Gilling et al. [63]	Prospective interventional	eCoin	46	63.4 (NR)	97.8%	12
	Rogers et al. [51]	Prospective interventional	eCoin	133	63.9 (10.9)	98.5%	11
	Dorsthorst et al. [64]	Prospective interventional	Revi	20	56.1 (NR)	80.0%	36
	Heesakkers et al. [52]	Prospective interventional	Revi	151	58.8 (12.5)	100.0%	12
	Total/weighted averages			**350**	**61.2**	**98.0%**	**13.0**

Bold indicates Headers and totals/weighted averages by neuromodulation type

As the initial phase of the InSite trial was randomized (comparing SNM to standard medical therapy at 6 months), this study was reported as a RCT

iTNM implantable tibial neurostimulation, *NR* not reported, *PI* Prospective Interventional, *RR* Retrospective Review, *RCT* randomized control trial, *SD* standard deviation, *SNM* sacral neuromodulation

[a]Number fully implanted at study baseline

[b]If patient follow-up was not completed on a pre-planned schedule, average length of follow-up has been reported

average of 98.9% for iTNM (n = 350) and 83.3% for SNM (n = 1107)], and nearly all patients in both groups had previously been treated with oral medications [weighted average of 92.6% for iTNM (n = 330) and 99.7% for SNM (n = 1175)]. The weighted average number of UUI episodes per day was also similar, with 4.6 per day for patients treated with iTNM (n = 350) and 5.0 per day for patients treated with SNM (n = 1150). While a limited number of studies reported the duration of symptoms, likely due to the potential for patient recall bias, all reporting studies noted patients had an average of 4 or more years of OAB symptoms prior to the use of neurostimulation [51, 56, 57, 59, 61, 62, 65–67, 70]. A potentially confounding factor was the concomitant use of oral OAB medications at baseline, as many studies did not report, and a few studies [52, 55, 61–65] included patients on medications; however, baseline symptoms reported reflected the severity of OAB symptoms with current use of such medications.

Efficacy Measures: Improvements to OAB Symptoms

For this meta-analysis, primary outcome measures relating to OAB symptoms collected in voiding diaries were defined as the percentage of patients with ≥ 50% improvement of UUI symptoms (UUI response rate), percentage of patients with ≥ 50% improvement of OAB symptoms (overall OAB response rate), and percentage of patients with ≥ 50% of UF symptoms (frequency response rate). Secondary measures of efficacy were mean decrease in UUI episodes, mean change in urinary frequency, and short-term (< 6 month) impacts on UUI episodes.

Results for UUI response rate were available for four iTNM studies and eight SNM studies; weighted averages from these twelve studies showed that UUI responder rates were similar for both iTNM and SNM, with responder rates of 71.3% (n = 350) and 71.8% (*n* = 950), respectively (see Table 2 and Fig. 3). Similarly, results for OAB response rates were available from two iTNM studies and eight SNM, and weighted averages from these ten studies demonstrated similar response rates of and 79.4% for iTNM and 73.9% SNM studies (see Table 2 and Fig. 3; definitions by study have been provided in Supplementary Table S5). Frequency response rates were a planned primary outcome measure; however, this measure was not reported in the four iTNM studies included in this analysis, so comparison with SNM was not possible. Therefore, results reported for urinary frequency in just the six applicable SNM studies are summarized in Supplementary Table S6.

As studies with multiple designs (RCTs, interventional studies, retrospective data collections, etc.) were allowed in the primary analysis, the distribution of endpoint data by study type was examined, and key primary endpoint data were also separately analyzed for interventional and observational studies. As seen in Fig. 4A, similarities in results across all studies despite differences in study design provide confidence that overall results are representative. Results for SNM in interventional and observational studies were similar (Fig. 4B); differences were primarily driven by very positive data from the two interventional Axonics studies [58, 59]. All four iTNM studies were interventional in nature, and their results compared to both interventional and observational SNM studies remained similar. Interventional iTNM studies had a weighted average UUI responder rate of 71.3% (*n* = 350), while interventional SNM studies had a weighted average UUI responder rate of 74.0% (*n* = 661) in interventional studies and 66.5% in observational studies (*n* = 289). OAB response rates were also similar, with weighted average response rates of 79.4% (*n* = 171), 82.5% (*n* = 393), and 64.7% (*n* = 367) in interventional iTNM, interventional SNM, and observational SNM, respectively. Secondary measures of efficacy relating to OAB symptoms collected in voiding diaries included reduction in UUI episodes and changes in urinary frequency. The weighted average of the decrease in UUI episodes was again similar for iTNM and SNM studies, with an average decrease of 3.0 (*n* = 350) and 3.5 (*n* = 1150) UUI episodes, respectively. There appeared to be differences in the decrease of urinary frequency between iTNM and SNM studies [weighted average of 2.0 (*n* = 304) vs. 5.5 (*n* = 1041), respectively]; however, this was likely due to differences in the baseline frequency reported in the iTNM versus SNM studies [weighted averages of 10.2 (*n* = 171) vs. 15.1 (n = 1041) voiding episodes per day, respectively]. This difference in baseline urinary frequency was largely driven by significantly greater baseline voiding frequencies describing the study populations noted in studies completed in Asia (21.6–29.2 voiding episodes per day) [55, 56, 62, 70].

As early clinical impacts are important in clinical practice, impacts on the reduction of UUI episodes at 3 and 6 months were also examined. Similar to longer term results, impacts on UUI response rate were similar for SNM and iTNM, with SNM studies showing a reduction of ≥ 50% UUI episodes in 76.8% (*n* = 631) and 67.9% (*n* = 721) of patients at 3 and 6 months, respectively, and iTNM studies showing a similar results in 69.0% (*n* = 197) and 74.4% (*n* = 304) of patients at the same timepoints (based on weighted averages). A summary of secondary endpoints is presented in Table 3, with study-specific data presented in Supplementary Tables S7, S8, and study specific short-term data in S9.

Positive Impacts on Quality of Life (QoL)

The OAB-q is one of the most commonly used instruments to assess QoL in OAB-related studies [72], and therefore the aggregate health-related quality of life (HRQoL) score from this instrument was used to assess QoL impact, where the minimally important difference was ≥ 10 points [73]. The weighted average of the percent of patients with a ≥ 10 point change on the HRQoL was 83.2% (*n* = 171) and 48.4% (*n* = 340), for iTNM and SNM, respectively; admittedly, there were

Table 2 Summary of primary efficacy endpoints among included studies

	References	Device name	No. of patients[a]	UUI response rate (≥ 50%)	OAB response rate (≥ 50%)[b]
SNM	Blok et al. [58]	Axonics	51	88%	90%
	Pezzella et al. [59]	Axonics	129	93%	NR
	Zhang et al. [56]	BetterStim	70	69%	79%
	Amundsen et al. [30][c] (SNM group)	InterStim	139	50%	NR
	Chartier-Kastler et al. [65] (De Novo Group)	InterStim	169	68%	62%
	Chartier-Kastler et al. [65] (Replacement Group)	InterStim	60	67%	65%
	Ismail et al. [66]	InterStim	34	NR	63%
	Peeters et al. [69] (OAB UUI group)	InterStim	70	NR	70%
	Peeters et al. [69] (OAB UF group)	InterStim	34	NR	68%
	Siegel et al. [57]	InterStim	272	76%	82%
	Groen et al. [71]	NR	60	62%	NR
	Weighted average			**71.8%**	**73.9%**
	No. of patients[a]			950	760
iTNM	Gilling et al. [63]	eCoin	46	65%	NR
	Rogers et al. [51]	eCoin	133	68%	NR
	Dorsthorst et al. [64]	Revi	20	58%	75%
	Heesakkers et al. [52]	Revi	151	78%	80%
	Weighted average			**71.3%**	**79.4%**
	No. of patients[a]			350	171

Bold indicates Headers and totals/weighted averages by neuromodulation type

iTNM implantable tibial neuromodulation, *NR* not reported, *OAB* overactive bladder, *SNM* sacral neuromodulation, *UUI* urgency urinary incontinence

[a]Number fully implanted at study baseline

[b]OAB response was improvement in a combination of more than one urgency and/or frequency-related voiding diary parameter. Definitions have been reported in Supplementary Table S4

[c]UUI response rate was estimated based on data provided in a graphical figure

only two SNM studies available to contribute to this weighted average, with much lower HRQoL scores associated with one study SNM [57]. When evaluating HRQoL scores directly,

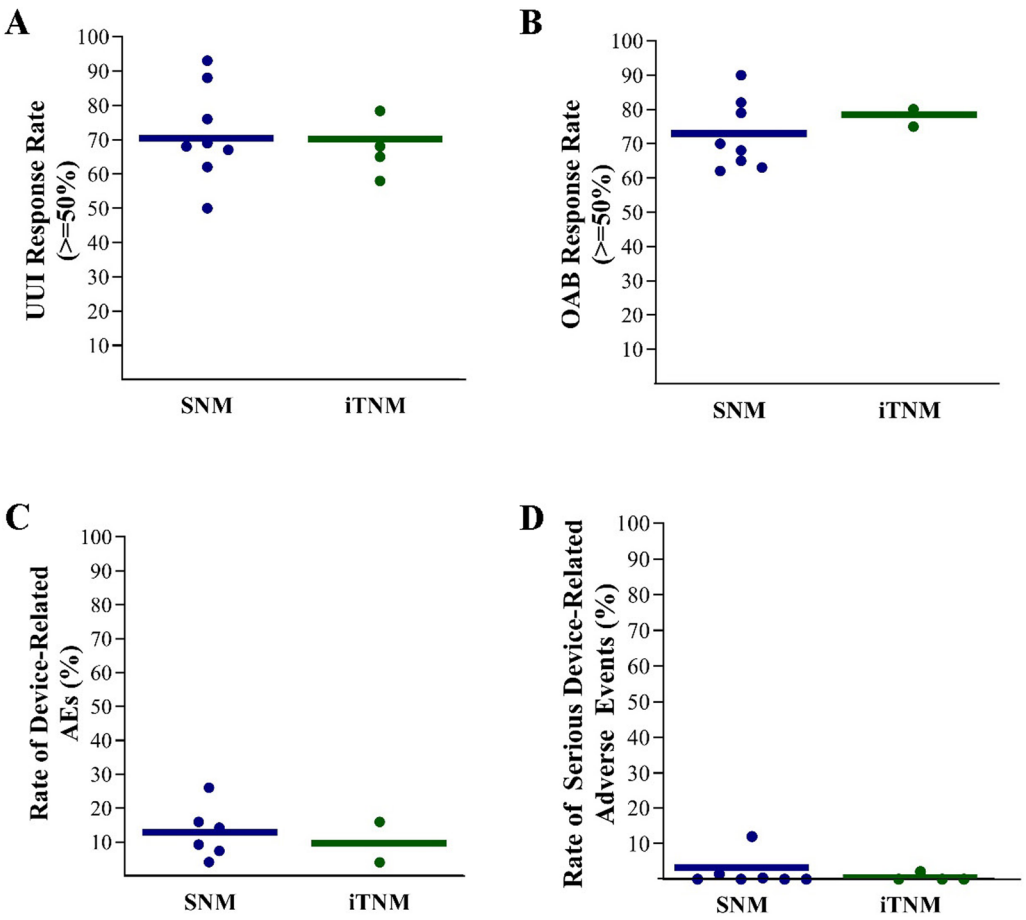


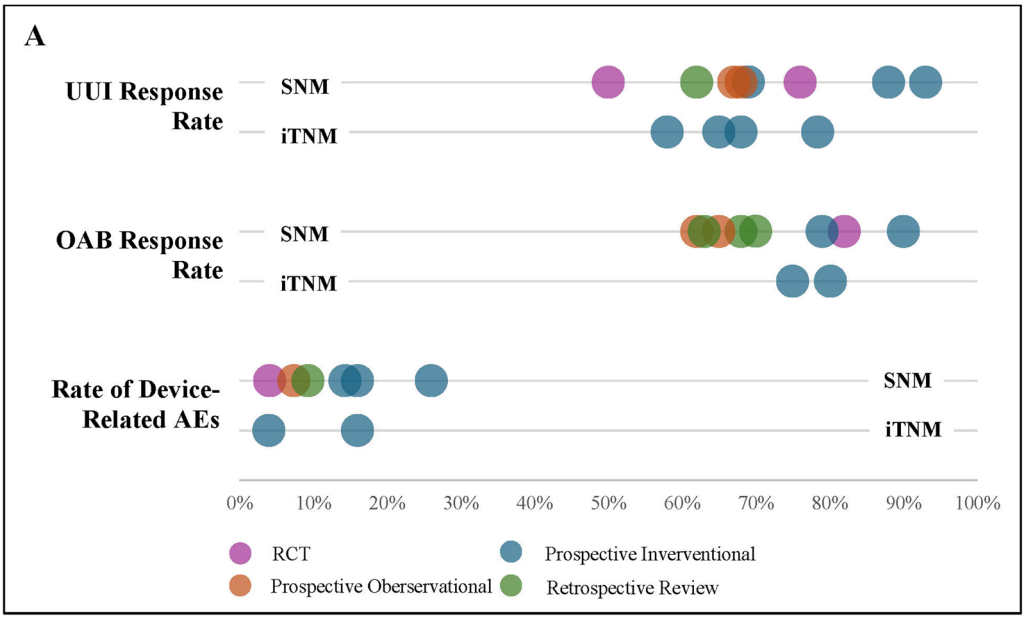
Fig. 3 Summary of key efficacy and safety measures (weighted averages). **A** UUI Response (≥ 50%) in included studies was 71.8% for SNM studies and 71.3% for iTNM studies. **B** OAB Response (≥ 50%) in included studies was 73.9% for SNM studies and 79.4% for iTNM studies. Definitions for OAB response are provided in Supplementary Table S4. **C** Rate of device-related AEs in included studies was 12.7% for SNM and 9.6% for iTNM studies. **D** Rate of device-related SAEs in included studies was 3.3% for SNM and 0.3% for iTNM studies. *AE* adverse event, *iTNM* implantable tibial neuromodulation, *OAB* overactive bladder, *SAE* serious adverse event, *SNM* sacral neuromodulation, *UUI* urgency urinary incontinence

there was an average increase of 34.5 points (n = 133) for iTNM and 35.1 points (n = 427) for SNM patients in the selected studies.

Additionally, the percentage of subjects following treatment achieving a patient global impression of improvement (PGI-I) score of ≥ "better" was 88.5% (n = 197) for iTNM and 74.9% (n = 207) for SNM. Therapy satisfaction, while reported less frequently among the selected studies, was 95% (n = 151) for iTNM and 75.5% (n = 334) for SNM (Table 3).

Revisions, Explants, and Lead Migrations

In this meta-analysis, rates of permanent explant, surgical revision, and lead migration were much lower in iTNM studies (weighted averages of 0–1.7%), versus in SNM studies (weighted averages of 5.6–26.8%), as shown in Table 4. While the ankle does experience a high degree of motion, the weighted average of migration in iTNM was 1.7%, which may be influenced by the design of the iTNM devices:



B

		SNM		iTNM
		Interventional	Observational	Interventional
UUI Response Rate	**Weighted Average**	**74.0%**	**66.5%**	**71.3%**
	Range	50-93%	62-68%	58-78%
	N of Studies (total)	5	2	4
	Axonics	2	1	N/A
	InterStim	2	0	N/A
	Other/NR SNM	1	1	N/A
	eCoin	N/A	N/A	2
	Revi	N/A	N/A	2
	N of Patients	661	289	350
OAB Response Rate	**Weighted Average**	**82.5%**	**64.7%**	**79.4%**
	Range	79-90%	62-70%	75-80%
	N of Studies (total)	3	3	2
	Axonics	1	0	N/A
	InterStim	1	3	N/A
	Other/NR SNM	1	0	N/A
	eCoin	N/A	N/A	0
	Revi	N/A	N/A	2
	N of Patients	393	367	171
Device-Related Adverse Event Rate	**Weighted Average**	**13.3%**	**9.3%**	**9.6%**
	Range	4-26%	N/A	4-16%
	N of Studies (total)	5	1	2
	Axonics	2	0	N/A
	InterStim	1	1	N/A
	Other/NR SNM	2	0	N/A
	eCoin	N/A	N/A	1
	Revi	N/A	N/A	1
	N of Patients	391	43	284

Fig. 4 Key efficacy and safety measures by study type. **A** Percentages compared by study design. **B** Weighted averages compared by study design. *AE* adverse event, *iTNM* implantable tibial neuromodulation, *N/A* not applicable, *NR* not reported, *OAB* overactive bladder, *RCT* randomized clinical trial, *SNM* sacral neuromodulation, *UUI* urgency urinary incontinence

Table 3 Secondary endpoints: (A) Reduction in UUI episodes and frequency, (B) quality of life and therapy satisfaction, (C) short-term impacts on reduction of UUI episodes

A		Baseline UUI episodes	Average decrease in UUI episodes[b]	Baseline frequency	Average decrease in frequency[c]
SNM	**Weighted average**	**5.0**	**3.5**	**15.1**	**5.5**
	Range	2.4–8.9	1.6–7.1	11.6–29.2	2.1–13.9
	No. of patients[a]	1150	1150	1041	1041
iTNM	**Weighted average**	**4.6**	**3.0**	**10.2**	**2.0**
	Range	4.3–6.5	2.5–3.5	10–12.4	1.8–2.7
	No. of patients[a]	350	350	171	304

B		% reporting ≥ 10pt improvement in HRQoL[d]	Average HRQoL score improvement[e]	% Reporting PGI-I improvement[d]	% reporting therapy satisfaction[f]
SNM	**Weighted average**	**48.4%**	**35.1**	**74.9%**	**75.5%**
	Range	40–82%	29–39.2	68–89%	53.6–94%
	No. of patients[a]	340	427	207	334
iTNM	**Weighted average**	**83.2%**	**34.5**	**88.5%**	**95.0%**
	Range	73–85%	N/A	70–94.2%	N/A
	No. of patients[a]	171	133	197	151

C			UUI response rate (≥ 50%)	
			3 months[g]	6 months[h]
SNM		**Weighted average**	**76.8%**	**67.9%**
		Range	53–87%	53–94%
		No. of patients[a]	631	721
iTNM		**Weighted average**	**69.0%**	**74.4%**
		Range	68–69.3%	69–85%
		No. of patients[a]	197	304

Bold indicates Headers and totals/weighted averages by neuromodulation type

HRQoL health-related quality of life, *iTNM* implantable tibial neuromodulation, *PGI-I* patient global impression of improvement, *SNM* sacral neuromodulation, *UUI* urgency urinary incontinence

[a]Number fully implanted at study baseline

[b]Change in UUI episodes was reported in 13 SNM studies and four iTNM studies. Baseline UUI values reflect reports from studies that provided information regarding the average decrease in UUI episodes only

[c]Change in frequency was reported in 10 SNM studies and three iTNM studies. Baseline frequency values reflect reports from studies that provided information regarding the average decrease in frequency episodes only. In one iTNM study, the average decrease in frequency was provided; however, the baseline frequency was not reported

[d]Based on reported data from two SNM and two iTNM studies

[e]Based on reported data from five SNM and one iTNM studies

[f]Based on reported data from four SNM and one iTNM studies

[g]Based on reported data from five SNM and two iTNM studies

[h]Based on reported data from six SNM and three iTNM studies

for instance, the eCoin device is placed into a tissue pocket created during implantation, and, as the device has more surface area than a traditional thin lead, it may be less likely to migrate from the site of stimulation. The Revi device has 4 suture holes, which allows placement of sutures to anchor the device to the open fascia, securing it in place and reducing the risk of migration. It lies flat under the skin and does not protrude after implant, reducing the risk of migration caused by patient manipulation.

Common reasons for surgical revision within the selected studies were due to battery depletion requiring exchange, lead migration, electrode failure, loss of effectiveness, and adverse events such as infection.

Safety Measures

While revision rates increase over the implanted lifetime of neuromodulation devices, most device- and procedure-related adverse events typically occur within the first several months following device implantation. Importantly, the safety profile of both iTNM and SNM devices is notably very good, with low rates of device-related serious adverse events [weighted average of 0.3% (n = 350) in iTNM studies and 3.3% (n = 892) in SNM studies], device-related adverse events [weighted average of 9.6% (n = 284) in iTNM studies and 12.7% (n = 434) in SNM studies], and procedure-related events [weighted average of 10.6% (n = 151) in iTNM studies and 11.6% (n = 129) in SNM studies]. Additionally, weighted averages for the rates of infection, pain, and wound healing events were similar for both iTNM and SNM, as shown in Table 5 and Fig. 3. Of note, different devices within the iTNM and SNM categories may have somewhat different risk profiles in relation to device-related AEs: for instance, such events were reported at 4.0% for Revi and 16.0% for eCoin, the two iTNM devices with published data currently available.

DISCUSSION

Neuromodulation for lower urinary tract indications has been an accepted therapy for voiding dysfunction refractory to behavioral and/or pharmacologic therapy for more than 25 years. Since the late 1990s, SNM has been established as a highly efficacious method of controlling symptoms of OAB, with a positive safety profile. The sacral nerves are significant targets for stimulation due to the density of motor and sensory neural elements contained within these nerves.

Recently, other peripheral nerves have been identified as being potential targets for neuromodulation of pelvic dysfunction, such as urinary incontinence, based upon the historic known efficacy of percutaneous tibial stimulation. Percutaneous stimulation of the tibial nerve has demonstrated efficacy and safety despite the need for recurrent stimulation exposures and substantial patient and healthcare system burden. Based upon this experience, implantable technologies have evolved for tibial stimulation.

As technology advances, use of minimally invasive treatment options for OAB are becoming more and more common [17, 25, 74]. The results of this meta-analysis support iTNM as having similar efficacy and safety compared to SNM, despite key differences in stimulation location, implantation procedure, and treatment regimen. Additionally, a trend for higher patient satisfaction and patient global impression of improvement was seen with iTNM versus SNM.

While both SNM and iTNM are minimally invasive therapies, procedural differences exist that should be noted. Most SNM permanent implants are done under sedation or general anesthesia, and most iTNM options are completed under local anesthesia, with sedation allowed for physician or patient preference but not required. Additionally, sacral leads must be implanted with the use of fluoroscopy, which is not needed for iTNM devices, reducing radiation exposure to both the provider and patient. For currently available SNM devices, both a lead and a neurostimulator are implanted, whereas both eCoin and Revi (iTNM options) implants are completed in a single piece, with some impacts

Table 4 Summary of rates of explants, revisions, and lead migrations among included studies

	References	Device name	No. of patients[a]	Rate of permanent explant	Rate of surgical revision	Rate of lead migration
SNM	Blok et al. [58]	Axonics	51	13.7%	NR	2.0%
	Pezzella et al. [59]	Axonics	129	3.9%	8.5%	2.3%
	Zhang et al. [56]	BetterStim	70	11.4%	NR	0.0%
	Al-Azzawi et al. [60]	InterStim	15	NR	NR	13.3%
	Amundsen et al. [30] (SNM group)	InterStim	139	8.6%	2.9%	NR
	Chartier-Kastler et al. [65]	InterStim	229	14.8%	38.9%	10.9%
	Ismail et al. [66]	InterStim	34	6.3%	46.9%	NR
	Kaaki et al. [67]	InterStim	55	27.3%	18.2%	3.6%
	Moon et al. [62]	InterStim	40	NR	NR	0.0%
	Peeters et al. [69]	InterStim	104	18.0%[b]	40.6%[b]	NR
	Siegel et al. [57]	InterStim	272	19.1%	30.9%	NR
	Groen et al. [71]	NR	60	3.3%	25.0%	NR
	Weighted average			**13.7%**	**26.8%**	**5.6%**
	No. of patients[a]			**1143**	**1011**	**589**
iTNM	Gilling et al. [63]	eCoin	46	NR	NR	2.2%
	Rogers et al. [51]	eCoin	133	NR	NR	1.5%
	Dorsthorst et al. [64]	Revi	20	2.9%	0.0%	NR
	Heesakkers et al. [52]	Revi	151	0.7%	NR	NR
	Weighted average			**1.0%**	**0.0%**	**1.7%**
	No. of patients[a]			**171**	**20**	**179**

Bold indicates Headers and totals/weighted averages by neuromodulation type

iTNM implantable tibial neuromodulation, *NR* not reported, *OAB* overactive bladder, *SNM* sacral neuromodulation

[a]Number fully implanted at study baseline

[b]Note that surgical revision and explant rates for patients with OAB were pooled with other indications

to the complexity of the procedure. These differences result in a generally less invasive procedure for iTNM devices; however, patient and provider preferences will likely influence what type of procedure is best suited to an individual patient, as both procedures have positive safety results. The posterior tibial nerve and sacral nerve originate from a similar level in the spinal cord and therefore both SNM and iTNM devices are capable of stimulating the same neural network, providing a plausible rationale for the comparable efficacy observed. While both iTNM and SNM target stimulation of the sacral nerve plexus, the location of initial stimulation (and therefore of the neurostimulation implant) differs significantly. iTNM devices are implanted in the inner aspect of the ankle just above the medial malleolus; SNM leads are implanted in

Table 5 Summary of primary safety endpoints among included studies

	References (Device name)	No. of patients[a]	Rate of device-related SAEs	Rate of device-related AE	Rate of procedure-related AEs	Rate of infection	Rate of pain	Rate of wound-healing AEs
SNM	Blok et al. [58] (Axonics)	51	0.0%	26.0%	NR	NR	2.0%	NR
	Pezzella et al. [59] (Axonics)	129	0.0%	15.5%	11.6%	NR	10.1%	NR
	Zhang et al. [56] (BetterStim)	70	0.0%	14.3%	NR	NR	7.1%	NR
	Al-Azzawi et al. [60] (InterStim)	15	NR	NR	NR	20.0%	26.7%	NR
	Amundsen et al. [30] (InterStim) (SNM group)	139	NR	NR	NR	NR	6.0%	NR
	Chartier-Kastler et al. [65] (InterStim)	229	12.0%	NR	NR	4.4%	6.2%	NR
	Goudelocke et al. [61] (InterStim)	68	1.5%	7.4%	NR	NR	NR	NR
	Kaaki et al. [67] (InterStim)	55	NR	NR	NR	1.8%	5.5%	NR
	Meng et al. [68] (InterStim) (InterStim group)	43	NR	9.3%	NR	NR	NR	NR
	Moon et al. [62] (InterStim)	40	NR	NR	NR	NR	5.0%	NR
	Peeters et al. [69] (InterStim) (OAB UUI group)	70	NR	NR	NR	2.9%	NR	4.3%
	Peeters et al. [69] (InterStim) (OAB UF group)	34	NR	NR	NR	0.0%	NR	2.9%
	Siegel et al. [57] (InterStim)	272	0.4%	NR	NR	NR	14.7%	NR
	Zhang et al. [70] (InterStim)	34	NR	NR	NR	0.0%	5.9%	NR

Table 5 continued

	References (Device name)	No. of patients[a]	Rate of device-related SAEs	Rate of device-related AE	Rate of procedure-related AEs	Rate of infection	Rate of pain	Rate of wound-healing AEs
	Liao et al. [55] (SacralStim)	73	0.0%	4.1%	NR	NR	1.4%	NR
	Weighted average		**3.3%**	**12.7%**	**11.6%**	**3.7%**	**8.5%**	**3.8%**
	No. of patients[a]		892	434	129	437	1107	104
iTNM	Gilling et al. [63] (eCoin)	46	2.2%	NR	NR	13.0%	13.0%	NR
	Rogers et al. [51] (eCoin)	133	0.0%	16.0%	NR	6.8%	1.5%	3.8%
	Dorsthorst et al. [64] (Revi)	20	0.0%	NR	NR	NR	NR	NR
	Heesakkers et al. (52) (Revi)	151	0.0%	4.0%	10.6%	1.3%	4.6%	6.6%
	Weighted average		**0.3%**	**9.6%**	**10.6%**	**5.1%**	**4.7%**	**5.3%**
	No. of patients[a]		350	284	151	330	330	284

Bold indicates Headers and totals/weighted averages by neuromodulation type

AE adverse event, *iTNM* implantable tibial neuromodulation, *NR* not reported, *SNM* sacral neuromodulation

[a]Number fully implanted at study baseline

the lower back along the S(sacral)3 nerve root, with the internal pulse generator (IPG)—which includes the battery—generally implanted in a subcutaneous pocket in the upper buttock. Other procedural differences—such as requirements for sedation/anesthesia, use of fluoroscopy, procedure time, amount of implanted hardware—as well as differences in how patients interact with their devices, also vary greatly between currently available iTNM and SNM options.

The ability to alter stimulation parameters such as polarity, current delivery, current frequency, and pulse width are all critical to successful efficacy and durability of neuromodulation therapy. The capability of ongoing modulation of these parameters over time has now been demonstrated as a successful strategy to improve the durability of successful outcomes, and to salvage those individuals who have not initially attained therapeutic goals with base device settings. The ability to alter stimulation parameters both prior to and during ongoing treatment, both by medical care providers and individual patients, also varies by device. Such differences may result in the development of patient and clinician preferences over time, including preferences for both type of device and mode of therapy delivery. Recently, results of a patient preference survey indicated that iTNM may indeed expand the subset of patients interested in considering minimally invasive therapies for treatment of OAB [75].

While similar efficacy was seen for both iTNM and SNM, it is also notable that these results were similar despite the lack of any neuromodulation treatment trial for enhanced patient selection with iTNM prior to device implantation. With SNM, a trial phase of stimulation is first required to assess the responsiveness of the patient with respect to the impact of neuromodulation on their OAB symptoms. The trial phase is accomplished either with implantation of a simple wire—PNE—or a

surgically implanted tined lead—staged trial. This trial then eliminates "non-responders" from subsequent full device implantation and further study involvement and follow-up from the SNM studies. Of the 16 SNM studies included in this analysis, 14 involved a trial phase with either PNE or a staged technique; only 2 SNM studies (Axonics) [58, 59] did not include a trial prior to full implantation. In those with a trial, a 27% failure rate (weighted average) was observed, with such patients deemed neuromodulation "non-responders" and subsequently not permanently implanted (Supplementary Table S10). As this meta-analysis only considered SNM results in the permanently implanted patients, it is noteworthy that therapeutic impact on OAB symptoms between iTNM and SNM was so similar, even after removing "non-responders" from SNM study populations. Interestingly, the SNM study with the most positive efficacy results (ARTISAN, Axonics; [59]) was the only SNM study that did not implement a trial phase into their procedural or analysis requirements. As additional long-term data becomes available for iTNM devices, it will be useful to confirm if this trend for similar clinical efficacy continues even without the requirement for pre-implantation trial.

Another key difference between current iTNM and SNM devices is the use of cyclic versus continuous stimulation. SNM studies included in the meta-analysis used continuous stimulation, and all four iTNM studies included involved cyclic stimulation with various regimens. Currently, there are growing questions in the field of neuromodulation regarding the potential benefits of cyclic therapy with a lower risk of nerve habituation and hypothesized subsequent potential loss of clinical efficacy [76–78]. While cyclic stimulation is still being tested in the field of SNM [78–80], it is very interesting that efficacy results in this meta-analysis are similar even with the less frequent use of stimulation seen in the iTNM studies.

One drawback of any permanently implanted medical device is the need for surgical intervention should an issue arise. For those devices with a fixed (vs. rechargeable) battery, surgical intervention to replace a depleted battery is required. Indeed, in this meta-analysis, the need for battery replacement was a key driver of the surgical re-intervention rate (all-cause re-intervention rate of 26.8% for included SNM studies). As technological advances permit the use of external battery systems with implanted electrodes and/or implanted batteries—rechargeable or fixed—with longer lifetimes, the need for surgical re-intervention for battery exchanges will decline, if not be eliminated. Indeed, in many SNM devices, longer battery life options have recently become available, and, as such, a lower re-intervention rate may be seen as future long-term data are available. It is also important to note that devices with rechargeable or external batteries currently require active patient involvement for their ongoing therapy, which may be perceived as a positive or negative therapeutic attribute, depending on individual needs and preferences. For example, Revi, an iTNM system with a wearable external battery, is recommended to be used at least once a day for 30 min, which may be perceived as burdensome to some patients due to a preference for 'set and forget' systems with implanted, non-rechargeable batteries (including options for InterStim, Axonics, and eCoin), while other patients may prefer having more control and flexibility over therapy delivery and symptom management. The recently completed ARTISAN-SNM study[59] used rechargeable SNM devices requiring interaction every 1–2 weeks had excellent patient follow-up and outcomes, and the recent OASIS study[52] required at least twice daily interaction with the Revi device, and 94% of patients reported willingness to continue treatment at 12 months. As more clinical evidence becomes available, it will be important to better understand the impact of device interaction for patient selection.

A challenge for neuromodulation in the intermediate future is the appropriate delivery of this therapy to individuals on demand and when needed. Recent changes in therapeutic guidelines would also suggest that implantable neuromodulation may become a key treatment option earlier in the course of pelvic floor conditions, potentially avoiding long-term primary and secondary therapies which have hitherto led to substantial patient dissatisfaction.

Overall, the availability of both iTNM and SNM as minimally invasive therapy options for the treatment of OAB represents significant

progress for patients. With recent concerns about the potential link between anticholinergic agents and dementia risk [22–24], minimally invasive, non-pharmacologic treatment like neuromodulation offer an efficacious alternative, aligning with the new AUA/SUFU guidelines that support earlier consideration of minimally invasive therapies [12].

Limitations

Several limitations should be considered in the present meta-analysis. While this meta-analysis featured a large number of studies and corresponding patients, 11 studies were considered to have a moderate risk of potential bias, most often related to challenges with randomization and blinding due to patient sensation of neurostimulation, along with the retrospective and single-center nature of several of these studies. Differences in study populations, geography, study methods, efficacy definitions, and stage of device development (i.e., pilot study vs. pivotal study vs. study completed post-marketization) may also impact generalizability of the results. Patient level data were not available for analysis, and therefore data for all endpoints were not always available for each study even if they had been collected. These elements, though possible with any meta-analysis and not specific to our review, should be considered when interpreting the presented results.

An additional limitation noted was the expected difference between the length of follow-up seen in the selected iTNM and SNM studies (weighted average of 13.0 and 39.2 months, respectively). While SNM devices have been available for commercial use in the US for almost 30 years (since 1996), iTNM was first FDA-approved less than 2 years ago (December 2022); accordingly, the average length of follow-up data available for SNM is much longer than iTNM. Importantly however, most device- and procedure-related AEs notably occur within the first several months following implantation for both iTNM and SNM devices. Further comparability between later revisions and/or explant rates will certainly need to be assessed. Clearly, devices designed with implanted batteries—both iTNM and SNM—will require eventual surgical replacement. Both the original implant and surgical revisions result in costs to medical systems and patients; published data comparing cost between iTNM and SNM are not yet available.

Challenges in comparing frequency of urination were also identified in this analysis, primarily because of consistent differences in urinary frequency reported in the studies completed in Asia, which ultimately may describe a more severe population of patients with OAB [55, 56, 62, 70]. While the reason for this difference is unclear, the frequency was reported with range of 10–14.9 in iTNM and SNM studies completed in North America, Europe, and the Middle East, compared with 21.6–29.2 in SNM studies in Asia, resulting in challenges in comparison of results related to urinary frequency. The impact of iTNM on urinary frequency needs to be further explored in future studies.

Lastly, none of the studies identified were head-to-head trials, limiting the ability for direct comparisons. Future RCTs are needed to provide additional clarity about comparative differences in efficacy and safety, and to provide further guidance regarding ideal patient selection for both methods of neuromodulation, tibial versus sacral.

CONCLUSIONS

This meta-analysis of 1766 patients in 20 clinical studies conducted in patients with OAB showed similar clinical benefits of iTNM and SNM for the treatment of OAB, with similar results in the percentage of patients with ≥ 50% reduction in UUI episodes and OAB symptoms, overall reduction in number of UUI episodes, and improvements in QoL measures. Noteworthy, this comparable efficacy is similar without the use of a trial phase of neuromodulation in the iTNM studies versus SNM studies. Current results suggest that iTNM may also have lower surgical re-intervention rates; however, additional follow-up time is needed to confirm if this trend will continue. Both iTNM and SNM have low rates of procedure- and device-related AEs.

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Declarations

Conflict of Interest. Cindy L. Amundsen is a Clinical Trial Investigator and a consultant for BlueWind Medical, and a Patient-Centered Outcomes Research Institute (PCORI) advisory board member. Suzette E. Sutherland is a Clinical Trial Investigator and consultant/advisory board member for BlueWind Medical, Caldera, and FemPulse, and a consultant/advisory board member for Boston Scientific. Stephanie J. Kielb is a consultant for BlueWind Medical. Roger R. Dmochowski is a consultant for BlueWind Medical and Sumitomo. The authors declare that these relationships have not influenced the design or reporting of this meta-analysis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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