General Section
Review

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Transcutaneous vagus nerve stimulation effects on chronic pain: systematic review and meta-analysis

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Abstract

Chronic pain is one of the major causes of disability with a tremendous impact on an individual's quality of life and on public health. Transcutaneous vagus nerve stimulation (tVNS) is a safe therapeutic for this condition. We aimed to evaluate its effects in adults with chronic pain. A comprehensive search was performed, including randomized controlled trials published until October 2023, which assessed the effects of noninvasive tVNS. Cohen's *d* effect size and 95% confidence intervals (CIs) were calculated, and random-effects meta-analyses were performed. Fifteen studies were included. The results revealed a mean effect size of 0.41 (95% CI 0.17-0.66) in favor of tVNS as compared with control, although a significant heterogeneity was observed ($\chi^2 = 21.7$, $df = 10$, $P = 0.02$, $I^2 = 53.9\%$). However, when compared with nonactive controls, tVNS shows a larger effect size (0.79, 95% CI 0.25-1.33), although the number of studies was small (n = 3). When analyzed separately, auricular tVNS and cervical tVNS against control, it shows a significant small to moderate effect size, similar to that of the main analysis, respectively, 0.42 (95% CI 0.08-0.76, 8 studies) and 0.36 (95% CI 0.01-0.70, 3 studies). No differences were observed in the number of migraine days for the trials on migraine. This meta-analysis indicates that tVNS shows promise as an effective intervention for managing pain intensity in chronic pain conditions. We discuss the design of future trials to confirm these preliminary results, including sample size and parameters of stimulation.

Keywords: Transcutaneous vagus nerve stimulation, Chronic pain, Meta-analysis, Neuromodulation

1. Introduction

Chronic pain—defined as pain that persists longer than 3 months—is a condition that profoundly affects individual lives and public health and represents one of the most significant causes of disability, affecting 1.9 billion people worldwide.[18,41] In 2020, the International Association for the Study of Pain defined pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage," which is valid for acute and chronic pain, including the 3 categories: nociceptive, neuropathic, and nociplastic pain.[35] Nociplastic pain was defined as a dysfunction of peripheral nociceptors and central sensitizations, causing pain without tissue lesions,[20] although mild nonclinical damage to the nervous system has not been fully investigated in chronic pain conditions.

The lack of effective treatment for chronic pain has led the United States to face public health challenges, with the overuse of classes of drugs, such as the opioids, what can cause further burden to the health system.[8,9] Therefore, it is pivotal to develop nonopioid therapies to expand the treatment options to address that problem. In this context, neuromodulation techniques, such as transcutaneous vagus nerve stimulation (tVNS), are potential alternatives for pain management targeting the central nervous system.[27]

The tVNS is a safe and noninvasive technique that can be approached by the stimulation of the vagal auricular or cervical bundles. Transcutaneous auricular VNS (taVNS) uses surface

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electrodes to apply the electrical stimulus over the skin of the outer ear, targeting afferent fibers of the auricular branch of the nerve, in which the ipsilateral nucleus of tractus solitarius (NTS) is activated through the vagal projections in the brainstem and forebrain.[15,16] However, transcutaneous cervical VNS (tcVNS) is also a noninvasive technique applied on the neck and has been approved by the US Food and Drug Administration for migraine and cluster headache.[3,17] Because of considerable innervation on the neck, nonvagal nerves are also stimulated during the intervention, which leads to some reported adverse events such as neck and oropharyngeal pain and dizziness.[36]

Some studies pointed out that tVNS could reduce allodynia, chronic migraine, and potentially other chronic pain conditions.[31,32,40] Based on that, it is likely that tVNS can have a clinically meaningful impact on pain syndromes. To assess that, the current systematic review with meta-analysis aimed to investigate the effects of tVNS for treating chronic pain conditions from the cumulative evidence of randomized controlled trials.

2. Methods

This systematic review and meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (2020) framework and was registered in the International Prospective Register of Systematic Reviews (CRD42023475504). We formulated our research question using the PICO strategy, defining the following components: individuals with chronic pain as the target population, tVNS as the intervention, any control group as the basis for comparison, and subjective or objective pain measures as the primary outcomes.

2.1. Eligibility criteria

All studies that met the following criteria were included: (1) RCTs, (2) investigating the use of noninvasive tVNS in chronic pain conditions, (3) with any control comparators, (4) reporting objective or subjective measures of pain as outcomes, and (5) on any timeframe. Studies with divergent design, outcome, and population, as well as duplicates, reviews, and background articles, were excluded.

2.2. Information sources

Electronic searches were systematically conducted by 2 investigators in the databases PubMed, EMBASE, and the Cochrane Library, between September and October 2023.

2.3. Search strategy and selection process

The terms used on the databases were "Vagus Nerve Stimulation" OR "tVNS" OR "VNS" OR "Auricular Stimulation" OR "Transauricular Stimulation" AND "Pain Management" OR "Chronic Pain" OR "Fibromyalgia" OR "Headache" OR "Migraine Disorders" OR "Long term pain" OR "Persistent Pain." These terms were searched on titles and abstracts, and mesh terms were used depending on the database.

Electronic searches and initial screening were performed independently by 3 investigators. Articles were initially selected based on titles and abstracts, after the automatic removal of duplicates using the Covidence online platform. Subsequently, full-text articles were screened against predefined eligibility criteria, and those meeting the criteria were selected for data extraction.

2.4. Data collection and data items

Two investigators conducted the data extraction process. The collected data were organized into spreadsheets, categorizing studies by specific characteristics, including author and publication year, country of origin, sample size, age and gender demographics, underlying health conditions, intervention details (device, dose, parameters, application area, etc), and preoutcome and postoutcome measure assessments.

The meta-analysis encompassed all studies with reported outcome measurements in the form of mean, mean difference, and SD. These values were either extracted directly from the articles or calculated based on the available data. Subgroup and sensitivity analyses were conducted, considering the characteristics of the studies, including observed conditions and interventions. To account for the anticipated variability between studies and ensure generalizability to comparable studies, a random-effects model was used. This approach also provides a more conservative estimation of mean effects.

2.5. Risk of bias and study quality assessment

The revised Cochrane risk-of-bias tool for parallel and crossover randomized trials was used to assess the risk of bias in the included studies. The revised Cochrane risk-of-bias tool for parallel and crossover randomized trials for parallel studies is structured into 5 domains (1 = bias arising from the randomization process; 2 = bias because of deviations from intended interventions; 3 = bias because of missing outcome data; 4 = bias in measurement of the outcome; and 5 = bias in selection of the reported result), and for crossover studies, 1 more domain is added (bias arising from period and carryover effects). This tool comprises various domains with signaling questions addressing distinct aspects of trial design, conduct, and reporting. The possible risk-of-bias judgements are (1) low risk of bias, (2) some concerns, and (3) high risk of bias. The assessment was conducted by 2 investigators, and any discrepancies between assessments were solved through consensus.

2.6. Synthesis method

We described the data using the characteristics mentioned earlier. Studies meeting the inclusion criteria for the meta-analysis were pooled based on the mean difference and SD of pre–post measurements for each group. We used the standardized mean difference as a measure of the effect size, after Cohen's *d* interpretation, where effect sizes are categorized as small (0.2), moderate (0.5), and large (0.8). For the assessment of publication bias, we adopted the visual inspection of the distribution of the standard difference in means by the SEs and the Duval and Tweedie's trim-and-fill method. For the comparisons and generation of plots, we used the software Comprehensive Meta-Analysis version 3 (Biostat, Englewood, NJ).

3. Results

3.1. Study selection and characteristics

A comprehensive depiction of the selection process, including excluded records and the reasons for their exclusion, is presented in **Figure 1**. We identified 15 eligible studies, with 9 using tcVNS and 6 using taVNS. Among these, 12 studies reported data on pain intensity, primarily using numerical pain rating scales. **Table 1** provides an overview of the included studies, detailing general features such as authors, study design, sample characteristics,

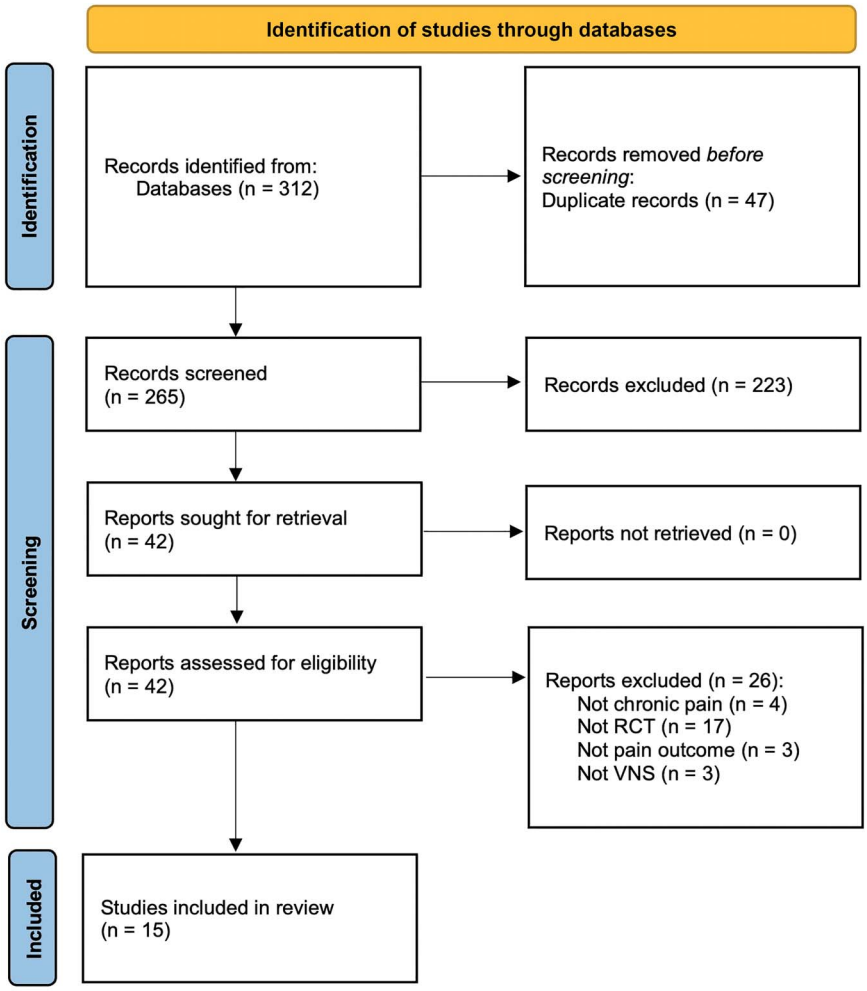

Figure 1. PRISMA flow chart displaying the selection process for the inclusion of the studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

intervention, outcome measures, results, as well as stimulation parameters, including frequency, intensity, duration, etc.

We were able to include 11 studies in the main meta-analysis assessing pain intensity,[1,2,4,21,22,25,26,30,33,38,43] whereas 1 study[29] was excluded because of unavailability of data. In addition, we identified that 6 of the 15 studies reported the number of migraine days, defined as episodes of migraine or headache occurring within a 28-day period, as a secondary pain outcome, and these were included in a secondary analysis.

3.2. Meta-analyses results

3.2.1. Effect of transcutaneous vagus nerve stimulation on pain intensity

The primary analysis aimed to compare the impact of tVNS against control on pain intensity. This analysis encompassed 11 studies with a total of 684 participants, aged between 30 and 58 years on average. The results revealed a mean effect size of 0.41 (95% confidence interval [CI] 0.17-0.66) in favor of tVNS, as shown in **Figure 2A**. A significant heterogeneity was observed. **Figure 2B** illustrates the prediction interval, indicating the dispersion of effect sizes across the studies and revealing that the true effect size for 95% of comparable populations falls within the interval of −0.31 to 1.14.

3.2.1.1. Sensitivity analyses

An examination of the distribution of study weights indicated that no single study significantly influenced the overall analysis, with each study contributing equally to the main result (ranging from 5% to 10%, without any outliers). However, to assess the impact of studies comparing tVNS with active controls such as exercise and active stimulation, which could potentially skew the point estimate and introduce heterogeneity, we conducted an analysis excluding these studies. The results, based on 3 studies involving 115 participants, revealed a reduction in variance while maintaining the direction and significantly increasing the magnitude of the pooled effect (0.79, 95% CI 0.25-1.33; $T^2 = 0.10$, $\chi^2 = 3.52$, $df = 2$, $P = 0.17$, $I^2 = 43.2\%$), as illustrated in **Figure 3A**.

3.2.1.2. Subgroup analyses

To assess the effects of taVNS and tcVNS separately compared with control, a subgroup analysis was conducted involving 11 studies. **Figure 3B** illustrates the results; it shows that both taVNS and tcVNS reached small to moderate effects sizes compared with control, respectively, 0.42 (95% CI 0.08-0.76) and 0.36 (95% CI 0.01-0.70). Similar effect size was observed when comparing tVNS with only sham and lower frequency tVNS (0.34, 95% CI 0.13-0.55, $I^2 = 3\%$; 6 studies).

Table 1

Characterization of the studies included in the systematic review (comparable pain outcomes).

Study	Country	Design	Mean age	Pain condition	Device/area	Stimulation parameters	Measures	Results Mean diff. ± SD
Abdel-Baset et al., 2023[1]	Egypt	RCT n = 66 taVNS × PNE	33.3 ± 8.2	Fibromyalgia	TENS7000: left cymba concha	25 Hz, 30 min, 2×/wk, 3 wk	VAS	taVNS improved pain (2.65 ± 0.59)
Bellocchi et al., 2023[4]	Italy	RCT crossover n = 32 taVNS × taVNS sham	58.0 ± 11.0	Systemic sclerosis	Not specified: left cymba concha	25 Hz or 1 Hz (sham), 0.2-5 mA, 240 min, daily, 8 wk	NRS	taVNS improved pain (1.5 ± 2.41)
Awaad et al., 2022[2]	Egypt	RCT n = 30 tcVNS/PT × tcVNS sham/PT	31.7 ± 6.37	Post–COVID-19 headache	TENS: left neck side	25 Hz, 2 mA, 30 min, 5×/wk, 4 wk	VAS	tcVNS improved pain (0.18 ± 0.63)
Li et al., 2022[22]	China	RCT n = 60 taVNS/electroacupuncture × citalopram	37.1 ± 8.32	Depression	Electronic acupuncture device (SDZII, Huatuo, China): cymba concha (+ acupoints GV20 and GV29)	4 Hz for 5 s + 20 Hz for 10 s, patient-adjusted intensity, dilatational waves, 30 min, 2×/d, 8 wk	VAS	No difference between groups (G1 = 3.26 ± 1.44; G2 = 3.38 ± 1.43)
Meints et al., 2022[26]	United States	RCT crossover n = 19 taVNS (RAVANS)/MM × taVNS sham (OFF)/MM	54.0 ± 16.0	Low-back pain	Uro Stim (Schwa-Medico, Germany): left cymba concha	7.0 mA (mean), DC, 27 min, 1 session	NRS	No difference between groups (G1 = 2.96 ± 3.71; G2 = 2.62 ± 3.46)
Najib et al., 2022[28]	United States	RCT n = 113 tcVNS × tcVNS sham	G1 = 40.3 ± 13.9 G2 = 44.6 ± 10.7	Migraine	gammaCore (electroCore, USA): neck (most painful side)	25 Hz, 60 mA (peak), sine waves, three 2 min 3×/d, 12 wk	# Migraine days	No difference between groups (G1 = 3.12 ± 3.95; G2 = 2.29 ± 3.84)
Paccione et al., 2022[33]	Norway	RCT n = 57 taVNS × aNVS	45.7 ± 10.3	Fibromyalgia	Portable device (not specified): left cymba concha or left ear lobe	2× 15 min daily, 2 wk	NRS	No difference between groups (G1 = 0.82 ± 1.36; G2 = 0.86 ± 1.37)
Natelson et al., 2021[30]	United States	RCT n = 20 tcVNS × tcVNS sham	G1 = 53.9 ± 7.2 G2 = 55.7 ± 5.9	Gulf War illness	gammaCore (electroCore, USA): neck bilaterally	25 Hz or 0.1 Hz (sham), 30 mA or 1 mA, six 2 min 3×/d, 10 wk	NRS, # migraine days	No difference between groups (G1 = NRS: 1.41 ± 2.5, # days: 4.25 ± 0.49; G2 = 0.9 ± 2.45, 4.90 ± 8.95)
Zhang et al., 2021[43]	China	RCT n = 59 taVNS × aNVS	G1 = 30.0 ± 6.5 G2 = 31.0 ± 8.3	Migraine	Electronic acupuncture device (SDZII, Huatuo, China): left cymba concha or left helix tail	1 Hz, 1.5-5 mA, 30 min, 12 sessions, 4 wk	VAS, # migraine days	taVNS improved pain migraine (VAS 13.3 ± 22.73; # days 1.8 ± 0.56)
Kutlu et al., 2020[21]	Turkey	RCT n = 52 taVNS/exercise × exercise	39.0 ± 8.8	Fibromyalgia	TENS: tragus-concha bilaterally	10 Hz, patient-adjusted intensity, biphasic/as asymmetric waves, 30 min, 5×/wk, 4 wk	VAS	No difference between groups (G1 = 3.61 ± 3.21; G2 = 2.22 ± 2.72)
Diener et al., 2019[11]	Europe	RCT n = 332 tcVNS × tcVNS sham	G1 = 43.5 ± 11.1 G2 = 41.4 ± 12.3	Migraine	gammaCore (electroCore, USA): neck bilaterally	25 Hz or 0.1 Hz (sham), 60 mA (peak output), sine waves, 3×/d, 12 wk	# Migraine days	No difference between groups (G1 = 2.26 ± 3.6; G2 = 1.8 ± 3.44)
Martelletti et al., 2018[25]	Italy	RCT n = 243 tcVNS × tcVNS sham	39.2 ± 11.4	Migraine	gammaCore (electroCore, USA): neck bilaterally	25 Hz or 0.1 Hz (sham), 60 mA (peak), sine waves, 2-6 min each side within 20 min pain onset, 8 wk	0-3 pain scale	tcVNS improved pain (0.22 ± 0.08)
Silberstein et al., 2016[37]	United States	RCT n = 59 tcVNS × tcVNS sham (OFF)	G1 = 40.5 ± 14.2 G2 = 38.8 ± 11.1	Migraine	gammaCore (electroCore, USA): neck right side	60 mA (maximum), two 2 min 3×/d, 8 wk	# Headache days	No difference between groups (G1 = 1.4 ± 6.24; G2 = 0.2 ± 3.57)

(*continued on next page*)

Table 1 (*continued*)

Characterization of the studies included in the systematic review (comparable pain outcomes).

Study	Country	Design	Mean age	Pain condition	Device/area	Stimulation parameters	Measures	Results Mean diff. ± SD
Straube et al., 2015[38]	Germany	RCT n = 46 25 Hz taVNS × 1 Hz taVNS	G1 = 43.8 ± 11.5 G2 = 39.3 ± 12.4	Migraine	NEMOS (Cerbomed, Germany): concha cymba	25 Hz or 1 Hz, patient-adjusted intensity, 240 min/d, 12 wk	NRS, # headache days	No difference in pain intensity (G1 = 0.1 ± 1.1; G2 = 0.2 ± 1.0); decreased headache days (2.6 ± 1.07)
Napadow et al., 2012[29]	United States	RCT crossover n = 15 taVNS (RAVANS) × aNVS	36.3 ± 10.6	Pelvic pain	Cefar Acus II (Cefar Medical, Sweden): left concha cymba or left ear lobe	30 Hz, 0.43 mA (mean), rectangular waves, 1 session	NRS	No differences reported

aNVS, auricular nonvagal stimulation; GV20, Governor Vessel 20; GV29, Governor Vessel 29; Mean diff., mean difference between groups or in each group; MM, mindfulness meditation; NRS, Numeric Rating Scale; PNE, pain neuroscience education; PT, physical therapy; RAVANS, respiratory-gated auricular vagal afferent nerve stimulation; RCT, randomized controlled trial; taVNS, transcutaneous auricular vagus nerve stimulation; tcVNS, transcutaneous cervical vagus nerve stimulation; TENS, transcutaneous electrical nerve stimulation; VAS, Visual Analogue Scale; #, number.

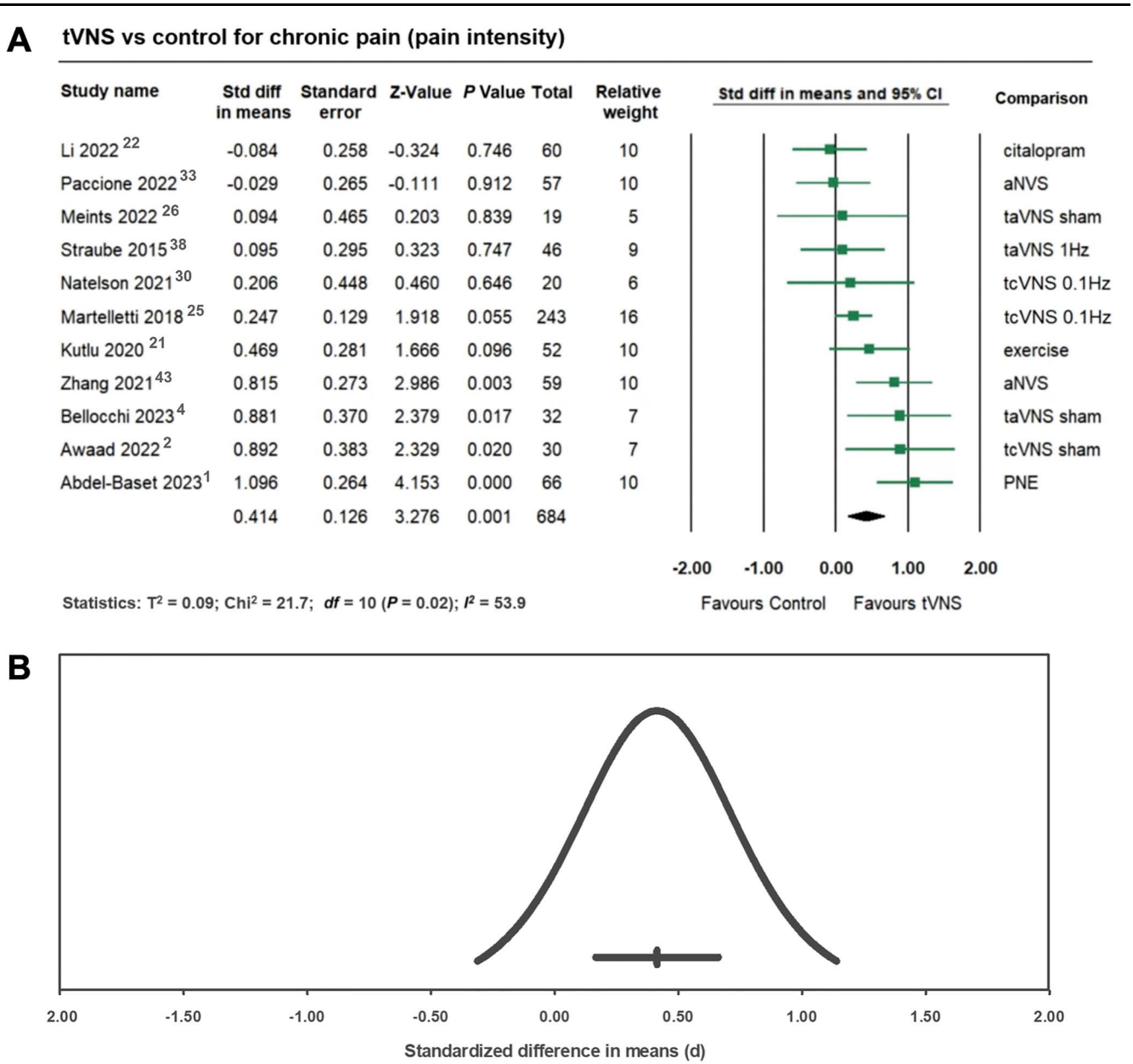

Figure 2. Results of the main analysis. (A) Forest plot showing the comparison of tVNS and control for the outcome of pain intensity in chronic pain conditions, using the random-effects model. (B) Distribution of the true effects. The mean effect size is 0.41, with the true effect size for 95% of comparable populations falling within the interval of −0.31 to 1.14. aNVS, auricular nonvagal stimulation; PNE, pain neuroscience education; tVNS, transcutaneous vagus nerve stimulation.

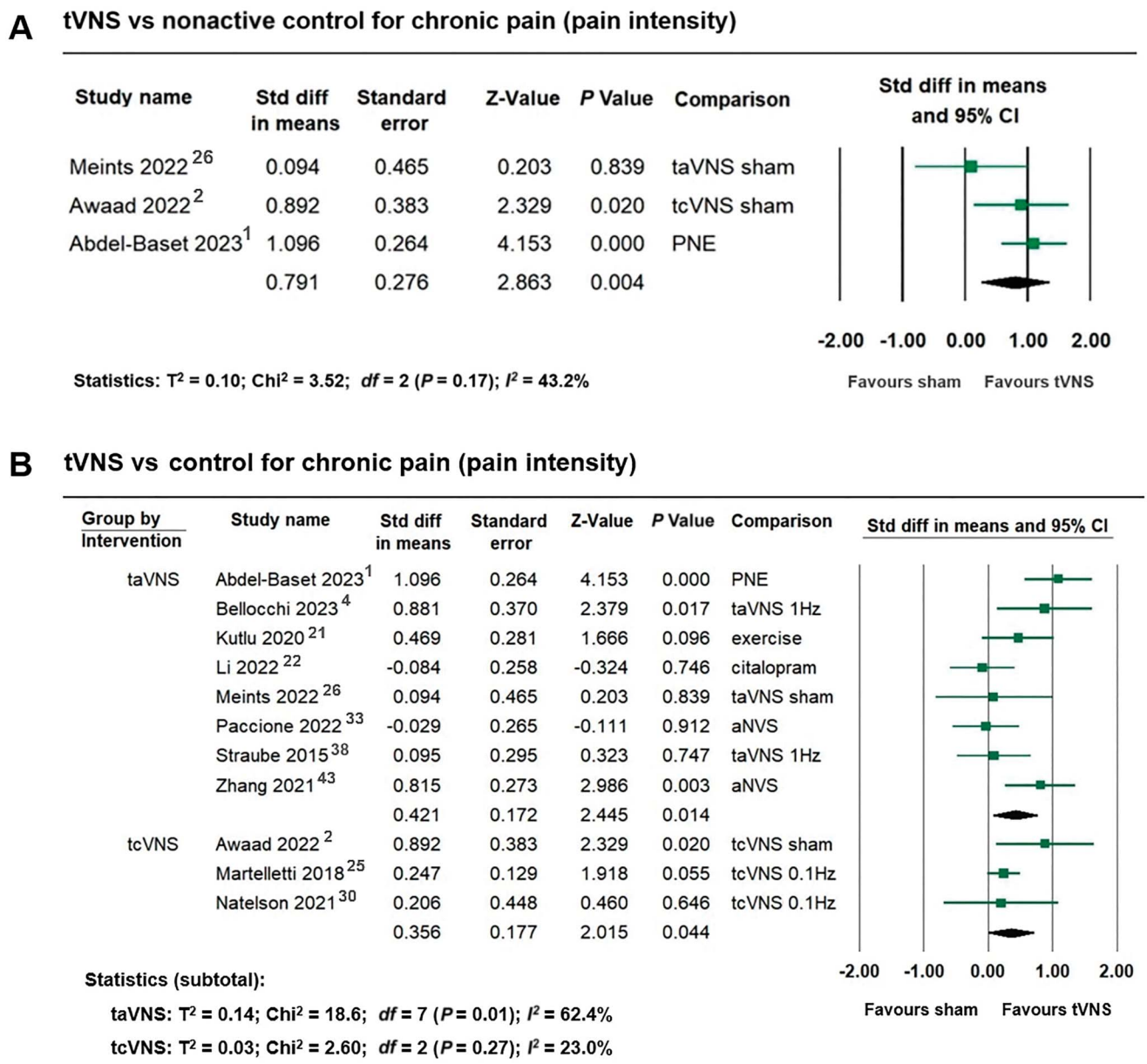

Figure 3. Forest plot showing the results of the subanalyses for pain intensity. Random-effects model (95% confidence interval). (A) Sensitivity analysis comparing tVNS with nonactive controls. (B) Subgroup analysis: separate effects of taVNS and tcVNS against control. aNVS, auricular nonvagal stimulation; PNE, pain neuroscience education; tcVNS, transcutaneous cervical vagus nerve stimulation; tVNS, transcutaneous vagus nerve stimulation.

3.2.2. Effect of transcutaneous vagus nerve stimulation on number of headache/migraine days

Six studies, involving 629 individuals with a mean age range of 30.0 30 to 56 years, reported the number of headache/migraine days as a pain outcome. Among these studies, 4 focused on individuals with chronic migraine, whereas one addressed widespread pain syndrome. The comparison between tVNS and control regarding this outcome did not reveal a significant difference (0.14, 95% CI −0.09 to 0.37), as depicted in **Figure 4A**.

3.2.2.1. Sensitivity analysis

Another analysis was conducted, excluding studies with active control interventions. This analysis comprised 2 studies with 172 individuals, comparing tcVNS with tcVNS sham. No statistical differences were observed, with a small effect size (0.22, 95% CI −0.08 to 0.52), as shown in **Figure 4B**.

3.2.3. Publication bias assessment/small-study effect

Figure 5 displays a funnel plot of SEs by standardized difference in means, which we used to assess publication bias. The plot suggests an absence of unpublished studies in our analysis. Using Duval and Tweedie's trim-and-fill method, it is estimated that 2 studies may be missing from this analysis. When these missing studies are imputed into the analysis, it results in a corrected mean effect size of 0.29 (95% CI 0.02-0.56).

3.3. Study quality assessment and risk of bias

Overall, 5 of the included studies demonstrated a low risk of bias,[2,11,22,25,33] whereas 9 studies raised certain concerns regarding bias.[1,4,21,26,29,30,37,38,43] One study was rated as having high risk of bias.[28] The primary sources of bias reported

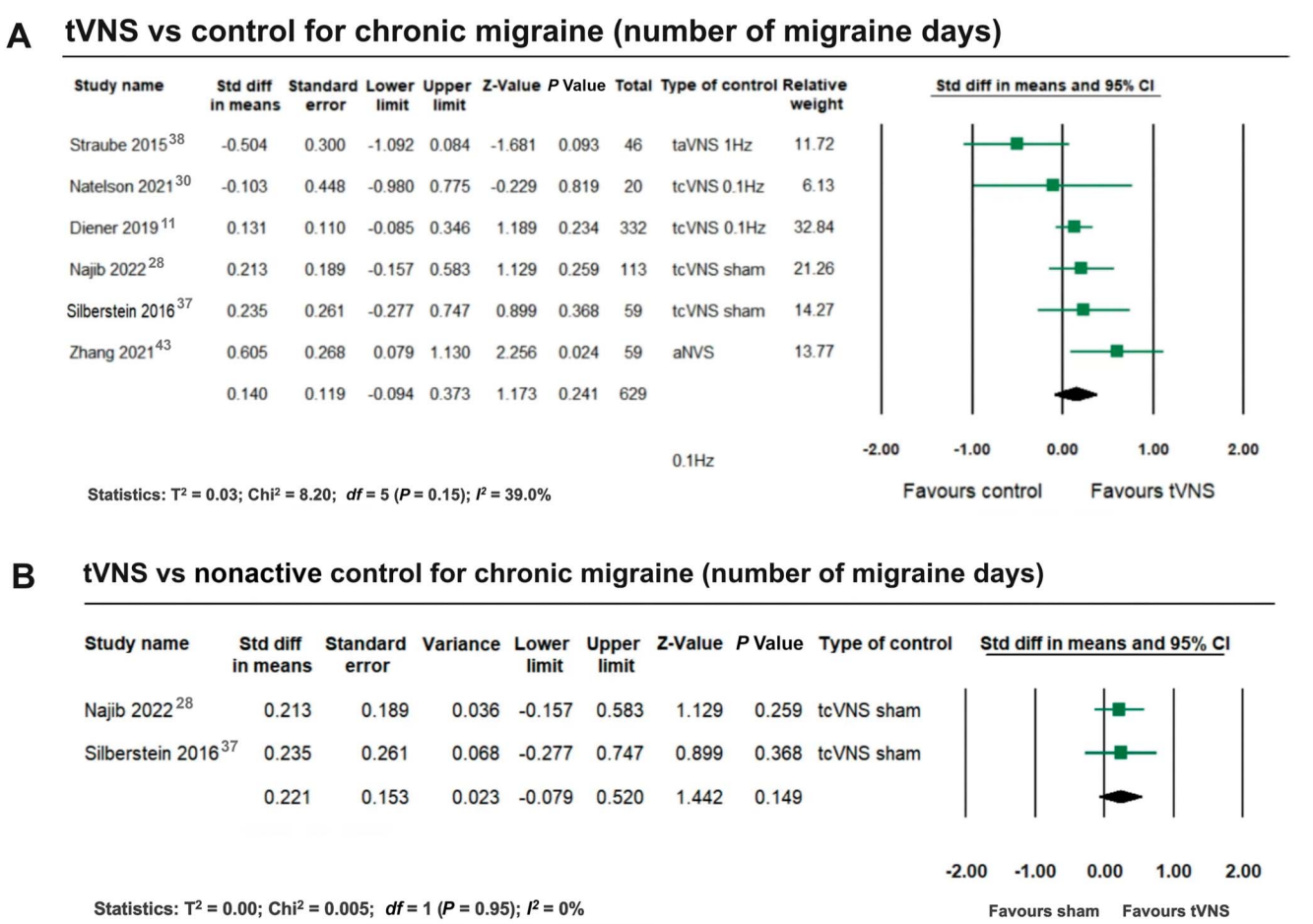

Figure 4. Forest plot showing the results of the subanalyses for the number of migraine days. Random-effects model (95% confidence interval). (A) Comparison of tVNS and control for the number of migraine days. (B) Sensitivity analysis: comparison of tVNS with sham control only. aNVS, auricular nonvagal stimulation; tVNS, transcutaneous vagus nerve stimulation.

included a lack of concealed allocation, nonblinding of assessors, absence of sample size calculation, sample loss over follow-up, and missing outcome data. The individual study results for each criterion are presented in **Figure 6**.

4. Discussion

The results of our analyses indicate that tVNS could be an effective intervention for managing pain intensity in chronic pain conditions. In the following sections, we will delve into the specific details of our analysis and explore the clinical and research implications of these findings.

4.1. Effect of transcutaneous vagus nerve stimulation on pain intensity

In our primary analysis, which encompassed 684 individuals, we observed a small to moderate effect size that favored tVNS over control interventions, whether they were active or sham. Furthermore, after removing potential sources of heterogeneity and all types of active control intervention from the analysis, the direction of the effect remained consistent, and the size of the effect was even larger. This indicates that the observed effect is in fact a reliable outcome from our analysis and that compared with sham, it might have an observable clinical impact.

We observed varying levels of heterogeneity in the initial analysis. According to the corresponding prediction interval, it is expected that in 95% of comparable populations, tVNS may have a broad impact. This impact can range from no discernible effects in smaller sample sizes to a range of small to high effect sizes in most populations (95% CI −0.31 to 1.14). From the subsequent sensitivity analysis, we noted a consistent reduction in the variance between the effect sizes of the studies. However, because of the smaller number of studies in that analysis, we cannot make a robust assumption regarding its heterogeneity. Yet, this reduction could likely be attributable to decreased sampling error.

We conducted a subgroup analysis to examine the individual effects of taVNS and tcVNS on pain intensity, considering that both were included in our study. This analysis showed a significant small to moderate effect size for both modalities against control, similar to what we found in our main analysis. It was also observed when comparing active tVNS against sham or lower frequencies tVNS (0.1-1 Hz). This consistency strengthens the validity of this result and stresses the effectiveness of tVNS for reducing pain.

When considering the potential impact of publication bias, the trim-and-fill method suggested that 2 studies may be missing from our analysis. However, it is essential to note that this observation raises a point of discussion. It is uncertain whether this truly reflects the absence of small studies reporting low effect sizes. Small studies often exhibit larger effect sizes because of their inherent characteristics related to sampling and measurement. Thus,

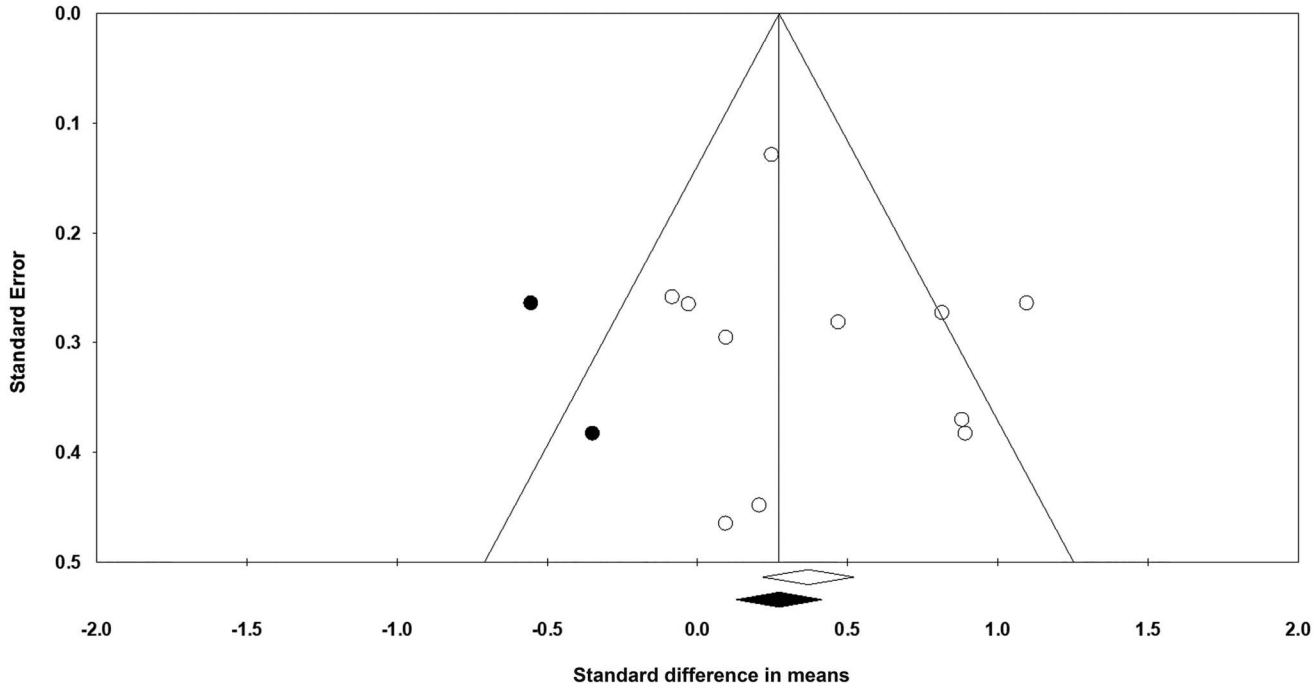

Figure 5. Funnel plot of SE by standard difference in means for the assessment of publication bias based on the trim-and-fill method. The empty diamond indicates the observed effect size (based on 11 studies). The full diamond indicates the predicted effect size (0.29, 95% CI 0.02-0.56) if the 2 missing studies were included in the analysis.

depending on the perspective, we might draw different conclusions. Our main effect size for pain intensity was 0.41 (95% CI 0.17-0.66), which accounts for the presence of potential small-study effects. However, if we consider the hypothetical exclusion of the 2 studies identified in the publication bias analysis, we would need to correct the effect size to 0.29 (95% CI 0.02-0.56). This correction could lead us to more conservative or stringent conclusions.

4.2. Effects of transcutaneous vagus nerve stimulation on the number of migraine days

In our secondary analysis, which involved 629 individuals diagnosed with chronic migraine conditions, we did not observe a significant difference even after removing potential sources of heterogeneity and comparing them against sham tVNS. This result may suggest that although tVNS may decrease the intensity of pain, it may have no measurable effect on decreasing the number of attacks in chronic conditions such as migraine. However, one of the studies that compared tVNS with sham showed a high risk of bias, and the other presented some concerns.[28,37] Noteworthy, no randomized controlled trial has compared the effect of taVNS with sham on decreasing the number of attacks/days in chronic migraine and other chronic pain conditions. More research is needed.

4.3. Feasibility and safety of transcutaneous vagus nerve stimulation

The primary distinction between transcutaneous tVNS and invasive electrical vagal stimulation lies in the absence of surgery, the need for

Figure 6. Results of the risk of bias and methodological quality assessment, according to the Cochrane Risk of Bias 2.0.

device implantation, and the associated costs, complications, and undesired side effects. Auricular and cervical modalities of vagal stimulation offer a promising noninvasive approach to treating chronic pain across a broader spectrum of patients and chronic conditions. These methods can selectively stimulate specific branches of the vagus nerve without indirectly affecting the vagus-innervated inner organs, particularly in the case of taVNS. Transcutaneous auricular VNS achieves this by physiologically stimulating the vagal projections in the brainstem and forebrain through the auricular concha and tragus—auricular regions innervated by the vagus nerve.[16]

The studies reviewed here did not report adverse effects. However, previous studies have generally found that tVNS, particularly taVNS, tends to have a low incidence of adverse effects. Commonly reported side effects include minor issues such as skin irritation, mild headaches, ear pain, headache, dizziness, prickling, tingling, and nasopharyngitis in the case of taVNS.[36] Notably, the risk of experiencing these side effects and their intensity seems to be similar in both active and control groups.[19]

4.4. Pain reduction mechanism of transcutaneous vagus nerve stimulation

Vagal electrical stimulation is known to modulate various cortical and subcortical areas, including vagal projections, the locus coeruleus, parabrachial area, hypothalamus, amygdala, anterior cingulate cortex, nucleus accumbens, thalamus, prefrontal cortex, postcentral gyrus, posterior cingulate cortex, and anterior insula.[34] It also influences several neural networks, such as the default mode network, executive network, and emotional and reward circuits. In addition, this stimulation affects the release of neurotransmitters, including GABA, norepinephrine, opioids, and serotonin, and it has demonstrated anti-inflammatory effects.[6,12,13,23,24,39] The modulation of these areas and networks is believed to underlie the effectiveness of VNS in chronic conditions such as depression and fibromyalgia. However, we did not find an effect for pain in fibromyalgia here—which was considered in only few small studies with inconsistent results—VNS remains a potential therapy for these conditions. However, the specific mechanisms responsible for VNS' analgesic effects are still a subject of ongoing research.

The studies included in this review primarily focused on the clinical alleviation of pain through tVNS and were not mechanistic in nature. An exception is the study by Zhang et al.,[43] which used fMRI imaging and found increased connectivity between the thalamus and the anterior cingulate cortex/medial prefrontal cortex, along with decreased connectivity between the thalamus and various brain regions. However, the precise interpretation of these findings in relation to the observed reduction in pain intensity remains unclear.

Previous mechanistic studies have suggested that both invasive and noninvasive VNS primarily modulate pain perception through shared anatomical pathways within the nociceptive system. These pathways include the endogenous opioid system and the central projections of vagal afferents, which intersect at key regions. Transcutaneous auricular VNS stimulates the afferent fibers of the vagus nerve that travel to the NTS and subsequently to locus coeruleus, periaqueductal gray, cortical and subcortical areas such as hypothalamus, amygdala, hippocampus, and frontal lobe, and from these areas to descending pain pathways.[34]

In addition, taVNS may trigger neuroplastic signaling mechanisms such as BDNF expression and RNA expression,[10] which may have a significant effect counteracting pain circuits with maladaptive plasticity. However, ongoing research continues to investigate these mechanisms, and conflicting evidence exists. For example, 1 alternative and complementary hypothesis is that concurrent activation of the anti-inflammatory system cascade may account for the measurable reduction in pain intensity.[5,7,14,34,42]

4.5. Parameters of transcutaneous vagus nerve stimulation

All studies in our review consistently targeted a specific area for stimulation, focusing on either the concha cymba for taVNS or the cervical branch for tcVNS. In terms of tcVNS, it was administered either bilaterally or unilaterally, whereas most taVNS studies applied stimulation to the left auricular concha. Importantly, the side of electrode placement did not significantly impact the reported analgesic effects (**Table 1**). In terms of stimulation devices, it varied from commercially available TENS equipment to more specialized portable devices tailored to tVNS.

The most used stimulation frequency in the reviewed studies was 25 Hz. However, individual studies did not show a consistent pattern regarding the frequency parameter, with some studies achieving significant effects using both 25- and 1-Hz frequencies.[2,4,43] Intensities were frequently tailored to individual needs, either to induce a tingling sensation or within a range of 1.5 to 60 mA (peak output). Interestingly, the choice of stimulation waveform did not seem to have a significant role in the protocols because no study discussed the implications of waveform type. This parameter varied between studies, with no clear standard established. In addition, waveform type was not reported in 8 studies.

Regarding the duration of stimulation, it ranged from short-term sessions of 2 to 6 minutes multiple times a day to continuous 30-minute sessions once a day. Treatment frequency and duration also varied from a single session in 1 study[26] to a more extended period of 4 to 12 weeks in most studies. The studies that demonstrated larger effects for pain intensity compared with sham or active stimulation (mostly taVNS) generally used frequencies of 1 and 25 Hz, intensities between 0.2 and 5 mA, and applied stimulation from 30 minutes per day (4 nonconsecutive hours per day in[4]), 3 to 5 times per week, about 20 sessions in total, for 4 weeks.[1,2,4,43]

4.6. Limitations of the study

The studies included in this review encompassed individuals with a range of chronic pain conditions, including fibromyalgia, migraine, back pain, and depression-related pain. These studies used various active and control interventions. Our meta-analysis and the observed pooled effects did not account for the potential subtleties in pain perception that may exist among these conditions. This is because the outcomes relied on subjective measures, such as numeric and visual scales. As a result, a limitation of this review is that it treated chronic pain as a single entity, whereas in reality, it is a diverse and multifaceted phenomenon and can manifest as nociceptive, neuropathic, and nociplastic.

Because of the limited number of studies available, we were unable to conduct condition-based subgroup analysis without introducing high levels of uncertainty. Furthermore, it was noticed that some studies used 0.1-Hz tVNS stimulation as a sham condition. Nonetheless, they used the other parameters such as intensity and duration as in the active intervention group. We did not include these studies in the sham comparisons as even at low frequencies, these stimulations can produce observable effects.

5. Conclusion, future directions, and clinical trial design

Overall, we conclude that tVNS can reduce pain intensity in chronic pain conditions with a measurable effect. However, the

clinical effect may vary across patients from a small to a highly relevant impact for most of them. According to our findings, future clinical trials should (1) choose carefully the sham/control condition as this has an important impact on the results—an active control may underestimate its effect estimates and real impact, and however, a biased control method may overestimate its effect sizes; (2) future clinical trials should test samples with at least 40 to 50 subjects according to the effect sizes we show in this review, and (3) future clinical trials should test several stimulation sessions (at least 10 sessions) with an appropriate duration (at least 20 minutes of stimulation and likely extended sessions of 60 minutes may provide better results). Finally, future clinical trials should try to understand whether taVNS has mostly a bottom-up effect, and thus, cortical structures are modulated for pain control, or its effects are mostly mediated by top-down effects (from the NTS to descending pain pathways).

Disclosures

H. Choi and J.-J. Song are directly associated with Neurive Co, a company developing neuromodulation technologies, such as taVNS, to treat common brain diseases. F. Fregni is supported by NIH grants and by a research grant and gift from Neurive to Spaulding Rehabilitation Hospital. Fregni is also a consultant for Neurive. The remaining authors have no conflicts of interest to declare.

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Author contributions: V. Costa conceptualized and designed the study, extracted data, conducted analyses, prepared data visualization, and drafted and revised the manuscript. A. C. Gianlorenço conceptualized and designed the study, oversaw analyses, drafted, and revised the manuscript. M. F. Andrade, L. Camargo, and M. Menacho extracted data, drafted, and revised the manuscript. M. Arias Avila and K. Pacheco-Barrios drafted and revised the manuscript. H. Choi, J.-J. Song, and F. Fregni conceptualized and designed the study, oversaw analyses, and critically reviewed and revised the manuscript.

Data availability: Data, including metadata spreadsheets, can be made available upon request. For inquiries or to request access to the data, please contact the corresponding author.

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