

Review – Neuro-urology

Tibial Nerve Stimulation for Treating Neurogenic Lower Urinary Tract Dysfunction: A Systematic Review

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Abstract

Context: Tibial nerve stimulation (TNS) is a promising therapy for non-neurogenic lower urinary tract dysfunction and might also be a valuable option for patients with an underlying neurological disorder.

Objective: We systematically reviewed all available evidence on the efficacy and safety of TNS for treating neurogenic lower urinary tract dysfunction (NLUTD).

Evidence acquisition: The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.

Evidence synthesis: After screening 1943 articles, 16 studies (4 randomized controlled trials [RCTs], 9 prospective cohort studies, 2 retrospective case series, and 1 case report) enrolling 469 patients (283 women and 186 men) were included. Five studies reported on acute TNS and 11 on chronic TNS. In acute and chronic TNS, the mean increase of maximum cystometric capacity ranged from 56 to 132 mL and from 49 to 150 mL, and the mean increase of bladder volume at first detrusor overactivity ranged from 44 to 92 mL and from 93 to 121 mL, respectively. In acute and chronic TNS, the mean decrease of maximum detrusor pressure during the storage phase ranged from 5 to 15 cm H₂O and from 4 to 21 cm H₂O, respectively. In chronic TNS, the mean decrease in number of voids per 24 h, in number of leakages per 24 h, and in postvoid residual ranged from 3 to 7, from 1 to 4, and from 15 to 55 mL, respectively. No TNS-related adverse events have been reported. Risk of bias and confounding was high in most studies.

Conclusions: Although preliminary data of RCTs and non-RCTs suggest TNS might be effective and safe for treating NLUTD, the evidence base is poor, derived from small, mostly noncomparative studies with a high risk of bias and confounding. More reliable data from well-designed RCTs are needed to reach definitive conclusions.

Patient summary: Early data suggest tibial nerve stimulation might be effective and safe for treating neurogenic lower urinary tract dysfunction, but more reliable evidence is required.

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1. Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) is highly prevalent, affects the lives of millions of people worldwide, and imposes a substantial economic burden on health care systems [1,2]. The prevalence of NLUTD may approach 100%, depending on the type and duration of the neurological disorder (eg, in multiple sclerosis [MS]) [3,4]. Quality of life is a major issue, and lower urinary tract function becomes one of the most challenging issues in a patient's life [5]. NLUTD may cause storage and/or voiding symptoms [1]. Although many different treatments are available, the management of NLUTD is challenging, not the least because the standard treatment modalities often have limitations.

Tibial nerve stimulation (TNS), introduced by Stoller in the late 1990s [6], is a promising therapy for nonneurogenic lower urinary tract dysfunction [7]. The tibial nerve is stimulated by an electrode inserted 4–5 cm cephalad to the medial malleolus. The flexion of the big toe or the movement of the other toes as well as a sensory response confirm the correct position of the needle electrode. TNS was found to be effective and safe for treating idiopathic overactive bladder in randomized controlled trials (RCTs) [8–10]. TNS might also be a valuable option in patients with an underlying neurological disorder. We performed a systematic review to assess and appraise the available evidence on the efficacy and safety of TNS for treating NLUTD.

2. Evidence acquisition

2.1. Data sources and searches

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [11]. The protocol for the review is available on PROSPERO (CRD42014008678; <http://www.crd.york.ac.uk/PROSPERO>). We systematically searched Embase, Medline, the Cochrane Central Register of Controlled Trials, and the Health Technology Assessment Database (from January 1, 1946, to January 23, 2015). No language restrictions were applied. We additionally searched the reference list of all included studies and any relevant review articles. Supplement 1 lists the search strategies.

2.2. Study selection

We aimed to include all original studies that reported efficacy and/or safety data on TNS for treating NLUTD including RCTs, comparative non-RCTs, and single-arm cohort studies. Nonoriginal articles, studies not published as full text, those including children only, and those not discriminating between nonneurological and neurological patients were excluded. There was no language restriction. All identified abstracts were imported into a bibliography management software (EndNote X5 [M.P.S.] or X7 [T.G., T.M.K.]; Thomson Reuters, Philadelphia, PA, USA) and sorted according to inclusion and exclusion folders by drag and drop. Abstracts of all identified studies were independently reviewed by two authors (M.P.S. and T.G.). Studies reporting

on TNS (defined as any electrical stimulation of the tibial nerve) for treating NLUTD (defined as any type of lower urinary tract dysfunction caused by a neurological disorder) were reviewed in full text.

2.3. Data extraction and risk of bias assessment

The variables assessed included year of publication, study type, number of patients, gender and age, underlying neurological disorder, duration of neurological disorder, acute (ie, stimulation during urodynamic investigation only) and chronic (ie, daily on weekly stimulation during 6–12 wk before neuro-urological assessment), TNS (percutaneous or transcutaneous, stimulation frequencies, pulse widths, stimulation signs [perception threshold and/or toe plantar flexion] and durations), TNS effects on urodynamic parameters, postvoid residual and bladder diary variables, patient adherence to TNS, and any adverse events. Data from eligible reports were extracted (by treatment group in comparative studies) in duplicate (M.P.S. and T.G.), and discrepancies were resolved by a third reviewer (T.M.K.).

The Cochrane Risk of Bias Assessment tool was used for RCTs [12]. This included the assessment of sequence generation; allocation concealment; blinding of participants, therapists, and outcome assessors; completeness of outcome data; selective outcome reporting; and other potential sources of bias (Supplementary Fig. 1 and 2).

Risk of bias in comparative non-RCTs was assessed using the described Cochrane tool and an extra item to assess the risk of findings being explained by confounding. This is a pragmatic approach informed by methodological literature pertaining to assessing risks of bias in nonrandomised studies [8,13]. A list of the four most important potential confounders for efficacy and safety outcomes was developed with clinical content experts (European Association of Urology [EAU] neuro-urology guidelines panel). For each study, we asked whether each prognostic confounder was considered and whether, if necessary, the confounder was controlled for in analysis. The potential confounding factors are underlying neurological disorder (eg, MS, Parkinson's disease), gender, type of therapy (acute or chronic TNS), and type of stimulation (transcutaneous or percutaneous TNS).

Risk of bias in noncomparative studies cannot be assessed with the approach just described that is designed to assess the internal validity of comparative studies. Therefore, concern was extended in noncomparative studies to address external validity by assessing whether study participants were selected consecutively or were representative of a wider patient population and whether the specified confounding factors were comparable across studies reporting on the same intervention. Attrition bias and selective outcome reporting were also assessed (Supplementary Figs. 1 and 2). This too is a pragmatic approach informed by the methodological literature [12].

2.4. Data synthesis

Effect estimates of TNS were calculated as the difference d between study completion x_1 and baseline x_0 (ie, 6–12 wk

after baseline). For each study the variance at time point x was calculated, using the standard deviation SD_x and group size n , as $VAR = SD_x^2/n$. The correlation coefficient was assumed to be 0.5, a conservative value that leads to the highest variance. Thus the variance of d (VAR_d) was $VAR_{X0} + VAR_{X1} - 2*0.5*\sqrt{(VAR_{X0} * VAR_{X1})}$ and the corresponding $SD_d = \sqrt{n * VAR_d}$. In case of missing SD_x these were imputed taking the largest of reported SD_x . Pooling of data via meta-analysis was planned for RCTs, but it was not possible because outcome measures of the different studies varied widely. In non-RCTs, no data pooling was planned due to different study designs and the expected clinical and methodological heterogeneity of included studies. However, forest plots were generated to provide a visual representation of results to show the direction and magnitude of effects. This was performed using the *metan* command of the Stata v.11.2 software package (StataCorp, College Station, TX, USA).

Risk of bias summary and graph (Supplementary Figs. 1 and 2) was generated using Cochrane RevMan software v.5.3 (Informatics and Knowledge Management Department, Cochrane, London, UK).

3. Evidence synthesis

3.1. Search results

Figure 1 shows the PRISMA flow diagram of the literature search and results. After screening of 1943 abstracts,

16 studies were included in a narrative synthesis [14] (Tables 1–3; Fig. 2A–2F): four RCTs [15–18], nine prospective cohort studies [19–27], two retrospective case series [28,29], and one case report [30].

3.2. Study and patient characteristics

Overall, the 16 included studies enrolled a total of 469 patients: 283 women (60%) and 186 men (40%). Patients had MS ($n = 279$), Parkinson's disease ($n = 92$), cerebrovascular accident ($n = 25$), incomplete spinal cord injury ($n = 16$), or complete spinal cord injury ($n = 2$). There were 8 “others” and 47 not reported. Five studies reported on acute (5 non-RCTs) and 11 on chronic (4 RCTs, 7 non-RCTs) TNS, 4 on transcutaneous (2 RCTs, 2 non-RCTs), and 12 on percutaneous (2 RCTs, 10 non-RCTs) TNS. None of the included studies reported on patient adherence to TNS.

3.3. Efficacy of tibial nerve stimulation

Treatment outcomes of RCTs and non-RCTs are shown in Tables 2 and 3. In acute and chronic TNS, the mean increase of maximum cystometric capacity (Fig. 2A) ranged from 56 to 132 mL and from 49 to 150 mL, respectively. The mean increase of bladder volume at first detrusor overactivity (Fig. 2B) ranged from 44 to 92 mL and from 93 to 121 mL, respectively. In acute and chronic TNS, the mean decrease of maximum detrusor pressure during the storage phase (Fig. 2C) ranged from 5 to 15 cm H₂O and from 4 to 21 cm

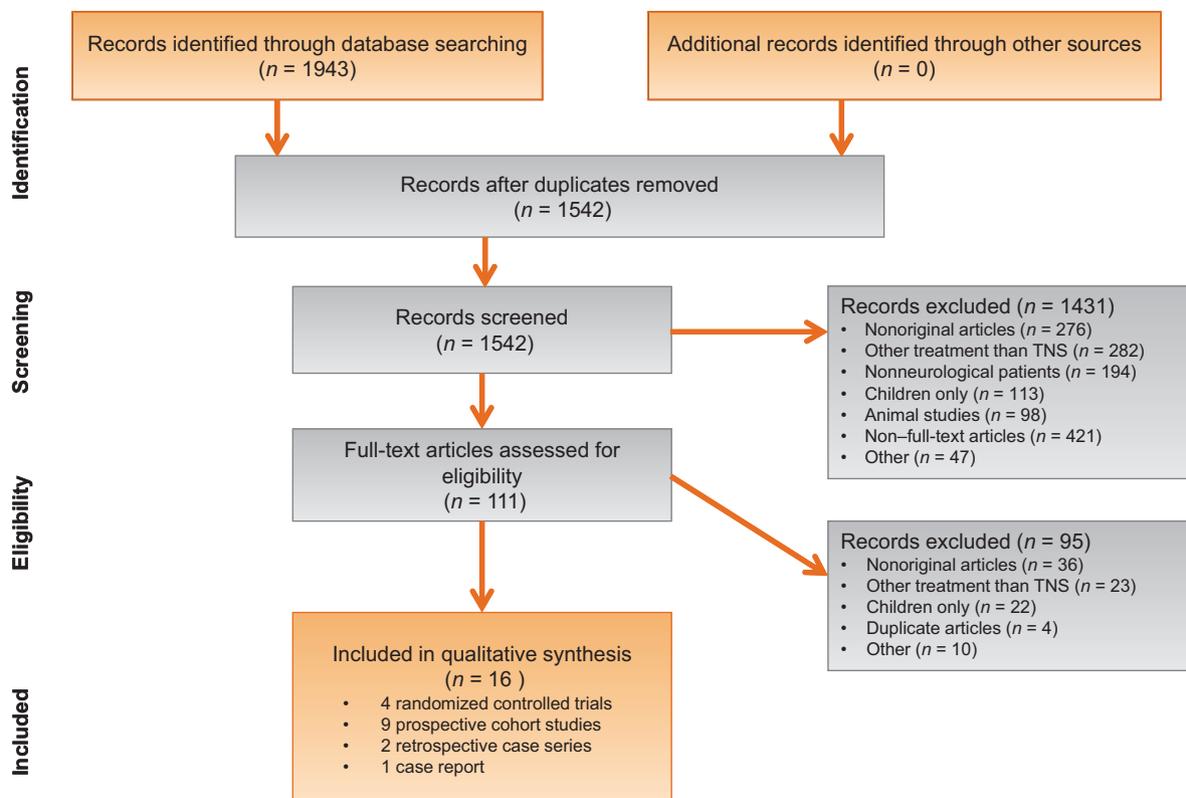


Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. TNS = tibial nerve stimulation.

Table 1 – Characteristics of included studies

Study	Total patients (female/male)	Type of therapy	Type of stimulation and/or treatment	Stimulation frequencies	Pulse width	Stimulation amplitude/pulse current	Stimulation duration	Test duration, d	Mean age, yr	Neurological disorder	Mean duration of neurological disorder, yr	No. of adverse events	Outcomes measured	
RCTs	Eftekhari et al [15]	Con 23 (23/0) Exp 17 (17/0)	Chronic	4 mg tolterodine/d 4 mg tolterodine/d and PTNS	Con NR	Con NR	Con NR	Con 30 min/wk	84 84	50 47	NR NR	NR NR	NPI, NPU	
	Gaspard et al [16]	Con 16 (9/7) Exp 15 (8/7)	Chronic	Pelvic floor muscle training TTNS	Con 10 Hz	Con 220 μ s	Con 1.5 \times toe plantar flexion threshold	Con 30 min/wk	63 63	44 41	MS 16 MS 15	10 8.6	0 0	NUE
	Monteiro et al [17]	Con 12 (0/12) Exp 12 (0/12)	Chronic	Stretching sessions of the lower limbs PTNS	Con 10 Hz	Con 200 μ s	Con Threshold perception	Con 30 min/wk	42 42	56 65	CVA 12 CVA 12	NR NR	0 0	NPI, NPU
	Perissinotto et al [18]	Con 5 (0/5) Exp 8 (0/8)	Chronic	Sham TTNS TTNS	Sham device 10 Hz	Sham device 200 μ s	Sham device 1.5 \times toe plantar flexion threshold	30 min/wk 30 min/wk	35 35	57 64	PD 5 PD 8	2 8.5	NR NR	MCC, N13, NU3, NF3, PVR
Non-RCTs	Amarencio et al [19]	44 (29/15)	Acute	PTNS	10 Hz	200 μ s	NR	<2 h	1	53	MS 13, PD 9, cSCI 15	NR	NR	MCC
	Andrews et al [30]	1 (0/1)	Acute	PTNS	25 Hz	250 μ s	30 mA	<2 h	1	64	cSCI 1	NR	0	MCC
	Fjorback et al [29]	12 (5/7)	Acute	PTNS	20 Hz	200 μ s	1.5 \times toe plantar flexion threshold	<2 h	1	46	MS 12	NR	NR	MDS, BDO
	Kabay et al [24]	32 (13/19)	Acute	PTNS	20 Hz	200 μ s	1.5 \times toe plantar flexion threshold	<2 h	1	64	PD 32	7	NR	MCC, MDS, BDO
	Kabay et al [25]	29 (17/12)	Acute	PTNS	20 Hz	200 μ s	1.5 \times toe plantar flexion threshold	<2 h	1	47	MS 9	9	0	MCC, BDO
	De Sèze et al [20]	70 (51/19)	Chronic	TTNS	10 Hz	200 μ s	Threshold perception	20 min/d	90	48	MS 70	13	0	V24, L24, PVR
	El-Senousy et al [28]	33 (8/25)	Chronic	PTNS	20 Hz	200 μ s	1.5 \times toe plantar flexion threshold	30 min/wk	84	62	PD 33	6	0	MCC, MDS, BDO, V24, L24
	Finazzi-Agrò et al [21]	14 (6/8)	Chronic	PTNS	20 Hz	200 μ s	5 mA	30 min/wk	84	52	MS 4, PD 2, CVA 1, iSCI 2, others 5	2	0	MCC, MDS, BDO, V24, L24
	Gobbi et al [22]	18 (16/2)	Chronic	PTNS	20 Hz	200 μ s	5 mA	30 min/wk	84	46	MS 18	15	0	V24, PVR
	Kabay et al [23]	19 (13/6)	Chronic	PTNS	20 Hz	200 μ s	1.5 \times toe plantar flexion threshold	30 min/wk	84	45	MS 19	8	0	MCC, MDS, BDO, V24, L24, PVR
	Ohannessian et al [27]	6 (6/0)	Chronic	TTNS	10 Hz	200 μ s	Threshold pain	20 min/wk	42	62	PD 3, others 3	NR	0	MCC
	Zecca et al [26]	83 (62/21)	Chronic	PTNS	20 Hz	200 μ s	1 \times toe plantar flexion threshold	30 min/wk	84	49	MS 83	14.4	0	MCC, V24, PVR

Acute = stimulation during urodynamic investigation only; BDO = bladder volume at first detrusor overactivity; Chronic = daily upon weekly stimulation during 6–12 wk before neuro-urological assessment; Con = control intervention; cSCI = complete spinal cord injury; CVA = cerebrovascular accident; Exp = experimental intervention; iSCI = incomplete spinal cord injury; L24 = number of leakages per 24 h; MCC = maximum cystometric capacity; MDS = maximum detrusor pressure during storage phase; MS = multiple sclerosis; NF3 = number of frequency episodes over 3-d period; N13 = number of incontinence episodes over 3-d period; NPI = number of patients with incontinence; NPU = number of patients with urgency; NR = not reported; NU3 = number of urgency episodes over 3-d period; NUE = number of urgency frequency episodes; PD = Parkinson's disease; PTNS = percutaneous tibial nerve stimulation; PVR = postvoid residual; RCTs = randomized controlled trials; TTNS = transcutaneous tibial nerve stimulation; V24 = number of voids per 24 h.

Table 2 – Treatment outcomes of randomized controlled studies

Study	Intervention	Patients, n	Maximum cystometric capacity, mL				Patients with incontinence, n				No. of urgency frequency episodes				Patients with urgency, n				Postvoid residual, mL			
			BL	UT	Difference	p value	BL	UT	Difference	p value	BL	UT	Difference	p value	BL	UT	Difference	p value	BL	UT	Difference	p value
Eftekhar et al [15]	Con	23					14	14	0	NR					NR	16	NR	NR				
	Exp	17					18	18	0						21	21	0					
Gaspard et al [16]	PFT	16									3.5	1.2	2.3	0.006								
	Exp	15									3	0.7	2.3	0.031								
Monteiro et al [17]	Con	12					10	10	0	NS					9	9	0	NS				
	Exp	12					11	7	4	<0.01					11	8	3	<0.01				
Perissinotto et al [18]	Con	5	215	220	5	0.86	3 ^a	3 ^a	0 ^a	^a NR	5 [*] /5 ^{**}	5 [*] /5 ^{**}	0 [*] /0 ^{**}	<0.04 [*] / ^{**} NR					43	61	18	0.46
	Exp	8	260	235	-25		6 ^a	4 ^a	2 ^a		8 [*] /6 ^{**}	1 [*] /2 ^{**}	-7 [*] /-4 ^{**}						73	37	-36	

BL = baseline; Con = control intervention; Exp = experimental intervention; NR = not reported; NS = not significant; PFT = pelvic floor muscle training; UT = under treatment.
 All reported values are means. P values show group comparison at the same timepoint.
^a Number of incontinence episodes over a 3-d period.
^{*} Number of urgency episodes over a 3-d period.
^{**} Number of frequency episodes over a 3-d period.

Table 3 – Treatment outcomes of nonrandomized controlled studies

Study	No. of patients/Type of therapy	Maximum cystometric capacity, mL				Maximum detrusor pressure during storage phase, cm H ₂ O				Bladder volume at first detrusor overactivity, mL				No. of voids per 24 h				No. of leakages per 24 h				Postvoid residual, mL			
		BL	UT	Difference	p value	BL	UT	Difference	p value	BL	UT	Difference	p value	BL	UT	Difference	p value	BL	UT	Difference	p value	BL	UT	Difference	p value
Amarenco et al [19]	44/acu	221	277	56	<0.0001					163	232	69	<0.0001												
Andrews et al [30]	1/acu	158	290	132	NR																				
Fjorback et al [29]	12/acu					85	80	-5	0.48	122	166	44	0.008												
Kabay et al [24]	32/acu	205	301	96	0.001	52	36	-15.3	0.002	145	245	100	0.001												
Kabay et al [25]	29/acu	194	286	93	<0.001					138	230	92	<0.001												
De Sèze et al [20]	7/chr													11.3	8.6	-2.7	<0.001	5.8	2.8	-3	<0.001	133	117	-16	NS
El-Senousy et al [28]	33/chr	233	329	96	0.0001	32	28	-3.9	0.03	150	271	121	0.0001	10.6	7.9	-2.7	0.001	3.5	2.2	-1.3	0.04				
Finazzi-Agrò et al [21]	14/chr	230	380	150	<0.01	64	43	-21	0.07	212	321	109	<0.01	15	8	-7	<0.01	6	2	-4	<0.01				
Gobbi et al [22]	18/chr													12	7	-5	<0.05					98	43	-55	0.02
Kabay et al [23]	19/chr	200	267	67	0.000	49	36	-13	0.001	124	216	93	0.000	11.5	5.6	-5.9	NR	7.2	4.1	-3.1	NR	83	48	-35	0.006
Ohannessian et al [27]	6/chr	211	260	49	0.6																				
Zecca et al [26]	83/chr	171	268	97	0.003									10	7	-3	0.03					101	52	-49	0.02

acu = acute therapy; BL = baseline; chr = chronic therapy; NR = not reported; NS = not significant; UT = under treatment.
 All reported values are means.

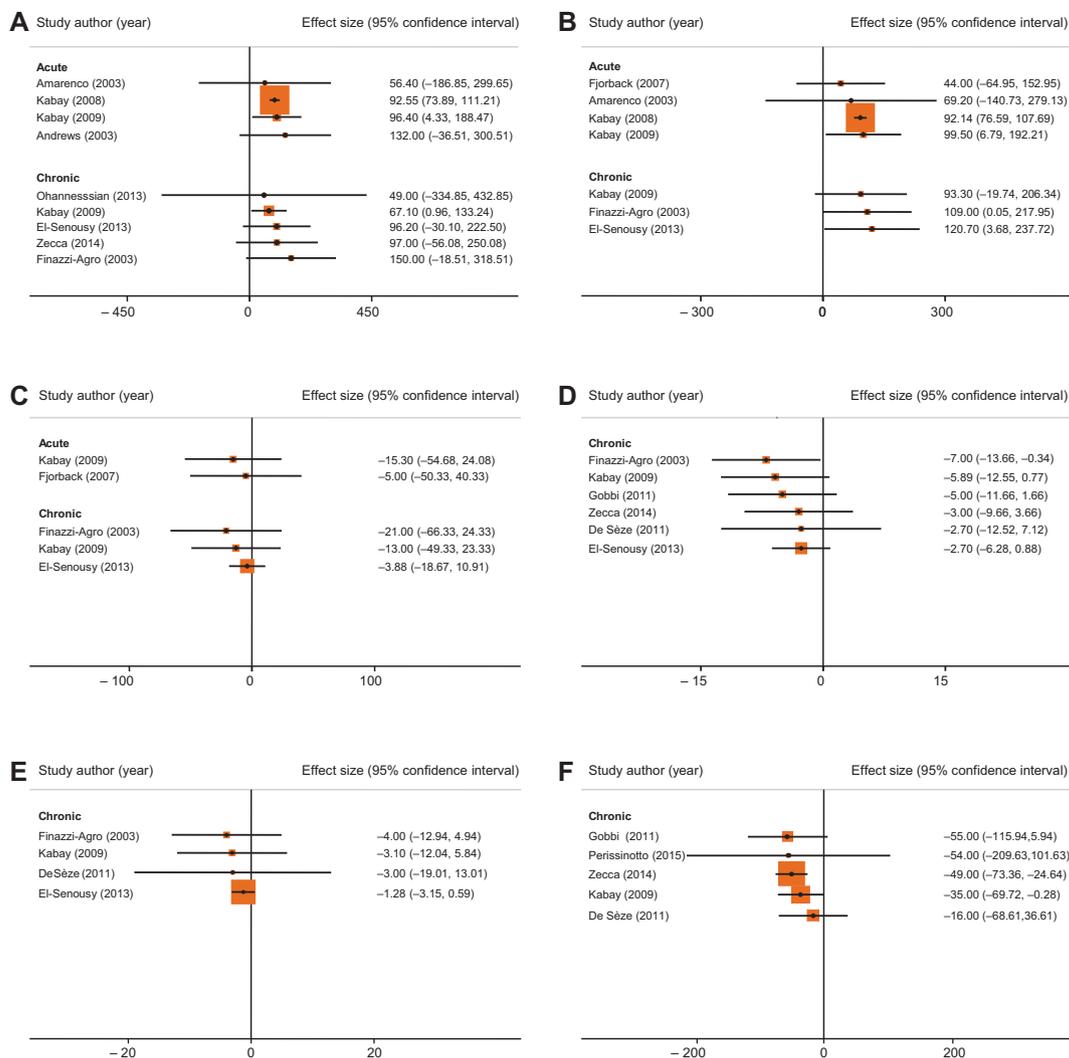


Fig. 2 – (A) Effects of tibial nerve stimulation on maximum cystometric capacity in milliliters; (B) bladder volume at first detrusor overactivity in milliliters; (C) maximum detrusor pressure during storage phase in centimeters of H₂O; (D) number of voids per 24 h; (E) number of leakages per 24 h; (F) postvoid residual in milliliters. Mean values with 95% confidence intervals. Positive values indicate an increase; negative values indicate a decrease.

H₂O, respectively. In chronic TNS, the mean decrease in number of voids per 24 h (Fig. 2D), in number of leakages per 24 h (Fig. 2E), and in postvoid residual in milliliters (Fig. 2F) ranged from 3 to 7, from 1 to 4, and from 16 to 55, respectively.

3.4. Safety of tibial nerve stimulation

No TNS-related adverse events have been reported.

3.5. Risk of bias and confounding

The risk of bias and confounding was relevant in both RCTs and non-RCTs. In particular, a high risk of selective outcome reporting bias was found (Supplementary Fig. 1 and 2).

3.6. Discussion

3.6.1. Principal findings

Improvement in urodynamic parameters (maximum cystometric capacity, bladder volume at first detrusor overactivity,

maximum detrusor pressure during storage phase), postvoid residual, and bladder diary variables (number of voids per 24 h, number of leakages per 24 h), as well as no stimulation-related adverse events indicate that TNS might be effective and safe for treating NLUTD. Although our findings are promising, the imprecision of the evidence appears to be high, with most of the studies small and hence underpowered to measure the main outcomes and to allow for subgroup analyses (eg, different neurological disorders, transcutaneous versus percutaneous TNS, stimulation parameters and duration), with significant risk of bias and confounding.

3.6.2. Findings in the context of existing evidence

In animal studies, detrusor overactivity could be suppressed by TNS [31,32]. In humans, TNS has also become a very promising noninvasive (transcutaneous TNS) or minimally invasive (percutaneous TNS) therapeutic option for refractory lower urinary tract dysfunction. Percutaneous TNS was found to be effective in 37–100% of patients with idiopathic overactive bladder, in 41–100% of those with nonobstructive

urinary retention, and in upon 100% of patients with chronic pelvic pain syndrome, children with overactive bladder or dysfunctional voiding, and in patients with NLUTD [7]. In addition, TNS might improve fecal incontinence [33], highlighting the potential in the neurological patient often with both lower urinary tract and bowel dysfunction, although there is no high level of evidence study assessing the combined dysfunction.

The exact mechanisms of action of neuromodulation procedures remain to be elucidated, but modulation of spinal cord reflexes and brain networks by peripheral afferents seems to be involved [34]. Plastic reorganization of cortical networks triggered by peripheral neuromodulation has been proposed [35]. In a positron emission tomography study of patients treated by sacral neuromodulation for urgency incontinence [36], the authors suggested that acute neuromodulation predominantly involves areas associated with sensorimotor learning that might become progressively less active during the course of chronic neuromodulation. In addition, the sympathetic nervous system might play a role, as indicated by studies of low-frequency pudendal nerve stimulation in cats with chronic spinal cord injury [37]. However, no literature is available about the mechanisms of action of TNS for treating NLUTD.

3.6.3. Implications for research

Considering the promising findings of our systematic review, further investigations are highly warranted. Appropriately designed RCTs are necessary to assess validated disease- and condition-specific quality of life data, urodynamic findings, short-, medium-, and long-term results, as well as cost-effectiveness issues. It would also be of great interest to directly compare transcutaneous and percutaneous TNS, especially considering that transcutaneous in contrast to percutaneous TNS can be easily used at home by the patient, which might represent a real advantage from both the patient's and the physician's perspective, saving time and resources. Importantly, stimulation parameters and duration varied widely between the different studies. This is because as yet there are no treatment standards for TNS and no guidelines for therapeutic and maintenance regimens. These must be developed through further research and testing. Although currently available TNS devices would allow a wide range of different stimulation settings, the parameters were usually not changed, but individual adjustment of the stimulation parameters by analogy with sacral neuromodulation might improve the response rate and warrants additional studies.

3.6.4. Implications for practice

The type and the inherent course of the neurological disorder highly influences lower urinary tract dysfunction and consequently the effect of a therapy [1,2]. Thus TNS might be initially successful in a patient with MS but become ineffective in the case of disease progression. In addition, early TNS during the spinal shock in patients with acute spinal cord injury might prevent detrusor overactivity and urinary incontinence as proposed for sacral neuromodulation [38]. Importantly, the treatment goal of TNS varies

between the different neurological disorders ranging from improving quality of life to protecting renal function by converting a high-pressure into a low-pressure system. This emphasizes the imperative for future TNS studies to investigate disease-specific stimulation effects.

The benefits of TNS are its noninvasiveness or minimally invasiveness allowing the performance of diagnostic measures such as repeated magnetic resonance imaging, additional positive effects on bowel dysfunction, easy application, and excellent safety profile, so that TNS might become a valuable treatment option for patients with NLUTD before more invasive methods are considered.

3.6.5. Limitations of this study

Although this report represents the first systematic review that aims to identify, assess, and appraise the available evidence of TNS for treating patients with NLUTD, certain limitations should be addressed. Methodology and data provided in the included articles varied widely. Almost every study had a before-and-after treatment design. SDs for baseline and follow-up measurements were missing in about a third of studies and had to be imputed. To calculate the SDs of mean differences would have required an estimate of the covariance. This was not reported, and we thus assumed it to be 0.5. Therefore, we would like to issue a note of caution when interpreting the summary figures reported. However, because our primary goal was providing a description of the evidence, we consider our approach to be acceptable. The included studies reported either on acute or on chronic TNS but not on both, and several clinically important outcome parameters were not consistently assessed such as subjective versus objective stimulation effects, duration of TNS effects, and patient adherence to TNS. The number of investigated patients and the follow-up was very limited. Moreover, although we identified four RCTs, they have a high risk of bias, are underpowered, and are generally imprecise. Finally, between-study heterogeneity was substantial, and scarcity of data did not allow for formal subgroup analyses of different neurological disorders, transcutaneous versus percutaneous TNS, stimulation parameters, and duration.

4. Conclusions

Some preliminary evidence indicates that TNS is effective and safe for treating patients with NLUTD. However, the overall quality of the evidence was low. Most of the studies were small and hence underpowered to measure the main outcomes with a significant risk of bias and confounding. In addition, it is unclear which stimulation parameters and maintenance regime are most effective. This review, although suggesting that TNS appears to be a promising and novel treatment for NLUTD, has demonstrated the need for more reliable data from well-designed, adequately sampled, and powered RCTs to reach definitive conclusions.

Author contributions: Thomas M. Kessler 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: Schneider, Gross, Kessler.

Acquisition of data: Schneider, Gross, Kessler.

Analysis and interpretation of data: Schneider, Gross, Bachmann, Kessler.

Drafting of the manuscript: Schneider, Gross, Kessler.

Critical revision of the manuscript for important intellectual content: Bachmann, Blok, Castro-Díaz, Del Popolo, Groen, Hamid, Karsenty, Pannek, 't Hoen.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2015.07.001>.

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