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Review Article

Neuromodulation for Gastroesophageal Reflux Disease: A Systematic Review

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Abstract

Background and objectives: In this systematic review, we evaluated the efficacy, mechanisms and safety of three neuromodulation therapies in patients with gastroesophageal reflux disease (GERD), including the effect of neuromodulation therapies on symptoms and key GERD pathophysiologies, lower esophageal sphincter (LES) pressure, esophageal motility, gastric motility, and parasympathetic activity. The first therapy is LES electrical stimulation using an implantable electrical stimulator, the second is transcutaneous electrical acustimulation, and the third is manual acupuncture.

Methods: A systematic review of literature according to the PRISMA guidelines was performed. Online databases searched include Medline (Ovid), Embase, and PubMed. Studies were assessed for inclusion and exclusion criteria with Covidence, a systematic review software.

Results: The analysis included thirteen clinical studies. Four papers included were registered under two open-label trials on ClinicalTrials.gov for LES electrical stimulation; Five randomized trials with sham-treated controls were analyzed for transcutaneous electrical acustimulation; Four studies, including three involving standard therapy controls and one involving sham-treated controls were included for manual acupuncture. All evaluated studies demonstrated significant beneficial effects on GERD symptoms, using patient-completed questionnaires, objective 24-h measurement of esophageal pH, and patient-reported use of proton pump inhibitors. In evaluating the effect on key GERD pathophysiologies, electrical stimulation significantly increased LES pressure, and transcutaneous electrical acustimulation significantly improved esophageal motility, gastric motility, and parasympathetic activity. None of the evaluated neuromodulation methods produced severe adverse effects.

Conclusions: Cumulative evidence from the evaluated studies indicates that neuromodulation therapies were effective in treating the GERD symptoms and key underlying GERD pathophysiologies. They are thus valuable options for individualized GERD treatment.

Keywords: Electrical stimulation; Lower Esophageal sphincter; Gastroesophageal reflux; GERD; Transcutaneous electrical acustimulation; Acupuncture; Neural stimulation; Neuromodulation; Gastric slow waves; Heart rate variability.

Abbreviations: DTSS, dyspeptic total symptom score; EA, electrical acupuncture; EM, esophageal motility; EM-DCI, esophageal motility distal contractile integral; FDA, USA Food and Drug Administration; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; GERD-HRQL, gastroesophageal reflux disease health-related quality of life; GERDQ, gastroesophageal reflux disease questionnaire; GERDSC, gastroesophageal reflux disease self-completed subject questionnaire for duration, frequency, and severity or heartburn, regurgitation, chest pain, and dysphagia; GSW, gastric slow waves; IPG, implantable pulse generator; LES, lower esophageal sphincter; LES-ES, lower esophageal sphincter electrical stimulation; MA, manual acupuncture; NERD, nonerosive reflux disease; PPI, proton pump inhibitor; RCT, randomized controlled trial; SF12, 12-item short form survey; SF36, 36-item short form survey; TEA, transcutaneous electrical acustimulation.

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Introduction

Gastroesophageal reflux (GER) is defined as back flow (i.e. reflux) of stomach contents into the esophagus. This is a normal physiological process that may have a protective role during meals and in the immediate postprandial period.[1] Repeated and persistent reflux over time however, can cause troublesome symptoms and/or complications, leading to a chronic condition known as GER disease (GERD).[2] GERD can be classified as nonerosive reflux disease (NERD), erosive esophagitis, or Barrett's esophagus.[3,4] NERD is the most common phenotype and accounts for up to 70% of GERD patients, whereas erosive esophagitis represents approximately 30%, and Barrett's esophagus accounts for 6–8% of the GERD patient

population.[5] The prevalence of weekly GERD symptoms in the USA is 20%,[6] accounting for 110,000 annual hospital admissions.[7] GERD leads to a diminished quality of life[8,9] and a high cost of disease management, exceeding $12 billion annually in the USA alone.[10]

After excluding functional esophageal disorders (e.g. reflux hypersensitivity and functional heartburn) and non-esophageal disorders,[11] key GERD pathophysiologies can be subdivided into three groups: (1) impaired esophageal clearance due to impaired esophageal motility (e.g., weak esophageal peristalsis); (2) esophagogastric junction or anti-reflux barrier dysfunction due to either a hypotensive lower esophageal sphincter (LES), transient LES relaxations, and/or dyssynergia between the LES and the crural diaphragm (e.g., due to the presence of a hiatal hernia); and (3) downstream gastric factors, including delayed gastric emptying and the presence of a gastric acid pocket.[12,13] Patients with more severe GERD symptoms exhibit increased sympathetic dominance compared to those with NERD.[14,15]

Treatment of GERD includes: (1) lifestyle modification, such as weight loss, smoking cessation and deep breathing; (2) medications, such as proton pump inhibitors (PPIs), prokinetics, histamine-2 receptor antagonists, and antacids; (3) endoscopic/laparoscopic surgical procedures, such as fundoplication[16]; and (4) neuromodulation therapies, the subject of this review. PPIs are commonly used for GERD, and whilst they are effective for symptomatic treatment by suppressing gastric acid production, they do not target any of the underlying pathophysiologies.[17] Prokinetics, such as dopamine-2 antagonists and 5-HT4 receptor agonists, can accelerate delayed gastric emptying but have little effect on esophageal motility and LES pressure. Furthermore, patients may also suffer from multiple side effects.[18] Endoscopic/laparoscopic surgical procedures can enhance LES pressure and thus lead to improved esophageal barrier function. However, they are associated with many short-term and long-term post-procedure complications, including gas bloating, dysphagia, and diarrhea.[19]

In summary, although various treatment options are available, none of the current therapies target the multiple pathophysiological mechanisms implicated in GERD. Several neuromodulation therapies have been trialed in the treatment of GERD. These include implantable LES electrical stimulation (LES-ES), transcutaneous electrical acustimulation (TEA), manual acupuncture (MA), and electroacupuncture (EA). In this systematic review, we evaluated the effectiveness of these neuromodulation therapies against GERD symptoms and on key GERD pathophysiologies, including LES pressure, esophageal motility, gastric motility, and parasympathetic activity.

Materials and methods

The systematic review was performed in accordance with the 2020 version of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[20]

Data sources and searches

On March 18, 2023, Medline (Ovid), Embase, and PubMed were searched for scientific papers published between 2003 and 2023. The search keywords are provided in Table 1.

Data collection and evaluation

All identified article titles were imported into the Covidence Systematic Review Software for review. Abstracts were initially screened, followed by full text reviewed by one author (JYW), in accordance with the inclusion and exclusion criteria. Papers were intermittently reviewed independently by a second author (JC).

Study selection

For TEA and MA, only sham-controlled randomized controlled trials (RCTs) were included, whilst for LES-ES, we included the open-label studies registered on ClinicalTrials.gov. The invasive nature of the LES-ES therapy suggests that inclusion of a sham group would be unethical. The criteria for inclusion were: (1) Randomised control trials (RCTs) for TEA and MA or trials registered on ClinicalTrials.gov (for LES-ES); (2) Study population with individuals 19 years of age and older; (3) Papers published in the English language; and (4) Papers with full text available. Studies published more than 20 years ago, studies with a population 18 years of age or younger, non-human studies and non-English papers were excluded.

Results

Search outcomes

A total of 349 records were imported into Covidence, 348 from three databases (227 from Embase, 64 from Medline, 57 from PubMed), and one record from an external source.[21] Of those, 134 duplicate records were removed and 215 were screened. Upon reviewing the titles and abstracts, 160 records were identified as irrelevant and thus excluded. The remaining 55 records were assessed by the inclusion criteria and 42 were excluded with reasons. Ten studies utilized interventions other than LES-ES, TEA, and MA, or included more than one intervention. Eight were not RCTs. Of those, six were either systematic or clinical reviews, one was a study protocol, and one was an MA study of a case series. Three included a pediatric population. Three were animal studies. Four examined a non-GERD population. Two studies measured non-functional outcomes, one of which observed patient-practitioner interactions and the other investigated the optimization of acupoint selection. Five papers were not available as full text. Seven papers reported intermediate study results and only the final results were included in this review. Ultimately, 13 articles were included in the analysis: LES-ES ($n = 4$), TEA ($n = 5$), MA ($n = 4$), EA ($n = 0$). The PRISMA flow diagram of study selection is shown in Figure 1.

LES-ES studies

In all evaluated LES-ES studies, bipolar electrical stimulation was delivered via two leads implanted approximately 1 cm apart in the LES submucosa and connected to an implantable pulse generator (IPG; Endostim LES Stimulation System; Endostim Inc., St. Louis, MO, USA). The IPG was placed in the subcutaneous pocket in the anterior abdominal wall. The LES-ES parameters were a frequency of 20 Hz, current amplitude of 3–8 mA (typically 5 mA), pulse width of 215 μs, train duration of 3 ms, and session duration of 30 m, with up to 12 sessions per day. Two pilot clinical studies were performed: NCT01578642 in Chile with $n = 21$ for 2 years[22,23]; and NCT02441400 at 16 sites across Europe and Latin America with $n = 94$ for 1 year and $n = 37$ for 2 years.[24,25] These studies were followed by a pivotal multicenter clinical study (NCT02749071), which took place in 2016–2019 ($n = 161$) across 18 sites in the USA and three sites in Europe. However, this study was either terminated or paused. As no results of the pivotal study have been published, only the results of two initial pilot studies are summarized in Table 2.[22–25]

Both clinical studies evaluated the effect of LES-ES on GERD symptoms during long-term follow-up of up to 4 years. In one clinical study (NCT02441400), GERD symptom score, assessed using the gastroesophageal reflux disease health-related quality of life (GERD-HRQL, a self-completed subject questionnaire for heart-

Table 1. Search keywords for Medline (Ovid), Embase, and PubMed

LES-ES	
Medline and Embase	“electrical stimulation” [MESH] AND (“GERD*” OR “GORD*”)
PubMed	(("electrostimulated"[All Fields] OR "electrostimulating"[All Fields] OR "electrostimulation"[All Fields] OR "electrostimulations"[All Fields] OR "electrostimulator"[All Fields] OR "electrostimulators"[All Fields] OR ("electric stimulation therapy"[MeSH Terms] OR ("electric"[All Fields] AND "stimulation"[All Fields] AND "therapy"[All Fields]) OR "electric stimulation therapy"[All Fields] OR ("electrical"[All Fields] AND "stimulation"[All Fields] AND "therapy"[All Fields]) OR "electrical stimulation therapy"[All Fields])) AND ("esophageal sphincter, lower"[MeSH Terms] OR ("esophageal"[All Fields] AND "sphincter"[All Fields] AND "lower"[All Fields]) OR "lower esophageal sphincter"[All Fields] OR ("lower"[All Fields] AND "esophageal"[All Fields] AND "sphincter"[All Fields])) AND ("gerd*"[All Fields] OR "gord*"[All Fields] OR "gastroesophageal reflux"[All Fields] OR "gastro-oesophageal reflux"[All Fields]))
TEA	
Medline and Embase	(‘transcutaneous electrical acustimulation’ [MESH] OR ‘transcutaneous electrical acupoint stimulation’ [MESH] or ‘TEA’ [MESH]) AND (‘GERD’ [MESH] OR ‘GORD’ [MESH])
PubMed	(("transcutaneous electrical acustimulation"[All Fields] OR "transcutaneous electrical acupoint stimulation"[All Fields]) AND ("gerd*"[All Fields] OR "gord*"[All Fields] OR "gastroesophageal reflux"[All Fields] OR "gastro-oesophageal reflux"[All Fields])
MA	
Medline and Embase	‘acupuncture’ [MESH] AND (‘GERD’ [MESH] OR ‘GORD’ [MESH] or ‘gastroesophageal reflux’ [MESH])
PubMed	(("acupunctural"[All Fields] OR "acupuncture"[MeSH Terms] OR "acupuncture"[All Fields] OR "acupuncture therapy"[MeSH Terms] OR ("acupuncture"[All Fields] AND "therapy"[All Fields]) OR "acupuncture therapy"[All Fields] OR "acupuncture's"[All Fields] OR "acupunctured"[All Fields] OR "acupunctures"[All Fields] OR "acupuncturing"[All Fields]) AND ("gerd*"[All Fields] OR "gord*"[All Fields] OR "gastroesophageal reflux"[All Fields] OR "gastro-oesophageal reflux"[All Fields]))
EA	
Medline and Embase	(‘electroacupuncture’ [MESH] OR ‘electrical acupuncture’ [MESH]) AND (‘GERD’ [MESH] OR ‘GORD’ [MESH] OR ‘gastroesophageal reflux’ [MESH])
PubMed	(("electroacupuncture"[MeSH Terms] OR “electrical acupuncture"[MeSH Terms]) AND ("gerd*"[All Fields] OR "gord*"[All Fields] OR "gastroesophageal reflux"[All Fields] OR "gastro-oesophageal reflux"[All Fields]))

EA, electroacupuncture; GERD, gastroesophageal reflux disease; GORD, gastroesophageal reflux disease; LES-ES, lower esophageal sphincter electrical stimulation; MA, mechanical acupuncture; MeSH, medical subject headings; TEA, transcutaneous electrical acustimulation.

burn, regurgitation, dysphagia and their influence on quality of life),[26] significantly decreased from 41 at baseline to 8.5 after LES-ES, a 79.27% decrease. Another clinical study (NCT01578642) also demonstrated significant improvements in GERD symptoms when comparing GERD-HRQL in the LES-ES arm vs. the PPI arm vs. individuals off-PPI vs. baseline. In the clinical study (NCT01578642), quality of life was measured using the 12-item short form survey (commonly known as the SF12) score, a health-related quality of life questionnaire consisting of 12 questions across eight domains,[27] with significant improvement in mental health at 6 months post LES-ES therapy observed vs. baseline: a 17.78% improvement for subjects on PPIs, and a 10.2% improvement for subjects off PPIs. Improvement in physical health at 6 months post LES-ES therapy vs. baseline was significant only for the off-PPI arm (at 18.68%). Patient satisfaction improved, with no subjects reportedly being dissatisfied with the management of their condition at 24 months. At 12 months, no subjects reported regular use of PPIs; while at 24 months, 76% reported no use, 14% reported occasional use, and 10% reported regular use. Outcomes suggest a sustained marked reduction in medication requirement post LES-ES therapy.

Several objective 24 h measurements of esophageal pH (distal pH, proximal pH, and DeMeester score) were reported. In measuring the percentage over 24-h, where esophageal pH was < 4 (24-h esophageal acid exposure), the NCT01578642 study[22] reported a decrease of 52.5% at the distal esophagus and 100% at the proximal esophagus. Seventy-one of the total number of subjects had either a normalized distal esophageal pH or a 50% or more decrease in distal acid exposure. The DeMeester score was reduced by 56.01% at 24 months. In the NCT02441400 study,[25] the distal 24-h acid exposure was reduced by 49.5% at 6 months and 67.3% at 12 months relative to baseline. Seventy-seven percent of patients had either normal or an over fifty percent reduction in proximal acid exposure.

In the NCT01578642 study, LES pressure, a key component of GERD pathophysiology, increased significantly by 52.43% ($p < 0.001$) post intervention at 3 months.[23] It is important to note that the results at the 2-year follow-up (Table 2) are shown as representative for the whole follow-up period, due to identical *p*-values being reported at other follow-up time points (1, 3, and 4 years), despite a gradually diminishing number of subjects at each follow-up time point due to attrition.

The main drawback of LES-ES therapy was the risk of surgery-related complications. Among 25 implanted subjects in the NCT01578642 study, three experienced transient postoperative nausea or vomiting that resolved within 1 day. Two experienced transient postoperative pain or discomfort in the shoulder that resolved within 1 day, and one developed a superficial skin infection at the IPG subcu-

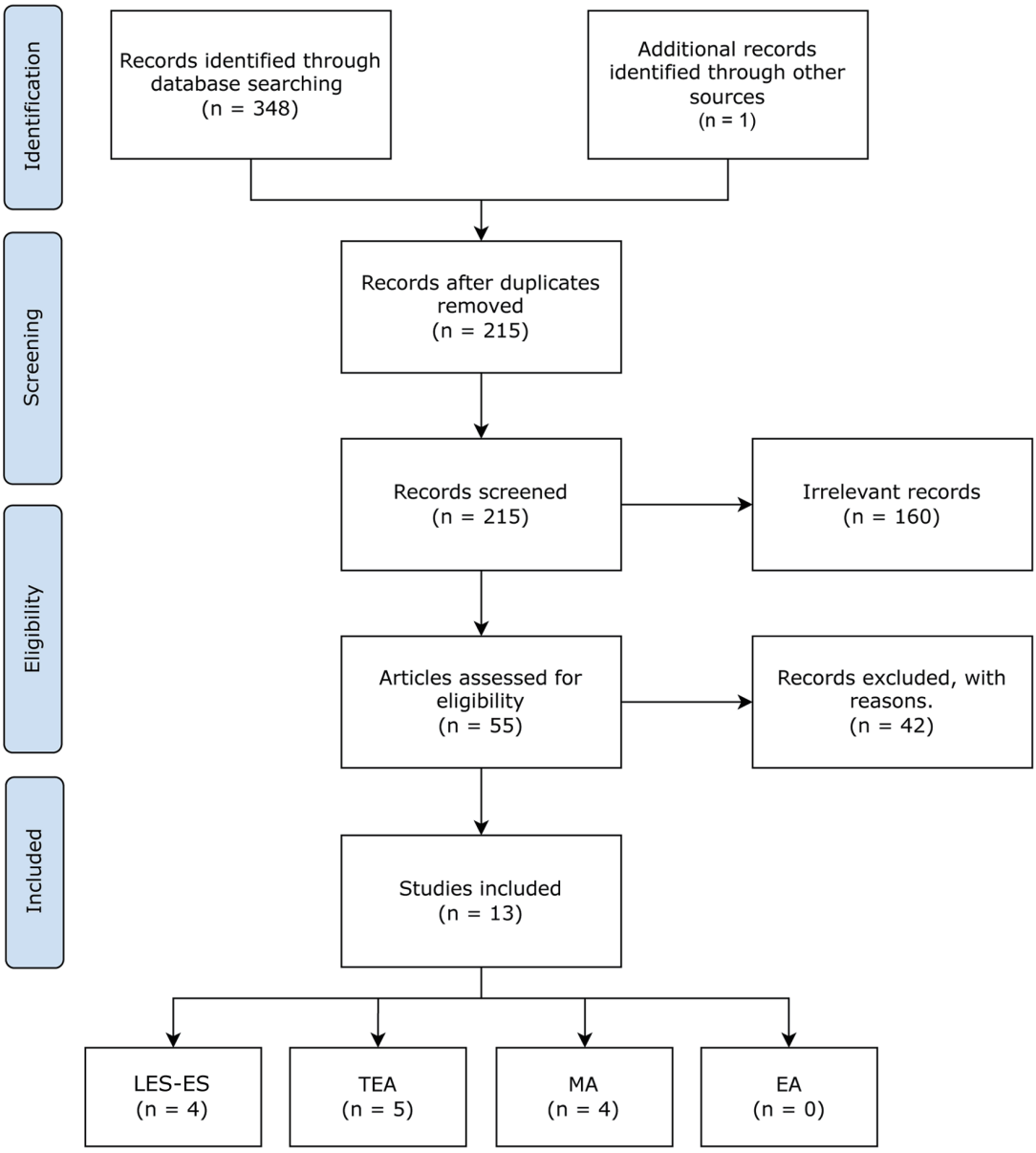

Fig. 1. PRISMA flow diagram of study selection. EA, electrical acupuncture; LES-ES, lower esophageal sphincter electrical stimulation; MA, manual acupuncture; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TEA, transcutaneous electrical acustimulation.

taneous pocket.[22] Among 37 implanted subjects in the NCT02441400 study, one had transient postoperative subcutaneous emphysema that resolved without intervention, none had esophageal obstruction, perforation, inability to belch or vomit, and the median hospital stay was 2 days.[24] Overall incidence of surgery-related adverse effects was comparable to that of other surgeries for implantable neuromodulation devices, such as those for sacral nerve stimulation.[28]

TEA studies

In all TEA studies, bipolar electrical stimulation was delivered transcutaneously through two skin surface electrodes at the ST36 acupoint on the leg, either alone or together with the PC6 acupoint on the wrist. Sham electrodes were placed 2–20 cm away from the acupoints. The skin electrodes were connected to the TEA device (MedKinetic, Ningbo, China). The TEA parameters include a frequency of 25 Hz, current amplitude 2–10 mA (at maximal level tolerated by the subject), pulse width of 500 μs, train on duration of 2 seconds and off duration of 3 seconds, session duration of 30 or 60 m, and 1 or 2 sessions per day. Acute TEA was performed by study investigators at the clinic, and chronic TEA was self-administered.[29–33] Results of six identified clinical studies are summarized in Table 3.[29–33]

TEA had significant beneficial effects on GERD symptoms, demonstrated through the gastroesophageal reflux disease questionnaire (GERDQ, a self-completed subject questionnaire for heartburn, regurgitation, sleep disturbance, use of over-the-counter medication for heartburn/regurgitation, upper stomach pain, and nausea)[26] and GERD-HRQL in three evaluated 4-week studies.[31–33] Zhang *et al*.[31]

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Table 2. Summary of clinical studies evaluating the effects of LES-ES therapy on the GERD symptoms and pathophysiology

Clinical trial NCT number	Subjects	Daily LES-ES duration, study duration	GERD symptoms					GERD pathophysiology	Reference
			GERD-HRQL and QOL	Distal pH < 4 (%)	Proximal pH < 4	De-Meester score	PPI use	LESEEP (at 3 mo.) (mmHg)	
NCT01578642	21	6 h, 2 years	**GERD-HRQL** B- on PPI 9.0 6 mo- 2.0 ***p* < 0.001** B- off PPI 23.5 6 mo- 2.0 ***p* < 0.001** **SF12 - mental** B- on PPI 45 6 mo 53 ***p* < 0.05** B- off PPI 49 6 mo 54 ***p* < 0.01** **SF12- physical** on PPI vs 6 mo ***p* > 0.05**[a] B- off PPI 45.5 6 mo- 54 ***p* < 0.01** **Patient satisfaction increased** B- off PPI 92% B- on PPI 71% 24 mo- 0%	B- 10.1 24 mo- 4.8 ***p* < 0.005** 71% subjects pH normalized or a decrease in pH by 50% or more	B- 0.4 24 mo- 0 ***p* < 0.005**	B- 36.6 24 mo- 16.1 ***p* < 0.002**	B- 1 OD post- 0.1 pills or less per day ***p* < 0.001** 12 mo- 95% PPI not required 1-reported occasional use. 0- regular use 24 mo 76% PPI not required 14% occasional 10% regular use	B- 10.3 3 mo- 15.7 ***p* <0.005**	22,23
NCT02441400	37	6 h, 2 years	B- 41 24 mo- 8.5 ***p* < 0.001**	B- 10.1% 6 mo- 5.1% 12 mo- 3.3% ***p* < 0.001** Either normalized or showed > 50% improvement in 77% patients at 12 mo		N/T	N/T	N/T	24,25

GERD pathophysiology was measured as *p*-value of LES end expiratory pressure. [a]lack of significance. B, baseline; GERD, gastroesophageal reflux disease; GERD-HRQL, GERD Questionnaire including heartburn, regurgitation and quality of life; LES, lower esophageal sphincter; LES-ES, LES electrical stimulation; LESEEP, LES end expiratory pressure; mo, month; NCT, national clinical trial; N/T, not tested; OD, once daily; PPI, proton pump inhibitor; SF12, 12-item short form survey.

Table 3. Summary of five clinical studies evaluating the effects of TEA and sham TEA therapy

Subjects in the TEA and sham TEA arms	Daily TEA duration, study duration	GERD Symptoms		GERD pathophysiologies					Reference
		GERDQ	GERD-HRQL	EM-DCI (mmHg.s.cm)	LESP (mmHg)	GSW (% normal slow waves)	DTSS	HF HRV	
30 ST36+PC6, 30 sham	0.5 h, 1 day	N/T	N/T	N/T	N/T	55.1 ± 3.7[a] 63.2 ± 4.2[b] $p < 0.05$	42.0 ± 3.3[a] 31.0 ± 3.5[b] $p < 0.01$	0.42 ± 0.03[a] 0.49 ± 0.04[b] $p < 0.05$	29
45 ST36, 15 sham	0.5 h, 1 day	N/T	N/T	$p > 0.05$[c]	*21.9*[d] **31.9**[d] 45.66% increase[d] $p < 0.001$	N/T	N/T	*0.27 ± 0.14*[d] **0.36 ± 0.18**[d] 33.33% increase[d] $p < 0.001$	30
26 ST36, 25 sham	0.5 h, 1 day	N/T	N/T	328.53 ± 387.18[a] 651.54 ± 472.99[b] $p < 0.001$ *300.25 ± 515.48*[d] **651.54 ± 472.99**[d] 117% increase[d] $p < 0.001$	*15.30 ± 7.44*[d] **22.84 ± 6.91**[d] 49.28% increase[d] $p < 0.001$	N/T	N/T	0.24 ± 0.06[a] 0.30 ± 0.08[b] $p < 0.001$	33
15 ST36+PC6, 15 sham	2 h, 4 weeks	9.3 ± 2.7[a] 7.1 ± 1.2[b] $p < 0.05$ *10.7 ± 2.2*[d] **7.1 ± 1.2**[d] 33.64% decrease[d] $p < 0.001$	7.2 ± 5.9[a] 3.1 ± 3.8[b] $p < 0.05$ *6.7 ± 3.0*[d] **3.1 ± 3.8**[d] 53.73% decrease[d] $p < 0.05$	*373 ± 194*[d] **593 ± 258**[d] 58.98% increase[d] $p < 0.05$	*Chronic TEA*[c] $p > 0.05$[c]	69.7 ± 10.1%[a] 81.8 ± 10.2% (Fed state)[b] $p < 0.05$ *67.5 ± 11.4%*[d] **81.8 ± 10.2%**[d] 21.19% increase[d] $p < 0.01$	42.7 ± 12.8[a] 59.3 ± 24.3[b] $p < 0.05$	0.34 ± 0.16[a] 0.50 ± 0.17 (acute)[b] $p < 0.05$ *0.32 ± 0.19*[d] **0.50 ± 0.17**[d] 56.25% increase[d] $p < 0.001$	31
5 ST36+PC6, 5 sham	1 h, 4 weeks	$p < 0.05$ Values not specified	N/T	N/T	52.2% increase[d] $p < 0.01$	N/T	N/T	N/T	32
26 ST36, 25 sham	3 h, 4 weeks	*12.31 ± 2.25*[d] **7.71 ± 1.60**[d] 37.36% decrease[d] $p < 0.001$ **Improves QOL** $p < 0.001$ for physical function, vitality, general health $p < 0.05$ for bodily pain, social functioning, emotional and mental health	N/T	N/T	N/T	N/T	N/T	N/T	33

Five clinical studies were included. To enable comparison with other acute and chronic studies, one paper[30] is presented twice to report results immediately post TEA and at 4 weeks post TEA. [a]sham TEA data; [b]TEA data; [c]lack of significance; [d]amount (%) and direction of change in the TEA arm comparing pre-therapy (italic) and post-therapy (bold). DTSS, dyspeptic total symptom score; EM-DCI, esophageal motility distal contractile integral; GERDQ and GERD-HRQL, GERD questionnaires including heartburn, regurgitation and quality of life; GSM, gastric slow waves; HF HRV, high frequency heart rate variability; LESP, lower esophageal sphincter pressure; N/T, not tested; QOL, quality of life; TEA, transcutaneous electrical acustimulation.

Table 4. Summary of two clinical studies evaluating the effects of MA on GERD symptoms and pathophysiology

Subjects in the MA and PPI arms	Daily MA duration, MA sessions per week, study duration	GERD symptoms			GERD pathophysiology		Reference
		GERDSC	SF36	pH < 4	LESP	DCI	
15 ST36+PC6+L3+CV12+CV17 15 PPI only	25 min, 2.5/week, 4 weeks	$p < 0.001$	$p < 0.05$	N/T	N/T	N/T	34
30 ST36+PC6+CV12+SP6 30 PPI+mosapride	25 min, 2.5/week, 4 weeks	$p < 0.01$	N/T	$p < 0.01$	N/T	N/T	35
32 ST36+ PC6+ CV10+ CV12+ CV13+ BL17+ BL18+ BL20 30 PPI only	Unknown number of sessions Unknown time of each session Study duration- 4 weeks total	$p < 0.0001$	N/T	N/T	N/T	N/T	36
33 ST36 + PC6 + SP4 35 Sham ST6 + PC6 + SP4	Unknown number of sessions Unknown time of each session Study duration- 4 weeks total	(GERDQ) $p < 0.01$ in the first week, then score returned to baseline	N/T	$p > 0.05$[c]	22.02 ± 10.03[a] 25.06 ± 11.48[b] $p > 0.05$[c]	1001.00[a] 1223.70[b] $p \leq 0.01$	37

[a]before MA, [b]after MA, [c]lack of significance. DCI, distal contractile integral; GERDQ and GERD-HRQL, GERD questionnaires including heartburn, regurgitation, and quality of life; MA, mechanical acupuncture; N/T, not tested; PPI, proton pump inhibitor; SF36, short form 36-item survey for quality of life.

and Ma *et al*.[33] reported a significant reduction of post-TEA GERDQ symptom scores of 33.6% and 37.3% respectively. The GERD-HRQL symptom score was reduced by 53.7% after 4 weeks of TEA treatment. Subjects in the sham TEA arm had no significant beneficial effects on GERD symptoms in any of the studies.

TEA also resulted in significant improvement of key GERD pathophysiologies. Distal esophageal motility (EM) was assessed with the distal contractile integral (EM-DCI), a parameter quantifying distal esophageal contraction. In Zhang *et al*.,[31] EM-DCI was increased by 58.98% at 4 weeks post TEA. Ma *et al*.[33] observed the effects of acute TEA, whereby EM-DCI was increased by 117%. The LES pressure was increased during TEA by 41.94%,[31] 45.66%[30] and 49.28%[33] post acute TEA, and 52.2% post chronic TEA.[32] Gastric motility was assessed by gastric slow waves (GSW), measured using surface electrogastrography. An increase in the percentage of normal slow waves suggests improved gastric motility. Zhang *et al*.[31] reported a 21.19% increase in the percentage of GSW post chronic TEA. The increase in the percentage of GSW was significant in the TEA groups,[29,31] but not the sham TEA groups. Dyspepsia was measured with a drink-induced dyspeptic total symptom score (DTSS). A significant reduction in DTSS was seen with TEA but not with sham TEA.[29,31] These improvements were hypothesized to be mediated by enhanced parasympathetic or vagal activity assessed by the high frequency component in the power spectrum of the heart rate variability signal derived from the electrocardiogram. Three studies observed enhanced parasympathetic activity in TEA relative to sham TEA and/or baseline.[29,31,32] Zhang *et al*.[31] demonstrated a 56.25% increase in the high frequency component during TEA, while Liu *et al*.[30] showed a 33.33% increase post-acute TEA, relative to values measured at baseline.

MA studies

In all MA studies, mechanical stimulation was delivered percutaneously via a sterile acupuncture needle (0.3 mm diameter and 40 mm length) inserted at selected acupoints to a depth of 15–30 mm while the subject was supine on a massage type table.[34] The studies included in this review used the PC6 and ST36 acupoints, as described in the TEA section. The first study used the L3 acupoint on the foot and CV12 and CV17 acupoints on the chest.[34] The second study also used the CV12 acupoint on the chest and SP6 acupoint on lower leg (Table 4).[34–37]

MA had significant beneficial effects on GERD symptoms. The gastroesophageal reflux disease self-completed subject questionnaire for duration, frequency, and severity or heartburn, regurgitation, chest pain, and dysphagia (GERDSC, a self-completed subject questionnaire for duration, frequency, and severity or heartburn, regurgitation, chest pain, and dysphagia)[38] improved by 74.72% immediately post acupuncture (from 18.83 ± 6.57 to 4.76 ± 7.58).[34] Improvement in individual parameters were reported by Dickman *et al*.[34] at 4 weeks post acupuncture compared to baseline. Improvements were 82.2% in daytime heartburn, 80.1% in night-time heartburn, 74.9% in acid regurgitation, 55.6% in dysphagia, and 82.4% in chest pain. At 4 weeks post MA, differences in the heartburn ($p < 0.001$) and chest pain ($p < 0.05$) scores in acupuncture subjects and those who were treated with double-dose PPIs were significant. Trinh *et al*.[36] observed the effects of thread-embedding acupuncture in symptom resolution in patients with GERD. The GERDSC score was significantly lower at week 2 ($p < 0.01$) and week 4 ($p < 0.0001$). Dickman *et al*.[34] measured quality of life with the SF36, a self-completed subject questionnaire.[39] The study revealed significant improvements in all parameters, 20.2% in physical function, 15.2% in bodily pain, 20.4% in general health, 12.7% in social function, 10.4% in role-emotion, and 2.8% in mental health. Zhang *et al*.[35] observed objective 24-h change in esophageal pH. The percentage of total time of reflux with pH < 4 was reduced significantly immediately after acupuncture from 16.27 ± 9.47 to 7.29 ± 8.20, a 55.2% reduction in esophageal pH exposure. Key GERD pathophysiologies were assessed in only one of these studies,[37] with significant increases in LES pressure ($p < 0.05$) and esophageal contraction (DCI, $p < 0.01$). However, this study demonstrated improvements in GERD symptoms only in the first week after intervention ($p < 0.001$). After the second week post follow-up, scores in GERDQ returned to baseline. This reveals an avenue for further research, in particular focusing on the lasting effects of MA in GERD symptom alleviation, as well as more studies of key pathophysiologies involved in GERD.

Discussion

This systematic review evaluated the efficacy, mechanisms and safety of three neuromodulation methods (LES-ES, TEA, MA)

Table 5. Summary of advantages and advantages of three evaluated neuromodulation methods for GERD treatment

Neuromodulation method	Advantages	Disadvantages
LES-ES	Targets LESP, an underlying GERD pathophysiology; "Implant it and forget it" approach of achieving high patient adherence in regular therapy use.	High cost and extensive clinical resources involved in implantation procedure; Risks associated with implantation surgery; Not FDA approved.
TEA	Targets three underlying GERD pathophysiologies: esophageal motility, gastric motility, parasympathetic activity; Non-invasive; Inexpensive; Can be used at home.	Requires patient to learn the locations of GERD-related acupoint(s), at least ST36.
MA	Employs traditional Chinese medicine techniques, which may be favored by a subset of patients; Minimally-invasive; Inexpensive.	No information is available about the long-term effects on underlying GERD pathophysiologies; May not be available in some Western communities; Requires a visit to an acupuncturist.

EA, electroacupuncture; GERD, gastroesophageal reflux disease; FDA, USA Food and Drug Administration; LES-ES, lower esophageal sphincter electrical stimulation; MA, mechanical acupuncture; TEA, transcutaneous electrical acustimulation.

in patients with GERD symptoms. All studies demonstrated significant beneficial effects on GERD symptoms, including the self-completed subject questionnaire (e.g., GERDQ, GERD-HRQL, and GERDSC), objective 24-h measurement of esophageal pH (distal and proximal pH, and DeMeester score), and patient-reported PPI use. In TEA studies,[29–33] ST36 was the most commonly used acupoint. In MA studies,[34,35] ST36+PC6+CV12 was the most common acupoint combination.

Of the GERD pathophysiologies, LES pressure was evaluated in a subset of LES-ES and TEA studies, but not in MA studies. In the LES-ES clinical trial NCT01578642,[22,23] LES pressure increased significantly after 3 months of therapy, but in the TEA studies,[30,32,33] the LES pressure increase was significant predominantly in the acute setting but not in one study[31] after 4 weeks of therapy. This suggests that direct stimulation of LES in LES-ES was more beneficial in improving LES pressure relative to TEA. TEA studies evaluated other key GERD pathophysiologies, including EM, gastric motility, and parasympathetic activity. Most of these studies observed significant improvement after TEA, both in the short and long-term (defined as the 4-week follow-up). This suggests that TEA targets these underlying GERD pathophysiologies. None of the evaluated neuromodulation methods were associated with severe adverse effects. Thus, they can be considered safe for long-term use.

Comparing and contrasting three evaluated neuromodulation methods for GERD treatment, there are several advantages and advantages associated with each method, which are outlined in Table 5.

More clinical studies need to be conducted to further evaluate the efficacy of the above three evaluated neuromodulation methods. The current outlook based on available studies appears positive, as all three methods result in improved GERD symptoms. In addition, LES-ES and TEA result in improved GERD pathophysiologies, while the effect of MA on GERD pathophysiologies is yet to be ascertained. The mechanisms targeted are in contrast with existing medications such as PPIs, which aim for symptom alleviation without any beneficial effects on key GERD pathophysiologies.[31,40]

LES-ES, TEA and/or MA may be prescribed as complementary therapies to lifestyle modifications. This may lead to longer-lasting and more sustainable results with fewer side effects, compared with medications alone, such as prokinetics.[18] For example, deep breathing, in combination with TEA, alleviates GERD symptoms[21] through targeting a number of GERD pathophysiologies: (1) increase parasympathetic activity,[41,42] thus mediating anti-hyperalgesia effects through cholinergic anti-inflammatory pathways, providing pain relief[43]; (2) increases crural diaphragm tone, thus increasing esophagogastric junction pressure, along with a decrease in the number and cumulative duration of transient LES relaxations,[44,45] thus improving the anti-reflux barrier; (3) increases LES pressure,[46] thus reducing gastroesophageal reflux. The use of TEA or MA can also replace surgical procedures for enhancing LES pressure and avoid post-surgical complications.

The availability of neuromodulation therapies provides clinicians with valuable options for optimizing the treatment for each GERD patient. For example, if PPI efficacy is suboptimal, clinicians may consider TEA or MA as an adjunct treatment. If the disease progresses to an extent where a largely invasive surgical procedure, such as Fundoplication, becomes a consideration for enhancing the LES pressure, they may instead opt for a reversible and less invasive LES-ES procedure.

It is of note that this review included only papers in English. Thus, a study limitation is the exclusion of results available from papers published in languages other than English. Nonetheless, results of the most updated and current English studies have been included, representing one of the key strengths of this review.

Conclusions

In conclusion, whilst none of the examined neuromodulation therapies targets all of the key pathophysiological mechanisms implicated in GERD, there is strong evidence that LES-ES, TEA, and potentially MA are effective therapies for treating many of the underlying GERD pathophysiologies, and are valuable options for individualized GERD treatment. As the sample sizes of the included studies were small, the results of this review support the conduct of additional, large studies to allow for a definitive conclusion on the efficacy of neuromodulation for GERD.

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Conflict of interest

Jiande Chen has been an Executive Editor-in-Chief of the *Journal of Translational Gastroenterology* since January 2023. Victor Pikov is the Founder and CEO of Medipace Inc. The other authors declare no other conflict of interests.

Author contributions

Conceptualization (JYW, JC), methodology (JYW, JC), writing and original draft preparation (JYW), draft review and editing (JYW, VP, JC), data analysis (JYW), resources (JYW, VP, JC), supervision and funding acquisition (JC). All authors have contributed significantly to the intellectual content of this review and agreed to the published version of the manuscript.

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