

# Treatment for overactive bladder

## A meta-analysis of transcutaneous tibial nerve stimulation versus percutaneous tibial nerve stimulation

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### Abstract

**Background:** We aim to compare the safety and effectiveness of transcutaneous tibial nerve stimulation (TTNS) versus percutaneous tibial nerve stimulation (PTNS) in treating overactive bladder.

**Methods:** A systematic search on PubMed, Embase, clinicalTrials.gov, and Cochrane Library Central Register of Controlled Trials from January 1, 1999 to November 1, 2020 was performed. The primary outcomes were the changes in a 3-day voiding diary. Quality of life scores were also evaluated. Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) was applied to conduct all statistical analyses.

**Results:** A total of 4 trials (2 randomized controlled trials, 1 retrospective study, and 1 before-after study) with 142 patients were eventually enrolled. Compared with PTNS, TTNS had a similar performance in the voiding frequency in 24 hours (mean difference [MD] = -0.65, 95% confidence interval [CI]: -1.35 to 0.05,  $P = .07$ ), the number of urgency episodes in 24 hours (MD = 0.13, 95% CI: -0.36 to 0.62,  $P = .60$ ), the number of incontinence episodes in 24 hours (MD = 0.01, 95% CI: -0.13 to 0.14,  $P = .93$ ), as well as in the nocturia frequency (MD = -0.14, 95% CI: -0.52 to 0.24,  $P = .47$ ). Moreover, comparable results were observed regarding HRQL scores ( $P = .23$ ) and incontinence quality of life scores ( $P = .10$ ) in both groups. The total complication rate in the current study was 2.1% (3/142). No adverse events were identified in the TTNS group.

**Conclusion:** Current data supported that TTNS is as effective as PTNS for the treatment of overactive bladder, moreover, with no reported adverse events. However, the evidence is low-grade and well-designed prospective studies with a large sample size are warranted to verify our findings.

**Abbreviations:** AEs = adverse events, I-QoL = incontinence quality of life questionnaire, OAB = overactive bladder, PTNS = percutaneous tibial nerve stimulation, TTNS = transcutaneous tibial nerve stimulation.

**Keywords:** overactive bladder, percutaneous tibial nerve stimulation, transcutaneous tibial nerve stimulation

### 1. Introduction

Overactive bladder syndrome (OAB) is defined as “urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with urinary incontinence (OAB-wet) or without (OAB-dry), in the absence of urinary tract infection or other

detectable disease” by the International Continence Society.<sup>[1]</sup> According to previous studies, the prevalence of OAB is around 17%, and that increases with age.<sup>[2]</sup> Although not life-limiting OAB is nevertheless life-altering and may have profound impact on a person’s quality of life, sexual function, ability to participate, and overall wellbeing.<sup>[3–6]</sup> Following behavioral and pelvic floor therapies, antimuscarinic agents are the mainstay of treatment. However, limited effectiveness, side effects, and high costs appear to restrict the adherence to this therapy, and ultimately limit its benefit for a broader group of patients with OAB.<sup>[2,7,8]</sup>

Over the past decade, posterior tibial nerve stimulation (TNS) has become a well-accepted third-line therapeutic option in patients with OAB.<sup>[9–12]</sup> The stimulation could be delivered to the posterior tibial nerve (PTN) through 2 distinct routes: using a surface electrode (transcutaneous tibial nerve stimulation [TTNS])<sup>[13]</sup> or using a gauge needle (percutaneous tibial nerve stimulation [PTNS]).<sup>[14]</sup> Although PTNS has proven to be effective and acceptable,<sup>[15–17]</sup> the alternative with transcutaneous stimulation may be more comfortable and feasible. Thus, we aim to include related studies to compare the safety and effectiveness of TTNS versus PTNS in treating OAB.

### 2. Materials and methods

#### 2.1. Identification of studies

The current review was performed in line with the preferred reporting items for systematic reviews and meta-analyses guide-

Editor: Vito Mancini.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are publicly available.

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How to cite this article: Yang DY, Zhao LN, Qiu MX. Treatment for overactive bladder: a meta-analysis of transcutaneous tibial nerve stimulation versus percutaneous tibial nerve stimulation. *Medicine* 2021;100:20(e25941).

Received: 3 January 2021 / Received in final form: 21 April 2021 / Accepted: 25 April 2021

<http://dx.doi.org/10.1097/MD.00000000000025941>

lines.<sup>[18]</sup> The current work did not need an ethic approval because the data were extracted directly from open-sourced studies instead of proprietary domains. A systematic search on PubMed, Embase, clinicalTrial.gov, and Cochrane Library Central Register of Controlled Trials for articles that compared TTNS with PTNS for OAB from January 1, 1999 to November 1, 2020 was performed. The search strategy was formulated according to the Participant, Intervention, Comparison, Outcome, and Study framework. We combined free entry terms and medical subject headings (MeSH) terms in our search equation for PubMed, and the equation was adapted for each database. The following strategy was used to conduct the searches: (((((((((PTNS) OR Percutaneous Tibial Nerve Stimulation) OR ((TTNS) OR Transcutaneous Tibial Nerve Stimulation) OR Tibial Nerve Stimulation) OR SANS) OR Stoller Afferent Nerve Stimulation)) AND (((((((("Urinary Bladder, Overactive"[Mesh]) OR Overactive Bladder) OR Overactive Urinary Bladder) OR Bladder, Overactive) OR Overactive Detrusor) OR Detrusor, Overactive) OR Overactive Detrusor Function) OR Detrusor Function, Overactive))). We also searched the reference list of all reviews and included studies manually to look for potentially eligible articles.

## 2.2. Inclusion criteria and exclusion criteria

Studies meeting the following eligibility criteria were included in this review. The Participant, Intervention, Comparison, Outcome, and Study principle included the following parts:

- (1) participants: patients suffering from OAB symptoms;
- (2) interventions: TTNS or PTNS;
- (3) comparisons: endpoints regarding efficacy and safety profile after 2 different interventions;
- (4) outcome: 3-day voiding diary (voiding frequency per day, daytime micturition frequency per day, nocturia episodes, the number of urgency episodes per day, the number of incontinence episodes per day, and mean voiding volume), urodynamic results (Qmax, Pdetmax, PdetQmax, and maximum cystometric capacity), response rates or side effects;
- (5) study: comparative studies (randomized controlled trial [RCT], retrospective study, and before-after study) with at least 1 evaluation parameter were accepted.

Articles should be excluded if

- (1) patients underwent other third-line treatments such as sacral nerve stimulation or botulinum toxin injection;
- (2) only 1 type of TNS was utilized;
- (3) a study design of case report, meeting, abstract, or review.
- (4) Besides, noncomparative trials or studies reported insufficient data were also excluded. However, there was no limitation regarding language and article status.

## 2.3. Study selection and data extraction

From the records identified by the database search, the abstracts were selected and reviewed by 2 independent investigators (D-Y Y and L-N Z) according to inclusion and exclusion criteria.

The following data items were collected from each study that was eligible for a meta-analysis: study type, the number of participants in the 2 groups, age of patients, duration of follow up, treatment protocol, the changes of OAB symptoms, and adverse events (AEs). Two authors initially selected articles

eligible and extracted the data needed, then the corresponding author doubled checked results. Disagreements were resolved by a discussion in group.

## 2.4. Outcomes

The primary outcomes including the voiding frequency in 24 hours, the number of urgency episodes in 24 hours, the number of incontinence episodes in 24 hours, and the night time micturition frequency were used to assess the effectiveness of 2 kinds of TNS. The secondary outcomes included health-related quality of life scale (HRQL), incontinence quality of life (I-QoL) questionnaire, and TNS-related complications (bleeding at the needle site and discomfort/pain over the needed area).

## 2.5. Quality assessment

The risk of bias (ROB) across RCTs was evaluated according to the Cochrane handbook.<sup>[19]</sup> ROB domains were judged as low, high, or unclear risk. Quality assessment of observational studies was performed using Newcastle–Ottawa scale.<sup>[20]</sup> The Newcastle–Ottawa scale employed the semi-quantitative principles of the star system to carry out the quality assessment and the highest attainable score was capped to 9 stars.

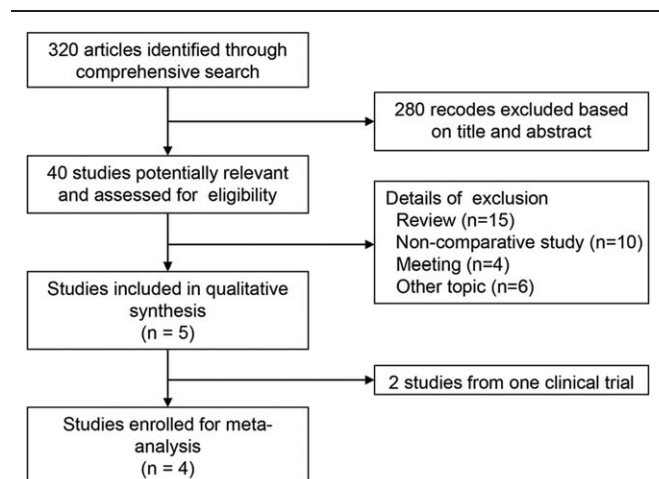
## 2.6. Data analysis

Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) was applied to conduct all statistical analyses. Odds ratios (ORs) and mean differences (MDs) with 95% confidence interval (CI) were calculated for dichotomous and continuous outcomes, respectively. Heterogeneity was evaluated by  $I^2$  test. The fixed-effect model was used in the absence of heterogeneity ( $I^2$  values < 50%), and random-effect method was used with  $I^2$  values  $\geq$  50%. Publication bias of primary outcomes was evaluated by funnel plot.

## 3. Results

### 3.1. Study characteristics

As shown in Figure 1, a total of 320 articles were identified initially through the systematic databases search. Two hundred



**Figure 1.** PRISMA flowchart of study selection. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

**Table 1**  
**Characteristics of included studies.**

Study (year)	Design	Duration (year)	Group	N (women/men)	Age (years)	Treatment protocol	Stimulation parameters	Follow-up
Ramírez-García (2019)	RCT	2015–2016	TTNS	21/13	62.4 ± 16	30 min/wk	20 Hz and 200 cycles	12 wk
			PTNS	25/9	56.8 ± 16	30 min/wk	20 Hz and 200 cycles	12 wk
Martin-García (2019)	RCT	2015–2016	TTNS	12/0	54 ± 12	≥30 min × 3/wk	20 Hz and 200 cycles	6 mo
			PTNS	12/0	58 ± 10	30 min/4 wk	20 Hz and 200 cycles	6 mo
Alfonso Barrera (2013)	R	2011–2012	TTNS	21/0	–	30 min/wk	20 Hz and 200 cycles	12 wk
			PTNS	13/0	–	30 min/wk	20 Hz and 200 cycles	12 wk
Maurelli (2012)	Before and after	–	TTNS	13/3	–	30 min/wk	20 Hz and 200 cycles	19.7 mo
			PTNS	13/3	–	30 min/wk	20 Hz and 200 cycles	–

PTNS = percutaneous tibial nerve stimulation, R = retrospective, RCT = randomized controlled trial, TTNS = transcutaneous tibial nerve stimulation.

eighty records were excluded based on previous defined inclusion and exclusion criteria. After removal of unavailable and noncomparative studies, 5 articles were selected in qualitative synthesis.<sup>[21–25]</sup> Notably, we observed that 2 studies<sup>[21,22]</sup> were established based on the same one clinical trial. Thus, only 1 study with adequate and available data were selected.<sup>[22]</sup> Eventually, a total of 4 trials (2 RCTs, 1 retrospective study, and 1 before-after study)<sup>[22–25]</sup> with 142 patients were enrolled. Table 1 shows the characteristics of each study included. The treatment protocols were shown in Table 2. It was noted that 30 min/wk with a stimulation parameter of 20 Hz and 200 cycles/s was applied in 3 studies.<sup>[22,24,25]</sup> Notably, the study by Maurelli et al<sup>[25]</sup> was a before-after study in which TTNS was used as a maintenance treatment after PTNS. Since the 2 interventions were carried out in the 2 independent phases with available data, it was eventually selected.

Regarding quality assessment of the included studies, ROB domains were judged as low risk in 2 RCTs<sup>[22,23]</sup> (Figure S1, Supplemental Digital Content, <http://links.lww.com/MD/G135>).

Quality assessment for non-RCTs<sup>[24,25]</sup> showed that all studies were ranked as high quality (Table S1, Supplemental Digital Content, <http://links.lww.com/MD/G136>).

### 3.2. Evaluation of effectiveness

For primary outcomes, 3 studies<sup>[22–24]</sup> reported the data on the voiding frequency, 3 studies<sup>[22,23,25]</sup> presented the data on the urgency episodes and incontinence episodes, and other 3 studies<sup>[22,24,25]</sup> contained the data on the night time micturition frequency. Polled results revealed that there were no statistical differences in voiding frequency in 24 hours (MD = -0.65, 95% CI: -1.35 to 0.05, *P* = .07), the number of urgency episodes in 24 hours (MD = 0.13, 95% CI: -0.36 to 0.62, *P* = .60), the number of incontinence episodes in 24 hours (MD = 0.01, 95% CI: -0.13 to 0.14, *P* = .93), as well as in the night time micturition frequency (MD = -0.14, 95% CI: -0.52 to 0.24, *P* = .47) (Fig. 2) in the 2 groups. No publication bias was identified regarding these primary outcomes (Fig. 3).

**Table 2**  
**The treatment protocol of nerve stimulation in each study.**

Study (year)	Group	Treatment protocol	Stimulation parameters	Electrode size	Location of electrode	Stimulator	Current range
Ramírez-García (2019)	TTNS	30 min/wk, for 12 wk	Biphasic square waves, 20 Hz and 200 cycles	32 mm	5 cm above the medial malleolus	TENS URO stim2	0.5–20 mA
	PTNS	30 min/wk, for 12 wk	Biphasic square waves, 20 Hz and 200 cycles	40 mm × 0.20 mm acupuncture needles (34 gauge)	Percutaneous insertion of a needle 5 cm above the medial malleolus	TENS URO stim2	0.5–20 mA
Martin-García (2019)	TTNS	≥30 min × 3/wk, for 6 mo	20 Hz and 200 cycles	30 mm	Three finger-breaths cranial to the medial malleolus	NeuroTrac Pelvitone	0–20 mA
	PTNS	30 min/4 wk, for 6 mo	20 Hz and 200 cycles	40 mm × 0.20 mm acupuncture needles (34 gauge)	Three finger-breaths cranial to the medial malleolus	AS SUPER 4 digital	0–20 mA
Alfonso Barrera (2013)	TTNS	30 min/wk, for 12 wk	20 Hz and 200 cycles	–	3 to 4 cm above the medial malleolus	Stimulator NeuroTrac	0–10 mA
	PTNS	30 min/wk, for 12 wk	20 Hz and 200 cycles	34-gauge needle	Percutaneous insertion of a needle 3–4 cm above the medial malleolus	Stimulator Urgent	0–10 mA
Maurelli (2012)	TTNS	30 min/wk, for average 19.7 mo	20 Hz and 200 cycles	–	5 cm above the medial malleolus	LogiSTIM	0–10 mA
	PTNS	30 min/wk	20 Hz and 200 cycles	40 mm × 0.20 mm acupuncture needles (34 gauge)	Percutaneous insertion of a needle 5 cm above the medial malleolus	LogiSTIM	0–10 mA

PTNS = percutaneous tibial nerve stimulation, TTNS = transcutaneous tibial nerve stimulation.

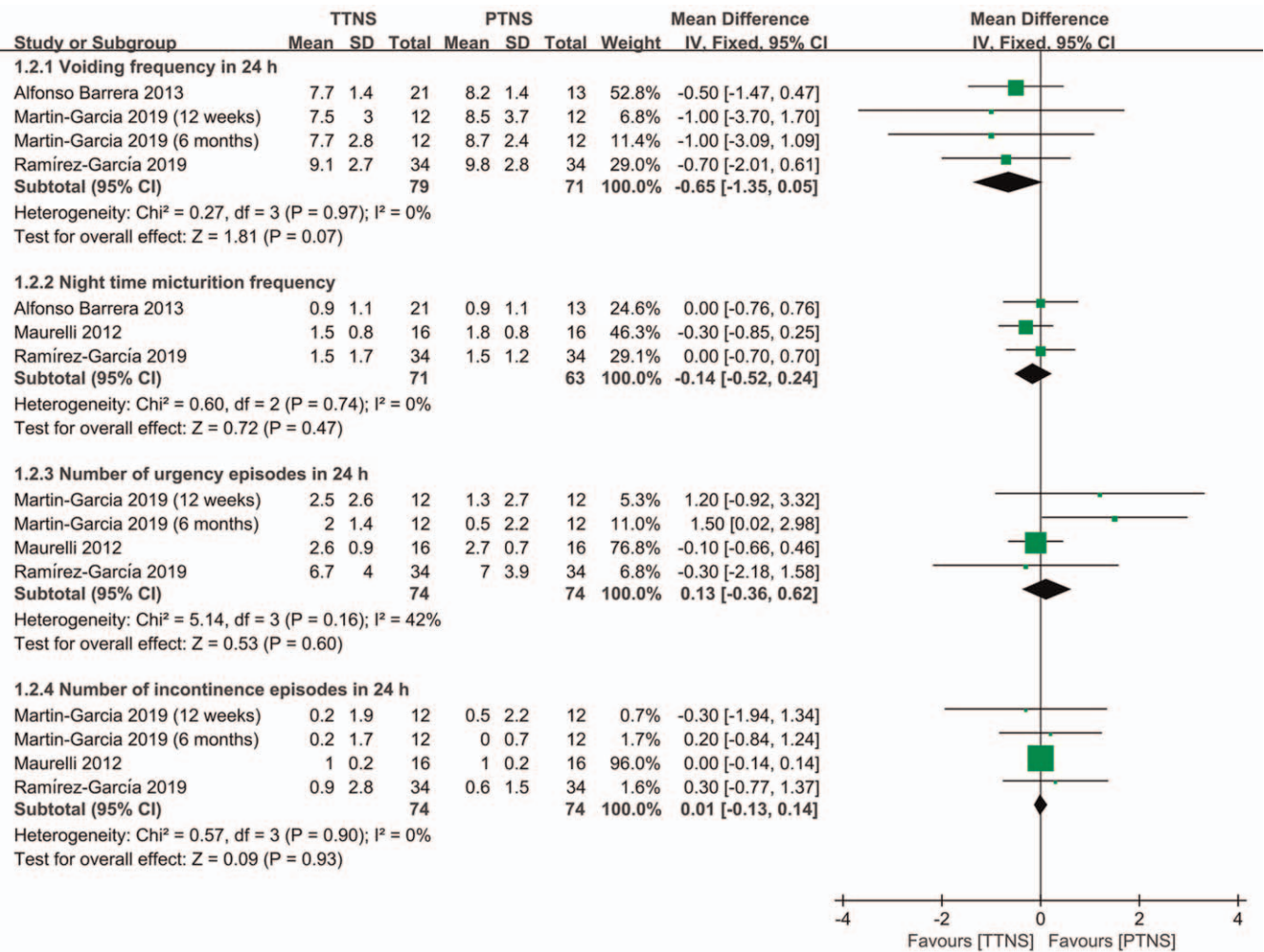


Figure 2. Forest plot for the changes of primary outcomes. PTNS = percutaneous tibial nerve stimulation, TTNS = transcutaneous tibial nerve stimulation.

In regard to patients' satisfaction, 2 studies<sup>[22,23]</sup> provided the data on HRQL scores, and another 2 studies<sup>[22,25]</sup> presented the data on I-QoL scores. As expected, similar results were noted in terms of HRQL scores (MD=3.80, 95% CI: -2.47 to 10.06, P=.23) and I-QoL scores (MD=6.93, 95% CI: -1.27 to 15.13, P=.10) in the TTNS and PTNS group (Fig. 4).

### 3.3. Safety profile

With regard to safety profile, the AEs were identified in the 4 studies,<sup>[22-25]</sup> and the total complication rate in the current study was 2.1% (3/142). Gratifyingly, no AEs were identified in the TTNS group. Additionally, only 3 patients with OAB after PTNS reported TNS-related AEs, including 2 had bleeding at the needle site and 1 experienced discomfort/pain over the needled area.

## 4. Discussion

To our knowledge, the present study is the first to investigate the effectiveness and safety profile between TTNS and PTNS. Notably, TTNS had a similar performance in voiding frequency per day (P=.07), the number of urgency episodes per day

(P=.60), the number of incontinence episodes per day (P=.93), as well as in nocturia episodes (P=.47), compared with PTNS. Moreover, comparable results were observed in terms of HRQL scores (P=.23) and I-QoL scores (P=.10) in the 2 groups. The total complication rate in the current study was 2.1% (3/142). Gratifyingly, no AEs were identified in the TTNS group.

The aim of neuromodulation in the field of urology is to target the innervation system of the lower urinary tract. The PTN is a distal branch of the sciatic nerve that originates in the pelvis (L5-S3 spinal roots) and descends towards the lower extremities.<sup>[26]</sup> Stimulation of the PTN delivers retrograde neuromodulation to the sacral nerve plexus that controls the bladder function. TNS is a form of neuromodulation involving the use of electrical impulses to address urinary symptoms.<sup>[26]</sup> Two routines were usually applied during TNS, including transcutaneous and percutaneous approaches. Two RCTs comparing PTNS with sham stimulation have proved PTNS effective and acceptable.<sup>[27,28]</sup> Findings showed that the PTNS group had a higher response rate and was superior to the sham group with greater improvements in frequency, nighttime voids, urgency, and urge incontinence. In addition, PTNS provided a continuous therapeutic effect in a retrospective study with a 9-year follow-up.<sup>[29]</sup>



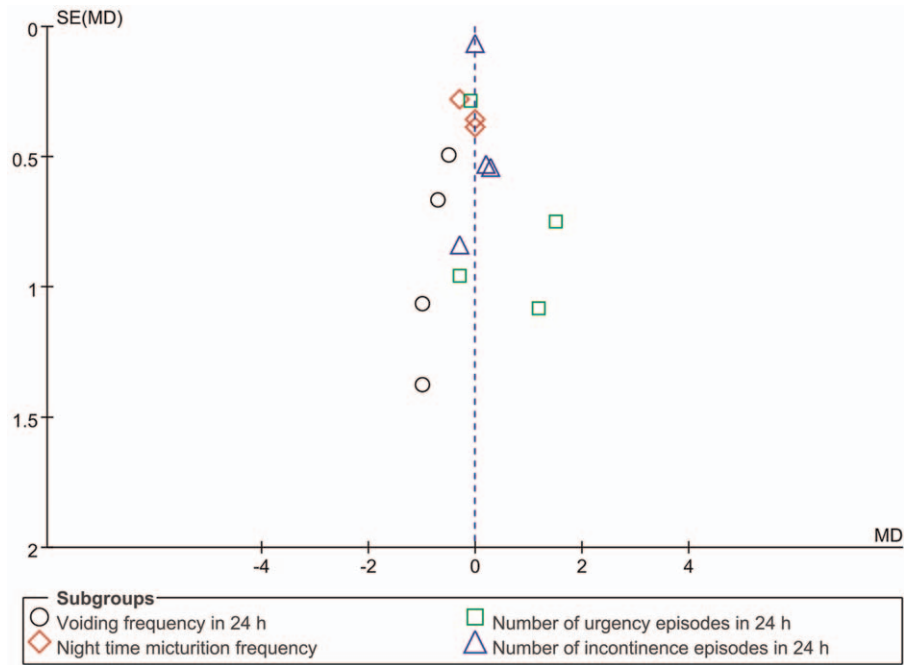


Figure 3. Publication bias of primary outcomes.

Moreover, a meta-analysis suggested that PTNS had a positive effect on sexual function.<sup>[30]</sup> Although the incidence was low, the major complication including the pain and infections at the puncture site should be noted and carefully handled. Despite low-grade evidence, the current study supported that TTNS is as effective as PTNS. The results were in line with the findings in a previous study.<sup>[13]</sup>

Nevertheless, PTNS involves delivery of an extended program of treatment (usually 30 min/wk, 12 sessions) by trained staff in a secondary care or clinic environment and thus completion involves a significant time and travel commitment by the patients with OAB.<sup>[27,28]</sup> The procedure is time-consuming and less cost-effective. Regarding TTNS, which is a noninvasive, safe

treatment for OAB, using only surface electrodes and may be self-administered by the person in their own home, thus supporting self-management and avoiding travel and staff costs. Surface electrodes used in TTNS explained zero AE in the current study. It is convenient because the program of delivery is decided entirely by the person with OAB and can therefore reflect personal choices and lifestyle.<sup>[13]</sup> Given its safety, low cost, ease of application, and potential to support self-administration, there is a clear impetus for further research to establish definitive evidence on the role of TTNS as second-line therapy, after lifestyle and behavioral changes have been implemented and as a direct alternative to pharmacological therapy in adults with OAB.<sup>[13]</sup> Nerve stimulations, such as sacral nerve stimulation,

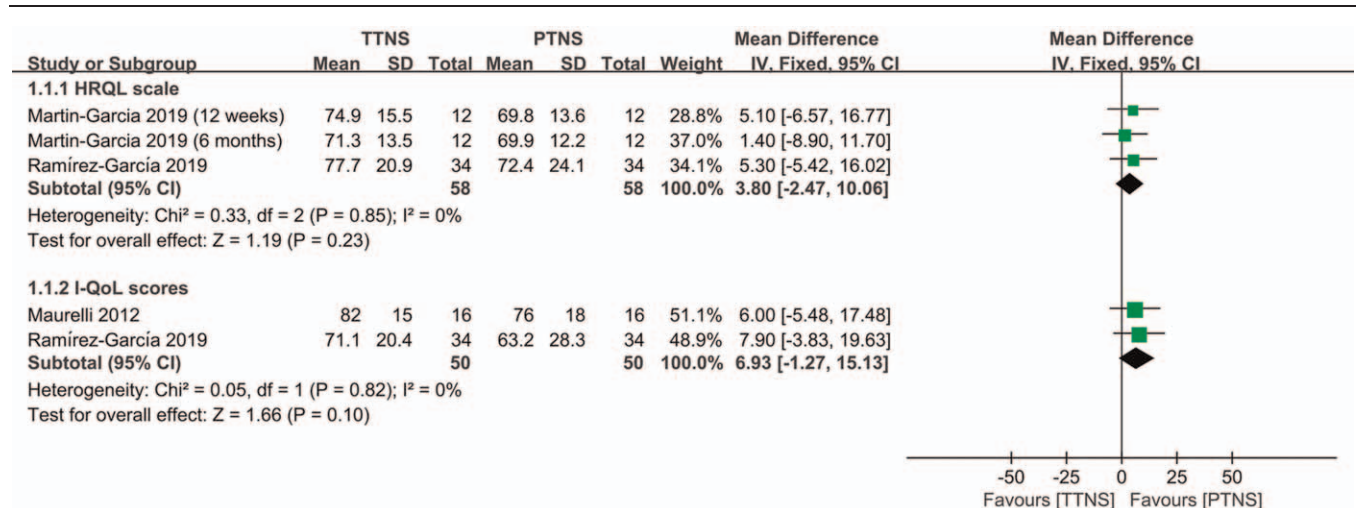


Figure 4. Forest plot for life quality scores. HRQL = health-related quality of life scale, I-QoL = incontinence quality of life questionnaire.

PTNS, and TTNS, deserve evaluation for patients with complicated lower urinary tract symptoms like the combination of OAB and underactive bladder,<sup>[31]</sup> despite further studies are needed.

It was clear that OAB symptoms, especially OAB-wet, had a negative effect on patient sexual function.<sup>[6]</sup> Unfortunately, there are limited data on the sexual function after TTNS. Moreover, we are unable to obtain a pooled result regarding evident cost-effectiveness with insufficient data between the 2 groups. Currently, there is no evidence of superior efficacy with longer duration of stimulation, and the optimum intervention program or schedule has not yet been established for TTNS.<sup>[32]</sup> Further long-term study should go on to shed some light on these topics.

Limitations in this review should be mentioned. Given that we have systematically searched the mainstream database and included all the comparative trials of TTNS versus PTNS for OAB, we could eventually select only 4 articles and the patient size ended up with 142. Moreover, only 2 RCTs were enrolled. Therefore, long-term RCTs with larger population should be conducted in the future to further verify our findings.

## 5. Conclusion

Due to a similar performance in the improvement of OAB symptoms, the current data supported that TTNS is as effective as PTNS for the treatment of OAB, moreover, without any reported safety concerns. However, the evidence is low-grade and well-designed prospective studies with a large sample size are warranted to verify our findings.

## Author contributions

**Conceptualization:** Ding-Yuan Yang, Liu-Ni Zhao, Ming-Xing Qiu.

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**Validation:** Ding-Yuan Yang, Liu-Ni Zhao.

**Visualization:** Ming-Xing Qiu.

**Writing – original draft:** Ding-Yuan Yang, Ming-Xing Qiu.

**Writing – review & editing:** Ding-Yuan Yang, Ming-Xing Qiu.

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