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Collaborative Review – Voiding Dysfunction

Efficacy and Safety of Sacral and Percutaneous Tibial Neuromodulation in Non-neurogenic Lower Urinary Tract Dysfunction and Chronic Pelvic Pain: A Systematic Review of the Literature

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Abstract

Context: Neuromodulation is considered in patients with non-neurogenic lower urinary tract dysfunction (LUTD) not responsive to conservative treatment.
Objective: To systematically review the available studies on efficacy and safety of sacral neuromodulation (SNM) and percutaneous tibial nerve stimulation (PTNS) in non-neurogenic LUTDs not responsive to conservative treatments.
Evidence acquisition: A literature research was conducted in PubMed/Medline and Scopus, restricted to articles in English, published between January 1998 and June 2017, with at least 20 patients and 6 mo of follow-up.
Evidence synthesis: Twenty-one reports were identified. Concerning SNM, the improvement of $\geq$50% in leakage episodes ranged widely between 29% and 76%. Overall dry rate ranged between 43% and 56%. Overall success/improvement rate in PTNS varied between 54% and 59%. Symptom improvement or efficacy in interstitial cystitis/bladder pain syndrome patients appeared to be lower compared with other indications in both techniques. Safety data showed fewer side effects in patients submitted to PTNS.
Conclusions: Neuromodulation gives good results and is a safe therapy for patients with overactive bladder or chronic nonobstructive urinary retention with long-lasting efficacy. Moreover, PTNS has been shown to have good success rates and fewer side effects compared with SNM. These data have to be confirmed with long-term follow-up.
Patient summary: Sacral neuromodulation can improve low urinary tract symptoms in selected patients; it appears to be a safe therapy for nonresponders to standard medical therapies. Percutaneous tibial nerve stimulation (PTNS) is a less invasive technique that gives good results in short time with fewer side effects. However, we must consider that PTNS has not been tested in the long term and results are lower if compared with SNM.

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1. Introduction

Sacral neuromodulation (SNM) has been approved by the US food and Drug Administration for overactive bladder (OAB) syndrome (urinary urgency, urinary frequency, nocturia, urgency urinary incontinence [UUI]) and chronic nonobstructive retention (CNoUR) [1–3]. However, the published data on effectiveness of SNM are scarce and contradictory. Moreover, no long-term data from well-designed studies are currently available [4–8].

Its use is indicated, in general, in patients who have failed conservative standard measures. Recent studies indicate that over 50% of individuals with OAB discontinue pharmacotherapy at 12 mo (regardless of the particular agent) due to lack of efficacy or due to intolerable side effects [2–9].

The mechanism of action of SNM is still not totally understood. Practically its function is based on mild electrical stimulation of the sacral nerves that can modulate neural reflexes that influence bladder and pelvic floor behaviour.

Patients who have at least 50% improvement in the main symptoms are considered to be a success and are candidates for implantation of a permanent implantable pulse generator [10].

Percutaneous tibial nerve stimulation (PTNS) is an alternative accepted neuromodulation therapy for non-neurogenic lower urinary tract dysfunction (LUTD) [11]. The believed working mechanism is that this approach can give a neural access to target the sacral plexus from an accessible, minimally invasive entry point into the nervous system via the posterior tibial nerve [12–16]. Both techniques have also shown beneficial effects in interstitial cystitis/bladder pain syndrome (IC/BPS), and the simplicity of the surgical technique and low patient morbidity associated with it make this an attractive option before cystectomy and urinary diversion [4–7].

Previous reviews have already demonstrated great discrepancy in terms of outcomes, symptom assessment, definition of cure/improvement, and range of treatments received before SNM or PTNS. Moreover, severity of symptoms was often not well described [17].

To try to clarify this situation and give the highest evidence available for the performance of neuromodulation in refractory LUTDs, we conducted a systematic review of neuromodulation efficacy and safety outcomes in the context of non-neurogenic LUTD management after a minimum follow-up of 6 mo.

2. Evidence acquisition

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [18,19].

A literature search was conducted on PubMed/Medline and Scopus in June 2017. The search strategy included the following terms: “sacral neuromodulation” AND “tibial neuromodulation” AND “lower urinary tract symptoms” AND “overactive bladder” AND “urinary retention” AND “chronic pelvic pain” AND “painful bladder syndrome”.

For pragmatic reasons, we limited our search to randomised and/or prospective trials and retrospective studies, written in English, with at least 20 human adult patients and 6 mo of follow-up, published between January 1998 and June 2017 (Supplementary material). To be included, the studies had to assess the efficacy and/or safety of the aforementioned techniques and/or predictors of success.

Articles were first screened and selected based on their abstract and then studied in detail. Two independent researchers evaluated the articles and discussed eligibility with one researcher, making the final decision. For every paper, we evaluated the following aspects: study design, baseline patient evaluation, reports of perioperative data, study outcome criteria for efficacy and safety, follow-up, drop-out rate (if applicable), ethics, and results. Efficacy and safety results were reported for each paper and pooled together according to each neuromodulation technique. Results of the systematic review were analysed regarding study methods, ethics, and outcome assessment in the context of currently active clinical research recommendations provided by the fourth International Consultation on Incontinence [20].

3. Evidence synthesis

3.1. Literature search results

The flow diagram is presented in Figure 1. Using the aforementioned research strategy, 2302 studies were identified. After applying the eligibility criteria, a total of 147 papers were assessed for eligibility.

Many studies included patients without preoperative stratification for different types of incontinence. These heterogeneous studies providing potentially confounding results were excluded from our analysis. After a second detailed selection, 21 papers reporting efficacy and/or safety outcome of SNM and PTNS were identified and included. The supplementary material shows the detailed reasons for exclusion of particular studies.

3.2. Risk of bias assessment

For assessing the risk of bias, we evaluated each paper at study and outcome level. At the study level, we evaluated any bias in the selection of patients enrolled, with the lowest risk in prospective randomised clinical trials with adequate methods of randomisation that guarantees concealment of the allocation of patients in each group; we also evaluated the risk of bias linked to the blindness towards the treatment of participants and personnel. At the outcome level, we evaluated any detection bias linked to the blindness of the outcome assessment, the completeness of outcome data or, on the contrary, the possible effect of missing data on the outcome measure, and the bias linked to possible omission of data (Fig. 2).

For nonrandomised studies, we applied the ROBINS-I tool to assess the methodological quality of observational studies [21]. We evaluated the presence of baseline

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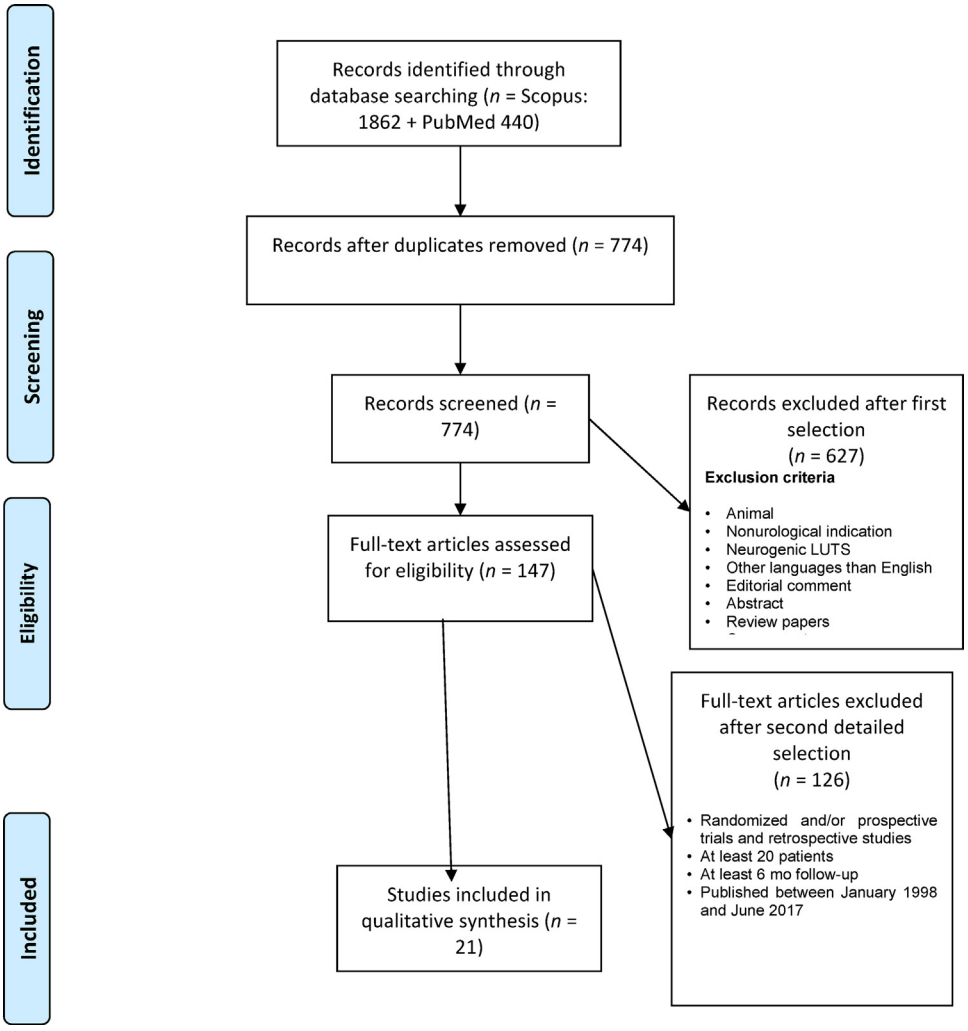

Fig. 1 – PRISMA flow diagram. LUTS = lower urinary tract syndrome; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

confounding factors or selection bias before starting the intervention, presence of any bias in classification of the intervention itself, and presence after the starting of the intervention of bias derived from deviations from the intervention, missing data, modality of measurement of the outcome, and selective reporting of data (Fig. 3).

3.3. *Efficacy data*

3.3.1. *Sacral neuromodulation*

3.3.1.1. Overactive bladder. A total of 9 studies assessing efficacy of SNM on OAB symptoms have been included in our review and included data on about 1181 patients (Table 1). All male or female patients included had urgency, urgency frequency, or urgency incontinence, refractory to standard treatments. Five randomised controlled trials (RCTs) were analysed. All but one presented the results of a comparison of outcome between patients refractory to standard medical therapy (SMT), randomised to SNM versus SMT [2,22–25].

Moreover, two prospective and two retrospective studies with long follow-up fulfilled our inclusion criteria [26–29].

Four RCTs including 298 patients (90% women) reported the results in terms of efficacy of SNM in OAB patients at a mean follow up of 9 mo.

In three studies, the comparison was made between implanted patients and a control group treated with standard therapy. All patients had severe OAB symptoms. The patients of the control group could crossover to SNM after the control phase. The results obtained were comparable with those submitted to immediate SNM. Two studies showed efficacy results in terms of leakage episodes, leakage severity, and pad usage/24 h [22,24]. Improvement of $\geq$50% in leakage episodes ranged widely between 29% and 75%. Overall dry rate (zero pads) ranged between 47% and 56%. Moreover, Weil et al [22] showed that the 85% of patients had $\geq$90% improvement in terms of the number of pads used in 24 h. Both studies also showed statistically significant improvement compared with baseline in terms of leakage severity (all $p < 0.001$). No improvements were shown in the control group. In the RCT by Hassouna and colleagues [23], efficacy was evaluated in terms of voids/day, volume voided, and degree of urgency. A total of 56% of patients in the implant group

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Fig. 2 – Risk of bias assessment in randomised studies.

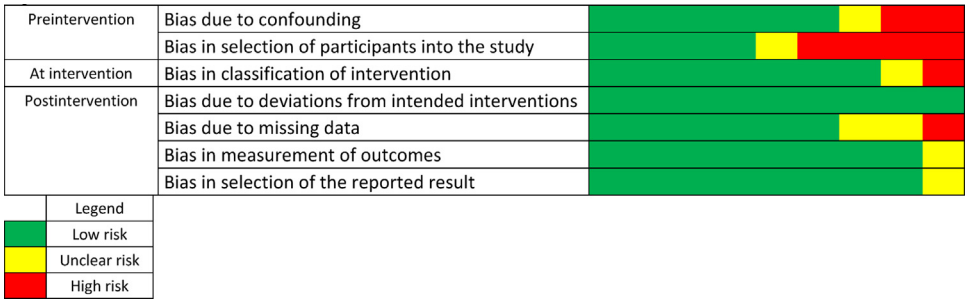

Fig. 3 – Risk of bias assessment in nonrandomised studies.

had a reduction of ≥50% in the number of voids or achieved a normal range (4–7 voiding episodes per day). Moreover, the study group showed significant differences in post-implant voided volumes and degree of urgency compared with the control group (all $p < 0.001$). In all the three studies, a significant rebound was observed to baseline levels when the stimulation was turned off, indicating that improvements strictly depend on active stimulation. All the studies showed sustained efficacy up to 6 mo [22–24].

Siegel and colleagues [2], in the InSite trial, showed OAB success rate (≥50% improvement in either leaks/d or voids/d from baseline, or return to normal frequency) of 76% for SNM and 49% ($p = 0.02$) for SMT. This success rate was to be higher compared with the aforementioned studies, but it has to be underlined that it is probably due to the inclusion of patients with mild to moderate symptoms only.

A fifth RCT, the Refractory Overactive Bladder: Sacral Neuromodulation vs Botulinum Toxin Assessment (ROSETTA) trial, involved 381 women with OAB wet randomised 1:1 to SNM and botulinum toxin injection, and evidenced a greater reduction in the number of urgency incontinence episodes per day in the botulinum toxin group, even if there was a positive effect for SNM also. On the contrary, they showed a greater incidence of urinary tract infections in the botulinum toxin group than in the SNM group. These results, although statistically significant, are of uncertain clinical importance [25].

Siegel and colleagues [26] reported the outcome after 3 yr of follow-up of the InSite trial. This second part of the study was designed as a prospective evaluation of efficacy and safety in the SNM arm with long follow-up, but the enrolment criteria in this phase are less tight. The study included 272 patients, and evidenced a reduction in the daily average number of leaks in OAB wet patients and complete continence in 43% of patients at 3 yr; in OAB dry patients, it evidenced a significant reduction in the number of daily voids and a return to normal voiding patterns in 66% of the patients.

The second prospective study included women with pelvic floor dysfunction. Overall 43 of them presented urinary problems. At a mean follow-up of 6.8 mo, the patients showed significant improvement in OAB scores (Electronic Personnel Assessment Questionnaire-Pelvic Floor [ePAQ-PF]). In particular, the mean ePAQ-PF score was 28.5 (preoperative) versus 20.9 (postoperative). It is of notice that together with urinary function, these women showed significant improvement in all pelvic floor dimensions, namely, bowel, vaginal, and sexual functions, demonstrating that SNM influences not only urinary or bowel function [27].

Failure rates ranged widely between 4% and 34% in the implantation groups. However, they were registered at different time points and in groups with different symptom severity [2,22–27].

Sutherland et al [28] and Peeters et al [29] also reported efficacy in their retrospective studies. Analysis of efficacy was performed on a total of 187 patients with a mean follow-up of 34.5 mo.

Sutherland et al [28] showed significant improvement in all the OAB symptom domains compared with baseline (all $p \leq 0.001$). It is of notice that of all the UUI patients who reported no pad usage, 96% experienced a reduction in pad

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Table 1 – Main characteristics of included studies for efficacy in OAB patients treated with SNM

Study	Design	Participants	Intervention (*n*)	Comparison	Follow-up	Cure/improvement/ success assessment	Cure/improvement/ success rate	*p*
Weil et al (2000) [22]	RCT (multicentre)	43	SNM: immediate implantation = 20	SMT (SNM delayed group) = 22	18 mo (median)	VD (mean leakage ep, leakage severity, pad usage)	IR: Mean leakage ep: 88% Leakage severity: 24% Pad usage: 90% Versus no difference	 <0.005 0.047 <0.005
Hassouna et al (2000) [23]	RCT (multicentre)	51	SNM: immediate implantation = 25	SMT (SNM delayed group) = 26	6 mo	VD (*n* voids/d, VV per void, degree of urgency) UDE → BV	IR: No. of voids/d: 56% vs 4% VV per void: 226 ± 124 vs 123 ± 75 Degree of urgency: 1.6 ± 0.9 vs 2.3 ± 0.5 BV: 227 ± 104 vs 325 ± 185	 <0.0001 <0.0001 0.01 0.008
Schmidt et al (1999) [24]	RCT (multicentre)	76	SNM: immediate implantation = 34	SMT (SNM delayed group) = 42	6 mo	VD (no. of leakage/24 h, leakage severity, No. of pads/ 24 h)	IR: No. of leakage/24 h: 2.6 ± 5.1 vs 11.3 ± 5.9 Leakage severity: 0.3 ± 0.9 vs 3.9 ± 3.8 Leakage severity: 1.1 ± 2.0 vs 6.3 ± 3.6	 All $p < 0.0001$
Siegel et al (2015) [2]	RCT (multicentre)	128	SNM = 51 (received full implant)	SMT = 71	6 mo	VD: >50% improvement in leaks/d or voids/d or return to normal frequency	SR: 61% vs 42% (ITT) and 76% vs 49% (ATA)	 0.02 0.002
Amundsen et al (2016) [25]	RCT (multicentre)	381	SNM 192	Onabotulinum toxin A injection = 194	6 mo	VD: reduction in mean daily episodes of urgency incontinence	Daily episodes of urgency incontinence: −3.25 (−3.64/−2.87) vs −3.89 (−4.26/−3.52)	 0.01
Jadav et al (2013) [27]	Prospective (cohort study)	43	SNM	Comparison with baseline	6.8 mo (median)	ePAQ-PF score (OAB symptoms)	IR: 20.9 ± 19.7 vs 28.5 ± 21.5	<0.05
Siegel et al (2016) [26]	Prospective (multicentre)	272	SNM	Comparison with baseline	3 yr	VD: >50% improvement in average leaks/d or voids/d or return to normal frequency	SR: OAB wet (urgency incontinence) Average leaks/24 h: 2.1 ± 2.3 vs 3.1 ± 2.7 Complete continence: 43% OAB dry (urgency) Voids/day: 4.8 ± 4.1 vs 12.6 ± 4.5 Return to normal voiding pattern: 66%	 <0.0001 <0.0001
Sutherland et al (2007) [28]	Retrospective (single centre)	83	SNM	Comparison with baseline	22 mo (mean)	VD/UDI-6 Mean voids/24 h Mean voids/night Mean leakage/24 h No. of pads/24 h	IR: 8.5 ± 5.0 vs 12.4 ± 5.1 1.6 ± 2.2 vs 2.3 ± 1.8 1.0 ± 1.4 vs 5.0 ± 4.7 0.3 ± 0.7 vs 2.3 ± 2.6	 <0.0001 0.0091 <0.0001 <0.0001
Peeters et al (2014) [29]	Retrospective (single centre)	104	SNM		46.88 mo (mean)	SR: >50%success in at least one voiding diary parameter	SR: 70% for UI and 68% for U/F	–

ATA = as treated analysis; BV = bladder volume; ep = episode; ePAQ-PF: Electronic Personnel Assessment Questionnaire-Pelvic Floor; IR = improvement rate; ITT = intention to treat; RCT = randomised controlled trial; SMT = standard medical therapy; SNM = sacral neuromodulation; SR = success rate; UDE = urodynamic examination; U/F = urinary frequency; UI = urinary incontinence; VD = voiding diaries; VV = voided volume.

usage and of them 50% were completely dry. In addition, in this case, the improvement was sustained on longer follow-up.

Peeters and colleagues [29] showed, in a big cohort of patients with OAB symptoms ($n = 104$), success rates of 70% and 68% in urgency incontinence and urgency frequency syndrome, respectively, at a mean follow-up of 47 mo.

Failure in these two studies was 13% and 64%, respectively. However, in both studies, the failure rate is probably overestimated, because the results were pooled and included also the failure rates of patients with CNoUR [28,29].

3.3.1.2. Interstitial cystitis/bladder pain syndrome. Only one study on IC/BPS fulfilled our inclusion criteria (Table 2). The overall success rate was 43% and the average improvement in the global response assessment scale was 80%. The results are lower in terms of success compared with the previous studies. This is probably due to the retrospective nature of the study. Another reason can be the broad pattern of symptoms characterising this syndrome, which are still not totally understood. The study presents, however, a low level of evidence; therefore, it is not possible to give clinically strong evidence for the treatment of this particular disease with SNM [7].

3.3.1.3. Chronic nonobstructive urinary retention. For the same reason, it is not possible to give definitive indication for the treatment of CNoUR (Table 3). Van Kerrebroeck et al [30] in 2007 showed, in their prospective results comparable with the aforementioned studies, a success rate of 58% in average catheterisation per day and 71% in average catheterised volume per day. The difference with baseline resulted to be statistically significant.

Peeters and colleagues [29] showed, on the contrary, a higher success rate (defined as >50% success in at least one voiding diary parameter) of 73% in idiopathic retention, and cure rates of 62.5% and 53%, respectively, in Fowler's and non-Fowler idiopathic retention.

3.3.2. Percutaneous tibial nerve stimulation

3.3.2.1. Overactive bladder. Efficacy of PTNS in OAB symptoms was studied in a total of four RCTs including 388 patients (Table 4).

One study compared efficacy of PTNS versus tolterodine. The authors showed that 79.5% of PTNS patients reported to be cured or improved compared with 54.8% of the tolterodine group ($p = 0.01$). Objective assessment by investigators was similar in the two groups but not statistically significant. These results showed that PTNS can be a good alternative therapy for OAB [16].

The same authors in a further RCT compared efficacy of PTNS versus sham stimulation. The global response assessment for OAB symptoms showed 54.5% of PTNS patients reporting moderately or marked improvement versus 20.9% in the control group ($p < 0.01$). Voiding diary parameters also showed statistically significantly better results in PTNS patients. However, efficacy in this study was lower compared with the previous one, and these results are

Table 2 – Main characteristics of included studies for efficacy and safety in interstitial cystitis patients treated with SNM

Study	Design	Participants	Intervention (n)	Comparison	Follow-up	Cure assessment	Cure rate	Assessment of improvement or success	Improvement rate	Success rate	p
Gajewski and Al-Zahrani (2011) [7]	Retrospective (long term)	44	SNM	–	61.52 mo (median)	–		GRA Patient's report to the surgeon	GRA: 80% (average improvement)	43%	

Study	Design	Participants	Interventions	Comparison	Timing	Assessment	Pain rate/complications	–	–	p
Gajewski and Al-Zahrani (2011) [7]	Retrospective (long term)	44	SNM	–	61.52 mo (median)	Patient's and surgeon's reports	Explantation rate 28% Four explantations for painful stimulation Revision: 50%			

GRA = global response assessment; SNM = sacral neuromodulation.

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Table 3 – Main characteristics of included studies for efficacy and safety in urinary retention patients treated with SNM

Study	Design	Participants	Intervention (n)	Comparison	Follow-up	Cure assessment	Cure rate	Assessment of improvement or success	Improvement rate	Success rate	p
Van Kerrebroeck et al (2007) [30]	Prospective (long term)	31	SNM	Comparison with baseline	49.3 mo (mean)	–		VD: Average cath./d Average cath. volume/d	1.9 ± 2.8 vs 5.3 ± 2.8 109.2 ± 184.3 vs 379.9 ± 183.8	58% 71%	<0.001 <0.001

Study	Design	Participants	Intervention	Comparison	Timing	Assessment	Pain rate/complications	–	–	–	p
Van Kerrebroeck et al (2007) [30]	Prospective (long term)	31	SNM	–	49.3 mo (mean)	Patient's and surgeon's reports	102 (67%) adverse events 24 patients → device related 97 patients → therapy related				

Cath. = catheterisation; SNM = sacral neuromodulation; VD = voiding diaries.

probably due to the intention-to-treat analysis conducted in the latter study [31].

The results of the RCT by Finazzi-Agrò et al [32] showed the superiority of PTNS compared with placebo ($p < 0.001$). The results of this study confirm that tibial neuromodulation can be considered a valid alternative therapy for detrusor overactivity with 71% of patients considered responders and that the relevance of the placebo effect seems to be negligible in this type of procedure.

On the contrary, the study of Gungor Ugurlucan and colleagues [33] showed a subjective cure rate higher in the group of patients treated with vaginal electrical stimulation compared to PTNS patients. However, improvement was observed in both groups compared with baseline although not statistically significant.

The prospective studies included in this session showed a success rate ranging between 56% and 59%. It has to be underlined that, in these studies also, the definition of success was different. In one of these studies, the authors considered successfully treating a patient who requested chronic therapy, while in the other improvement of ≥50% in incontinence episodes was considered successful [14,15].

3.3.2.2. Interstitial cystitis/bladder pain syndrome. Two studies analysed the efficacy of PTNS in IC/BPS patients (Table 4) [34,35]. One of them showed significant improvement in visual analogue scale and National Institutes of health Chronic Prostatitis Symptom Index scores (40% and 67% of patients, respectively) in PTNS patients compared with the sham group. They showed that PTNS can be an effective treatment to relieve pain in patients with category IIIB prostatitis or chronic pelvic pain [34].

The other RCT study comparing PTNS with traditional therapy in patients with chronic pelvic pain showed that pain decreased significantly in frequency and intensity in women treated with PTNS, and this improvement had a considerable effect on normal daily activities [35].

3.3.2.3. Chronic nonobstructive urinary retention. Only one study, assessing the efficacy of PTNS in nonobstructive retention, was included (Table 4). Of the 39 patients treated, 59% requested continuation of therapy over time and 41% reported significant improvement in voiding diary domain [36].

3.4. Safety

3.4.1. Sacral neuromodulation

No major complications were observed *(Tables 2–6)*.

The most common referred adverse event (AE) was pain at the implant site (range between 15% and 42%). Surgical revision rate ranged between 9% and 33%, and the most common reason was pain at the site of implantation. Implant site infections ranged between 3% and 6.1%. The ROSETTA study evidenced a lower risk of urinary tract infection for SNM (11%) than for botulinum toxin injections (35%) [25].

Peeters et al [29] proved that AEs are much more frequent in patients undergoing reoperation, as in the case

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Table 4 – Main characteristics of included studies for efficacy in PTNS-treated patients

Study	Design	Participants	Intervention (*n*)	Comparison	Follow-up	Cure assessment	Cure rate	Assessment of improvement/ cure/success	Improvement rate/cure	Success rate	*p*
Gungor Ugurlucan et al (2013) [33]	RCT	52	PTNS	ES	12 wk			VD	Mean micturition/d (7.4 ± 2.6 vs 5.8 ± 1.9)		0.03
Kabay et al (2009) [34]	RCT	89 (chronic prostatitis/ chronic pelvic pain)	PTNS pain	Sham	12 wk			VAS NIH-CPSI	Objective response in PTNS patients VAS: 40% NIH-CPSI 66.6%		
Van Balken et al (2001) [15]	Prospective (multicentre)	37	PTNS	–	3 mo	–		Request of chronic therapy		59.4%	
Peters et al (2009) [16]	Prospective, randomised	84	PTNS = 41	Tolterodine = 43	3 mo			GRA VD	79.5% vs 54.8%		0.01
Peters et al (2010) [31]	Double blind, prospective, randomised, multicentre	220	PTNS = 110	Sham = 110	3 mo			GRA (primary end point: moderate or marked improvement in OAB symptoms)	54.5% vs 20.9%		<0.001
Finazzi-Agrò et al (2010) [32]	Double blind, prospective, randomised, multicentre	32	PTNS (*n* = 17)	Placebo (*N* = 15)	After 12 treatments			VD (improvement of 50% or more in incontinence episodes)	71% vs 0%		<0.001
Vandoninck et al (2003) [14]	Prospective (multicentre)	80	PTNS		After treatment			VD (improvement of 50% or more in incontinence episodes)		56%	
Gokyildiz et al (2012) [35]	Prospective	24	PTNS Pain	Traditional pain therapy	12 wk			VAS	2.62 ± 2.70 vs 7.87 ± 0.88		<0.05
Vandoninck et al (2003) [36]	Prospective (multicentre)	39	PTNS (voiding dysfunction)	–	12 wk			Treatment continuation VD	59% 41%		–

ES = electrical stimulation; GRA = global response assessment; NIH-CPSI = National Institutes of health Chronic Prostatitis Symptom Index; OAB = overactive bladder; PTNS = percutaneous tibial neurostimulation; RCT = randomised controlled trial; VAS = visual analogue scale; VD = voiding diaries.

Table 5 – Main characteristics of included studies for safety in OAB patients treated with SNM

Study	Design	Participants	Intervention	Comparison	Timing	Assessment	Pain rate/complications	*p*
Weil et al (2000) [22]	RCT (multicentre)	43	SNM: immediate implantation = 20	SMT (SNM delayed group) = 22	Postop and during 6 mo follow-up	Patient's reports	Pain at implant site: 42%; lead migration: 21%; leg pain: 18% One explant for intractable pain Surgical revision: 9%	
Hassouna et al (2000) [23]	RCT (multicentre)	51	SNM: immediate implantation = 25	SMT (SNM delayed group) = 26	Postop and during 6 mo follow-up	Patient's reports	Pain at implant site: 15%; lead migration: 8.4%; infection: 6.1% Pain at lead site 5,4% Surgical revision: 33%	
Schmidt et al (1999) [24]	RCT (multicentre)	76	SNM: immediate implantation = 34	SMT (SNM delayed group) = 42	Postop and during 6 mo follow-up	Patient's reports	Pain at implant site: 15.9% Pain at lead site 19.1% Infection: 5.7% Lead migration: 7% [a] Surgical revision: 29% [a]	–
Siegel et al (2015) [2]	RCT (multicentre)	128	SNM: 51 received full implant	SMT = 71	Postop and during follow-up	AE assessment	Total significant AEs: 9.8% vs 5.3%	>0.05
Amundsen et al (2016) [25]	RCT (multicentre)	381	SNM 192	Onabotulinum toxin A injection = 194	6 mo follow-up	AE assessment	SNM Revision or removal of device: 3% Onabotulinum toxin A Intermittent self-catheterisation: 8% (1 mo), 4% (3 mo), 2% (6 mo) Risk of urinary tract injections: 11% vs 35%	<0.001
Siegel et al (2016) [26]	Prospective (multicentre)	272	SNM	Comparison with baseline	3 yr	AE assessment	Global device-related AE: 47% Undesirable change in stimulation: 18% Implant site pain: 13% Therapeutic product ineffective: 6% Lead migration: 4% Implant site infection: 4% Surgical intervention rate: 32% Device replacement 20% Device revision 4% Battery replacement: 11% Permanent explants: 13%	
Peters et al (2017) [37]	Observational, longitudinal, prospective data collection	407	SNM requiring reoperation (134)	SNM not requiring reoperation (273)	Mean: 28.9 mo (1.6–121.7 mo)	Predictors for reoperation	Wound infection (6.7% vs 1.1%) Back pain (3.0% vs. 0) Pain in legs (3.7% vs 0.7%) Pain at IPG site (26.9% vs 1.5%) Lead migration (6.7% vs 0%) Lead breakage (9.0% vs 0%) Device malfunction (13.4% vs 0%)	0.003 0.011 0.042 <0.0001 <0.0001 <0.0001 <0.0001
Sutherland et al (2007) [28]	Retrospective (single centre)	104 (included in safety analyses)	SNM	Comparison with baseline	22 mo (mean)	Surgeon's and patient's reports	Total AE: 53% (55 patients)	–
Peeters et al (2014) [29]	Retrospective (single centre)	104	SNM		46.88 mo (mean)	Surgeon's and patient's reports	Two wound hematoma and one wound seroma 26% device explantation [b]	–

AE = adverse events; IPG = implantable pulse generator; OAB = overactive bladder; RCT = randomised controlled trial; SMT = standard medical therapy; SNM = sacral neuromodulation.

[a] Safety data analysis was performed in all the randomised patients (including those not implanted, *n* = 157).

[b] Calculated on a total of 217 patients (including also patients with retention symptoms).

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Table 6 – Main characteristics of included studies for safety in PTNS-treated patients

Study	Design	Participants	intervention	Comparison	Timing	Assessment	Pain rate/complications	*p*
Van Balken et al (2001) [15]	Prospective (multicentre)	37	PTNS		3 mo	Patient's and surgeon's reports	Minor bleeding or temporary pain feeling → rarely	
Peters et al (2009) [16]	Prospective, randomised	84	PTNS	Tolterodine	3 mo	Patient's and surgeon's reports	No major complications	
Peters et al (2010) [31]	Double blind, prospective, randomised, multicentre	220	PTNS = 110	Sham = 110	3 mo	Patient's and surgeon's reports	Six PTNS: ankle bruising, discomfort at the needle site, bleeding, tingling in the leg; no AE in the sham group	
Finazzi-Agrò et al (2010) [32]	Double blind, prospective, randomised, multicentre	32	PTNS (*n* = 17)	Placebo (*N* = 15)	After 12 treatments	Patient's and surgeon's reports	No major complications	
Gokyildiz et al (2012) [35]	Prospective	24	PTNS	SMT	12 wk	Patient's and surgeon's reports	No major complications, slight pain on the leg in two and hematoma in one	
Vandoninck et al (2003) [36]	Prospective (multicentre)	39	PTNS (voiding dysfunction)	–	12 wk	Patient's and surgeon's reports	No major complications, slight transient pain	

AE = adverse events; PTNS = percutaneous tibial nerve stimulation; SMT = standard medical therapy.

of wound infection, back pain, pain in legs, and pain at implant site, and obviously in the case of lead migration, lead breakage, and device malfunction.

Peters et al [37] conducted a study to analyse preoperative predicting factors for reoperation in SNM implanted patients, with higher risks in a longer length of follow-up, in the presence of IC/BPS, in patients undergoing "other pelvic surgery", in female patients under hormone replacement therapy, and when more reprogramming events occur. A lower incidence was present in patients with hypertension, Parkinson disease, and previous stroke.

3.4.2. *Percutaneous tibial nerve stimulation*

No major complications have been shown in any of the aforementioned studies. The only events that have been reported were minor bleedings and temporary pain feeling. No surgery was requested to solve these AEs.

3.5. *Discussion*

The purpose of the present study was to systematically review the evidence for two available neuromodulation systems, namely, SNM and PTNS.

Given that about 50% of the studies included in the review are prospective or retrospective cohort studies (level of evidence 3) [38], which are known to be more prone to biases (lack of control arms, lack of blind randomisation, lack of standardised device setting), we have to conclude that the evidence for neuromodulation in LUTDs remains weak, and it is not possible to give clinical recommendations and guidelines based on the quality of the available studies.

Nevertheless, our results show an effective benefit from neuromodulation for decreasing incontinence episodes, pad use, and voiding frequency, and in improving bladder capacity and voided volume, with an overall success/improvement rate ranging from 61% to 90% for SNM [2,7,22–24,26,28,29] and from 54% to 79% for PTNS [14–16,31–36]. SNM also shows high rates of efficacy in the long term for patients with urgency incontinence, urgency frequency syndrome, and idiopathic retention refractory to conservative treatment [26,29,30]. Moreover, patients with idiopathic retention appear to have a better cure rate than for other types of LUTD [29].

Failure rate and surgical revision rates range from 4% to 64% and from 9% to 33%, respectively, in SNM patients. Reintervention rate is high in long-term follow-up series and tends to be within the first 2 yr postimplantation [26,28,29,37]. It has to be underlined that probably the AE rate is over-rated in the studies included. Patients treated before the introduction of the tined lead (which has been proved to result in less lead migration) have been included in many studies. Moreover, Schmidt and colleagues [24] included in the safety data all the randomised patients and not only the implanted ones, while Peeters and colleagues [29] calculated safety rates of a total of 217 patients (included the CNoUR ones). We can conclude that the overall safety is good but the reintervention rate remains high.

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PTNS has been shown to be less invasive and to be associated with fewer side effects compared with SNM but with higher failure rates (between 40% and 44%) [15,36]. However, the longest follow-up period of the studies on PTNS included in this review is 12 wk, so we consider it important to underline that further studies are needed to confirm the promising results of this procedure, to assess its exact role in these indications and evaluate its long-term efficacy [15,33–36].

3.5.1. Limitations

Although neuromodulation seems to offer promising results in patients refractory to SMT, the present review highlights the numerous limitations of the literature on this topic, underlining a low level of scientific evidence that is apparent in a large proportion of researches.

3.5.1.1. General characteristics of the included studies. The best evidence in this review should come from RCTs, but the majority of them were of low quality. There were biases concerning how patient allocation to treatment groups was done or whether the outcome assessor was blinded to treatment allocation. Moreover, most outcomes were also presented as within-group rather than as between-group comparisons [26,37]. Moreover, due to the intrinsic nature of the RCTs and the type of surgical approach, it was impossible to mask the physician or the patient, as during the procedure the patient has to be aware of the different sensations of SNM. Thus, the authors had to choose a delayed group, but the observation period could not last >6 mo since the control group consisted of patients still complaining of symptoms not responsive to standard treatments [2,22–24]. Only one trial, the ROSETTA study, represented a good-quality multicentre open-label randomised trial. The prospective design and the randomisation systems were adequate, but it was impossible, due to the different nature of the treatments in the two arms, to analyse the effects in a blinded fashion [25].

3.5.1.2. Outcomes. In general, outcome criteria differed for most of the studies. Most studies did not use standardised definition for key outcomes and improvement/cure of urinary symptoms, as well as incontinence rates at follow-up, when displayed, were gauged by patient- and surgeon-reported data. A comprehensive evaluation of both subjective and objective outcomes combined with assessment of satisfaction has not been conducted systematically [2,22–25].

Severity of urinary symptoms is often not well described, and thus the definition of improvement as a >50% decrease in the most disturbing symptom is an arbitrary cut-off, with a clinical importance not always being evident. Moreover, there is often discrepancy in the range of treatments that patients had received before implantation, as neuromodulation is considered a third-line therapy [39]. Therefore, a cautious approach to the aforementioned values is needed due to the same limitations regarding the lack of standardised definitions. A more systematic and up-to-date approach thus appears necessary to improve knowledge about neuromodulation efficacy outcomes. Moreover, an accurate and standardised definition of cure, improvement, or dry rate is mandatory. Beyond pad use assessment and bladder diaries, the use of more objective measurements such as pad tests and validated symptom questionnaires should be promoted.

3.5.2. What do we need?

For the aforementioned reasons, further research should be conducted according to more stringent requirements. Prospective studies are needed for each indication (namely, OAB, IC/BPS, and CNoUR), although large retrospective studies with long follow-up could still be useful as an intermediate step. Incontinence should be stratified as well as aetiologies, severity, and baseline symptoms using validated tools to make data comparable between different studies.

Primary end points should be focused on OAB/retention symptoms, with an accurate preplanned definition of success and appropriate methodology for its assessment, as the majority of the used cut-off is arbitrary.

Terms such as “social continence” and “improvement” should be avoided in order to have a more objective definition of outcomes.

Symptoms response, cure rate, satisfaction, and quality of life should be assessed using validated tools applicable to the vast majority of series.

Complications should be identified using standardised definitions, providing individual patient data and clear descriptive reporting of the “time to complication”. Follow-up should aim to exceed 1 yr for every patient, and long-term results beyond 5 yr of follow-up are highly desirable.

3.5.3. Future perspectives

A critical analysis of results of neuromodulation in specific conditions, such as BPS or nonobstructive retention, with real control individuals, to evaluate its effectiveness in treating such a complex disease should be provided. Moreover, in terms of SNM, new studies and technologies aiming at developing novel MRI-safe or rechargeable devices that do not require surgical replacement of the generator will represent a new era in the treatment and management of LUTDs and related complications in order to reduce reoperation rates.

Last but not least, a better subclassification of patient’s symptoms is needed since LUTDs are the clinical expression of a wide range of physiopathological mechanisms. In particular, patients may share a similar clinical phenotype, but the response to therapy may be different due to a different aetiology of the symptoms. Understanding the aetiology of the symptoms, thus, could represent the principal step to identify the best candidate for neuromodulation.

4. Conclusions

This review shows that SNM gives good results in terms of improvement in OAB symptoms and CNoUR symptoms, and is a safe therapy for nonresponders to SMTs. Moreover, it has been shown to have long-lasting efficacy over time.

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IC/BPS symptoms can also improve with neuromodulation; however, evidence still remains scarce.

PTNS therapy has been shown to have good results with fewer side effects in the short term. However, PTNS has not been tested in the long term. In clinical practice, this technique can be offered to those patients unwilling to undergo or not deemed fit for SNM, or in those cases when SNM is not reimbursed.

Our review of the literature is in line with current guidelines in which SNM can be offered to patients not responsive to standard treatment, with high success rates, before more aggressive surgery. It has to be once again underlined that the majority of studies included are prospective or retrospective cohort studies rending the evidence for neuromodulation in LUTDs weak. These results support the need of long-term follow-up and prospective randomised trials, with adequate numbers and validated questionnaires.

Author contributions: Manuela Tutolo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tutolo, De Ridder, Kessler, Peters, Spinelli, Sievert, Rashid.
Acquisition of data: Tutolo, De Ridder, Kessler, Peters, Spinelli, Sievert, Rashid.
Analysis and interpretation of data: Tutolo, Ammirati.
Drafting of the manuscript: Tutolo, Ammirati.
Critical revision of the manuscript for important intellectual content: Tutolo, De Ridder, Kessler, Peters, Spinelli, Sievert, Rashid.
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Appendix A. Supplementary data

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