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Review Article

Review Article

Efficacy of vagus nerve stimulation in gastrointestinal disorders: a systematic review

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Abstract

Dysfunction of the vagus nerve has been suggested as a contributing factor in various gastrointestinal disorders, prompting interest in vagus nerve stimulation (VNS) as a non-pharmacological therapy. We performed a systematic review to determine the efficacy of invasive and non-invasive VNS in gastrointestinal disorders, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), functional dyspepsia (FD), functional constipation, gastroesophageal reflux disease, and gastroparesis. We applied a systematic search of the literature in the PubMed, Embase, Web of Science, and Cochrane Library databases in order to identify studies comparing VNS with an adequate control condition (sham stimulation) in patients with gastrointestinal disorders. The primary outcome was adequate symptom relief. Methodological quality was evaluated using the revised Cochrane risk-of-bias tool. Meta-analyses were not performed due to study heterogeneity. Seven randomized controlled trials investigating non-invasive VNS were included, with a total of 644 patients: FD ($n = 426$), IBD ($n = 22$), IBS ($n = 92$), and abdominal pain-related functional gastrointestinal disorder ($n = 104$), with a mean age ranging from 15 to 65 years. Non-invasive VNS significantly improved symptoms across all subsets of patients, as measured differently according to disease type, compared with sham stimulation. Adverse events, if reported, were low, with no serious complications. Putative mechanisms of action were assumed to be related to anti-inflammatory and anti-nociceptive effects. Non-invasive VNS holds promise as a safe therapy for diverse gastrointestinal disorders. However, these findings are derived from studies with small sample sizes and provide preliminary insights. Further research is warranted to define its exact position within the therapeutic arsenal.

Keywords: vagus nerve stimulation; functional gastrointestinal disorders; gut–brain axis; inflammatory bowel disease; irritable bowel syndrome

Introduction

The vagus nerve

The vagus nerve is the main contributor to the parasympathetic nervous system [1]. Comprising both afferent (80%) and efferent (20%) nerve fibers, it enables a crucial function in the regulation of gastrointestinal sensitivity, motility, and immune function [2, 3]. Vagal afferents relay signals "up" from the gut to the brain and provide information about the inner organ's status through its innervation of the digestive tract [4], including the transmission of peripheral sensations such as pain, thereby fulfilling a fundamental role in visceral nociception [5, 6]. Concurrently, the vagal efferent response modulates preganglionic parasympathetic neurons of the dorsal motor nucleus of the vagus and/or preganglionic sympathetic neurons of the spinal cord, influencing gastrointestinal motility, immune function, and gastrointestinal nociception [3] (Figure 1). The communication network of the vagus nerve is closely intertwined with the enteric nervous system (ENS), resulting in a bidirectional flow of information known as the brain–gut axis, which is essential for maintaining physiological homeostasis [1].

The role of vagal dysfunction in gastrointestinal disorders

Dysfunction of the vagus nerve has been implicated in various gastrointestinal disorders, including those characterized by gut–brain interaction and chronic inflammation [4]. This dysfunction may manifest as a decrease in vagal tone, indicative of dysautonomia, and has been observed in conditions such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) [7, 8]. However, evidence regarding autonomic imbalance in IBS is conflicting and may vary depending on the predominant bowel pattern [9, 10]. The balance between the parasympathetic and sympathetic nervous systems, reflected by heart rate variability—an easily measurable autonomic parameter—is disrupted during acute stress, where sympathetic activation dominates [3, 11]. Although this balance typically returns after acute stress, it can remain disrupted for prolonged periods under chronic stress conditions, as observed in several gastrointestinal diseases (i.e. IBD, IBS) [12, 13]. Furthermore, an imbalance between the autonomic nervous system and the hypothalamic-pituitary-adrenal axis has been noted in these diseases and is believed to result from

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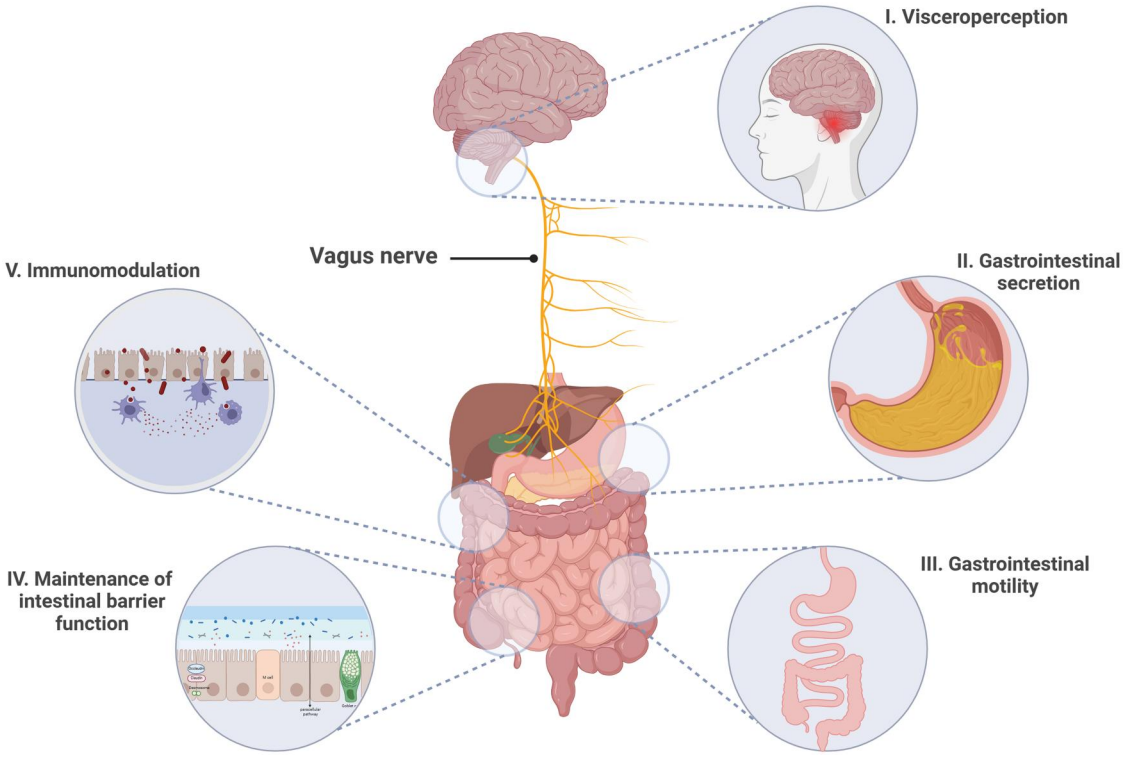

Figure 1. Role of the vagus nerve in the gastrointestinal tract. This image is created with BioRender.com.

dysregulation between the prefrontal cortex and the amygdala, both innervating areas of the central autonomic network [8]. Therefore, abnormal vagal tone could be both a cause and a consequence of such imbalances [3]. Considering this abnormal vagal tone and the widespread innervation of the vagus nerve of the gastrointestinal tract, along with its primary involvement in parasympathetic regulation of inflammation and motility, it could serve as a potent target for addressing gastrointestinal dysfunction and associated symptoms, including abdominal pain. Hence, vagus nerve stimulation (VNS) is becoming recognized as a potential non-pharmacological therapeutic approach for disorders involving gut–brain interaction [4].

Vagus nerve stimulation

VNS is a form of bioelectric medicine that uses electrical impulses to stimulate the vagus nerve, promoting organ functions and health with fewer adverse effects compared with drugs [1, 14, 15]. Based on the route of administration, VNS therapy can be categorized into two main types: invasive and non-invasive (Figure 2). Invasive VNS (iVNS) requires surgical implantation of electrodes on the cervical vagal nerve, connected to a pulse generator in the left ipsilateral infraclavicular pocket, facilitating intermittent electrical impulses to activate both afferent and efferent vagus nerve fibers [4]. iVNS is an established therapy for refractory epilepsy. Unlike iVNS, transcutaneous VNS (tVNS) permits non-invasive stimulation of the vagus nerve without the need for surgical procedures. Non-invasive VNS can be administered via transcutaneous stimulation of the cervical vagus on the neck [transcutaneous cervical vagus nerve stimulation (tcVNS)] or through stimulation of the auricular branch of the vagus nerve [transcutaneous auricular vagus nerve stimulation (taVNS)] by applying surface electrodes to the auricular concha [1]. The auricular branch being exclusively afferent in nature, taVNS allows afferent but not direct efferent stimulation, as opposed to tcVNS, which can elicit both direct afferent and efferent stimulation. Major advantages of non-invasive VNS include minimal side effects, although long-term effects have not been evaluated, and flexible adjustment of stimulation parameters to meet individual needs [4]. Although cost-effectiveness remains to be established, VNS may offer a more economically attractive alternative to many pharmacological therapies such as biologicals in treating IBD [14]. Non-invasive auricular percutaneous electrical nerve field stimulation (PENFS) represents another modality of neuromodulation, using specific stimulation parameters with miniature needle electrodes penetrating the skin of the external ear to affect the peripheral cranial neurovascular bundle (V, VII, IX, and X), including vagal nerve afferents projecting to brainstem nuclei such as the nucleus tractus solitarius (NTS) [16].

Mechanism of action of VNS

Previous studies involving VNS have demonstrated encouraging clinical responses in neurological disorders (i.e. epilepsy) [17], psychiatric disorders (i.e. treatment-resistant anxiety disorders) [18], and also in certain gastrointestinal disorders [1, 4]. Notably, VNS holds potential in gastrointestinal disorders by targeting nociceptive pathways and inflammation through its putative dual anti-nociceptive and anti-inflammatory properties [1, 4]. In the realm of visceral nociception, VNS is believed to restore homeostasis in gut–brain signaling and modulate intrinsic pain neuroregulatory processes, including peripheral and central sensitization [4] (Figure 3). This mechanism is particularly relevant for gastrointestinal conditions marked by chronic abdominal pain and heightened visceral sensitivity. This increased perception can be related either to inflammation, as seen in IBD, or to dysfunction of the gut–brain interaction, formerly known as functional gastrointestinal disorders, such as IBS and functional dyspepsia (FD), where no identifiable biochemical or structural abnormalities are present [4]. The therapeutic effects of VNS in inflammatory diseases are assumed to be related to dual anti-inflammatory mechanisms: stimulation of the cholinergic anti-inflammatory reflex pathway

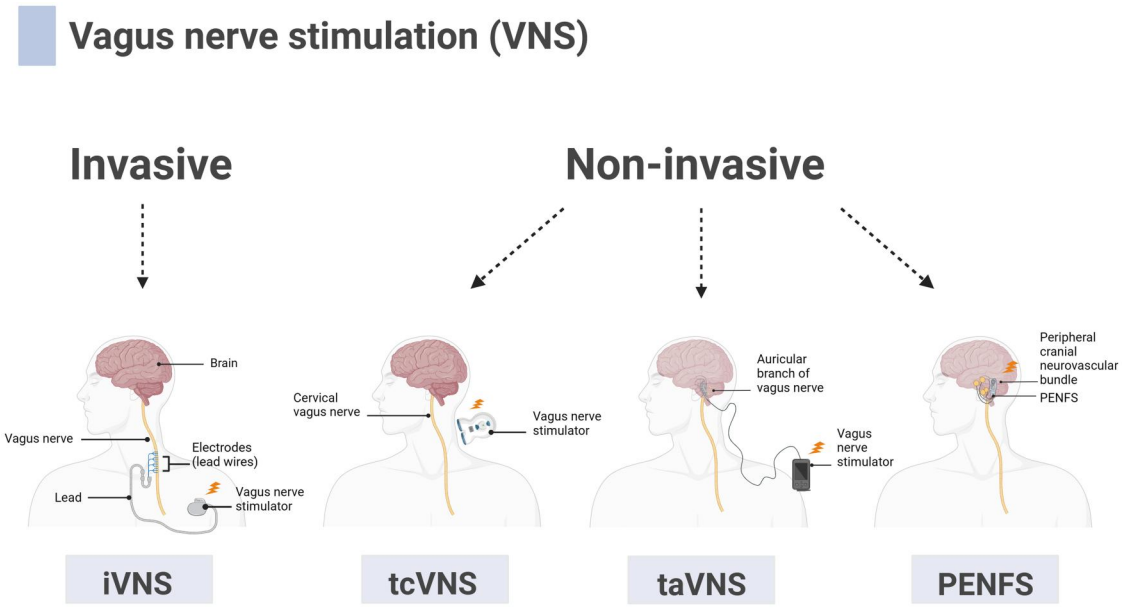

Figure 2. Different modalities of VNS. Based on the route of administration, VNS therapy can be categorized into two main types: invasive (iVNS) and non-invasive VNS (tVNS), including tcVNS, taVNS, and PENFS. This image is created with BioRender.com. VNS = vagus nerve stimulation, iVNS = invasive VNS, tVNS = transcutaneous VNS, tcVNS = transcutaneous cervical VNS, taVNS = transcutaneous auricular VNS, PENFS = percutaneous electrical nerve field stimulation.

through vagal efferents, along with the activation of the hypothalamic-pituitary-adrenal axis by vagal afferents [19, 20]. More recently, experimental evidence suggests VNS is also likely involved in the anti-inflammatory afferent pathway, which entails two distinct lines of immune-mediated signaling pathways from the vagal ganglia to the NTS [21], as illustrated in Figure 4. By enhancing vagal tone and mitigating the excessive release of tumor necrosis factor-alpha (TNF-α) and other pro-inflammatory cytokines, VNS holds potential for fostering resilience [1].

Aim of study

The primary aim of this systematic review was to investigate the clinical efficacy of both invasive and non-invasive VNS in gastrointestinal disorders, including IBD, IBS, FD, functional constipation, gastroesophageal reflux disease, and gastroparesis. This includes a systematic search of the current literature. In addition, potential adverse events associated with such therapy were assessed, as well as putative mechanisms of action.

Methods

This systematic review included a literature search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [22], and the study protocol was registered in PROSPERO International Prospective Register of Systematic Reviews under the registration number CRD42023478497.

Search strategy

A comprehensive and systematic search was performed in the databases PubMed, Embase (Ovid), the Cochrane Library, and Web of Science (Supplementary Data). The MesH terms used were as follows: "Inflammatory Bowel Diseases" OR "Irritable Bowel Syndrome" OR "Dyspepsia" OR "Globus Sensation" OR "Constipation" OR "Gastroparesis" OR "Gastric Emptying" OR "Gastroesophageal Reflux" OR "Abdominal Pain" AND "Vagus Nerve Stimulation" OR "Transcutaneous Electric Nerve Stimulation." Duplicates were removed, and the search results were recorded using Rayyan.

Eligibility criteria

Inclusion criteria were as follows: (i) interventional studies, both randomized and non-randomized trials; (ii) including participants with a diagnosis of IBD, IBS, FD, functional constipation, gastroesophageal reflux disease, or gastroparesis; (iii) reporting about invasive or non-invasive VNS compared with sham stimulation. Both invasive and non-invasive forms of VNS were included. Non-invasive forms of VNS included taVNS, tcVNS, and PENFS. PENFS was included due to its similarity with taVNS, where the stimulation point was localized in the external ear to modulate central pathways. Furthermore, both pediatric and adult subjects were included to provide the broadest possible perspective on the efficacy of VNS, although this might increase heterogeneity.

Exclusion criteria included as follows: (i) case reports, case series, and cohort studies; (ii) animal studies; (iii) studies written in a language other than English; (iv) articles that did report interventions other than VNS; (v) articles that did make a comparison to VNS different from sham stimulation as an appropriate control condition. There were no restrictions in terms of gender, age, ethnicity, or severity of disease.

Study selection

The study selection was conducted according to two stages. First, two reviewers manually screened the titles and abstracts of the retrieved articles independently to determine whether they fulfilled the eligibility criteria. Full-text copies of potential inclusion were then obtained and screened. Disagreements were resolved through consultation with a third reviewer. Only articles that met the eligibility criteria were included and analyzed.

Data extraction

After including eligible articles, two reviewers independently conducted the process of data extraction. Data related to the

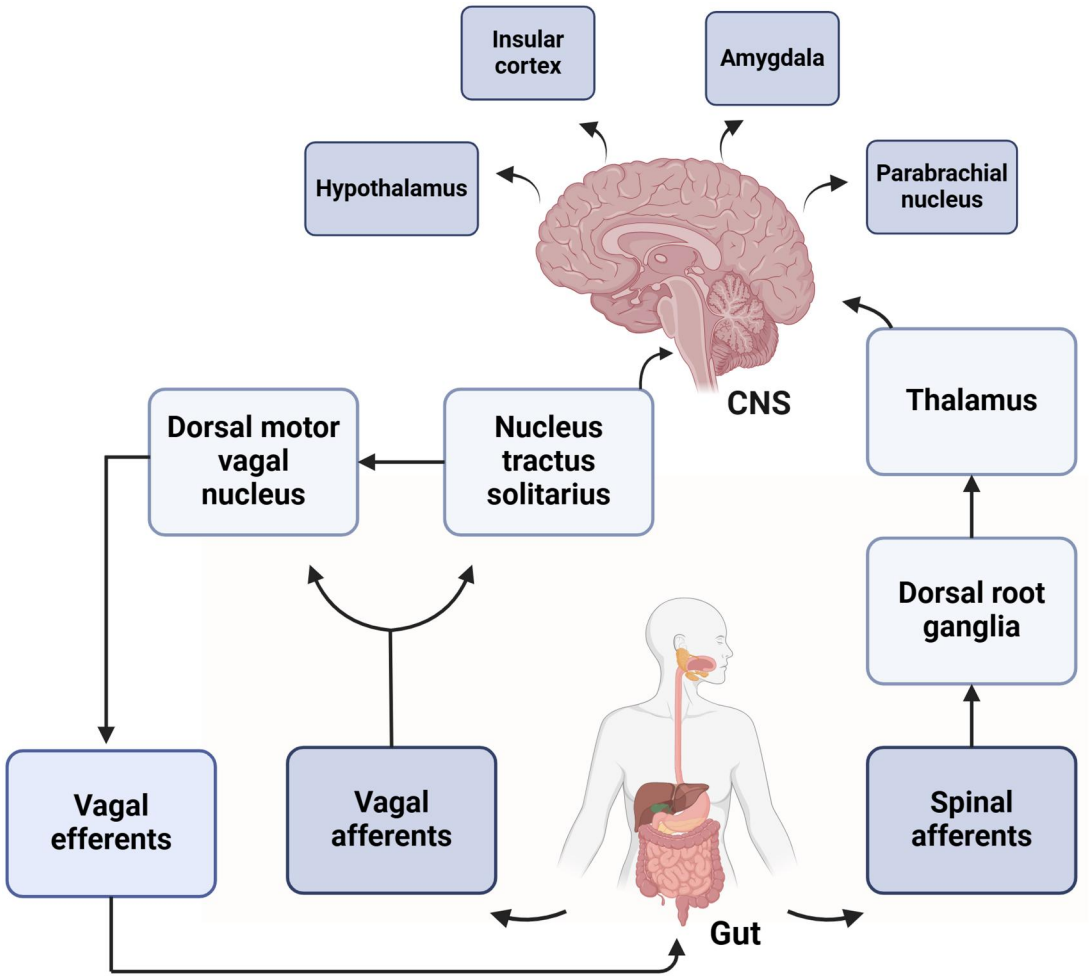

Figure 3. Mechanisms underlying visceral nociception of the digestive tract. The key neural pathways transmitting pain signals from the digestive tract to the brain encompass afferents from the spinal cord ascending through the dorsal root ganglia of the spinal cord to the thalamus and then subsequently to higher brain centers (the spinothalamic nociceptive pathway), alongside vagal afferents relaying information to the nucleus tractus solitarius in the dorsal brainstem, where they synapse with the dorsal motor vagal nucleus and with "higher" centers of the central nervous system, including the hypothalamus, amygdala, parabrachial nucleus, and the insular cortex. This image is created with BioRender.com.

study characteristics and outcome measures were abstracted into a standardized form that comprised the following information: first author, publication year, country, study design, disease, total study population, intervention, comparator, outcome, duration of follow-up, and patient characteristics (age, gender, and duration of disease). Missing information was registered as "not reported." There were no efforts made to contact the corresponding authors regarding any incomplete data.

Outcome measures

The primary outcome of the review was adequate symptom relief, defined as a clinically significant improvement of complaints, as far as these were reported in the respective studies. In other cases, the closest approximation to adequate symptom relief was considered as the primary outcome.

Secondary outcomes were anti-inflammatory effects, measured by biological markers of inflammation, and adverse events of VNS.

Quality assessment

Two researchers independently assessed the methodological quality of each included study by using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [23]. Evaluating the risk of bias involved assessing five domains, which encompassed the risk of bias arising from the randomization process, the effect of assignment to intervention, missing outcome data, measurement of the outcome, and the selection of the reported result. Each domain was judged as having a low risk of bias, some concerns, or a high risk of bias. Disagreements were resolved by discussion between the two investigators.

Results

Study selection

The initial search identified a total of 2,467 records (PubMed 181; Embase 752; Cochrane Library 1,367; Web of Science 167), and 1,973 abstracts were screened after removal of duplicates. Ten articles were searched for full-text screening, of which only a conference abstract was available for three articles. A total of seven articles were assessed for eligibility and included in this qualitative analysis. Figure 5 outlines the details of the literature search and selection process.

Study characteristics

All included studies were randomized controlled trials, which enrolled patients in the period between 2015 and 2021 (Table 1). Each study investigated non-invasive electrostimulation in patients with a gastrointestinal disorder, comparing it with sham

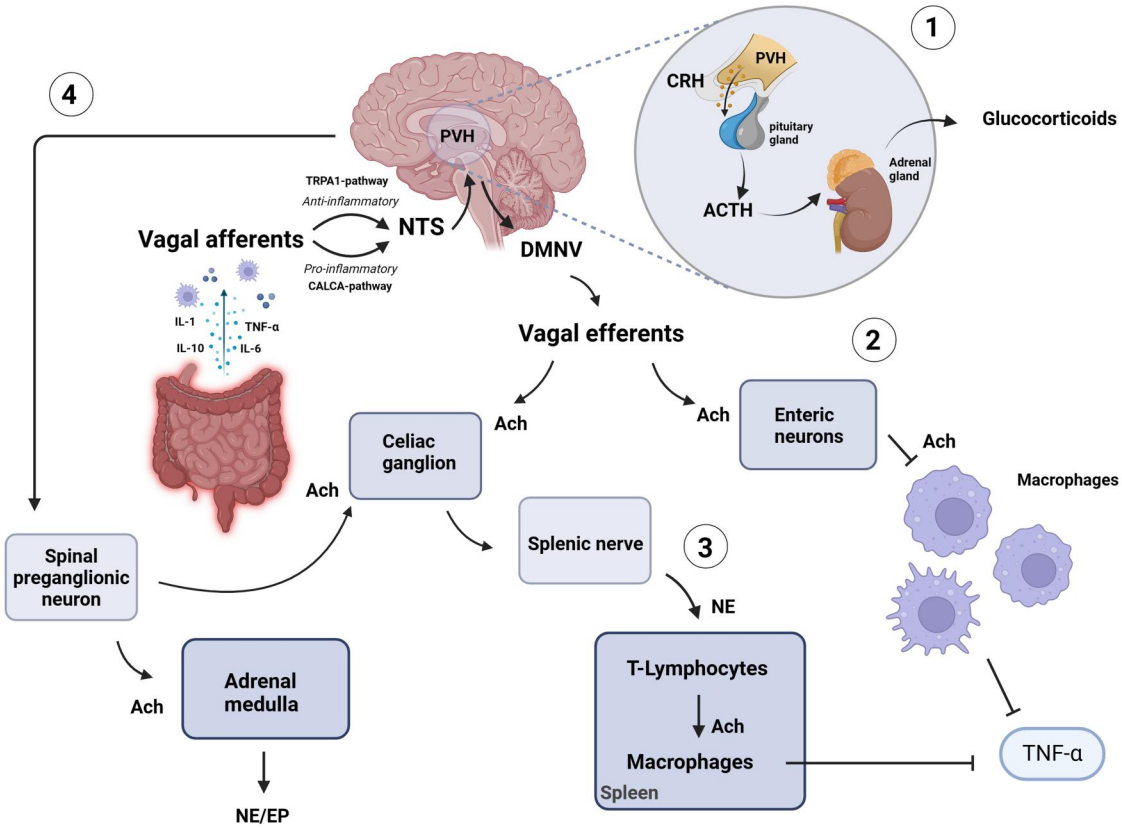

Figure 4. Anti-inflammatory properties of the vagus nerve. The anti-inflammatory effect of vagus nerve stimulation in inflammatory diseases is believed to be based on different pathways: (1) activation of the hypothalamic-pituitary-adrenal axis via vagal afferents, (2) activation of the cholinergic anti-inflammatory pathway, (3) the non-neuronal cholinergic pathway via vagal efferents, and (4) activation of the vagal afferent pathway, including the TRPA1 pathway (anti-inflammatory signals) and the CALCA pathway (pro-inflammatory signals). This image is based on information provided in the article of Bonaz *et al.* [14] and was created with BioRender.com. IL-1 = interleukin 1, IL-6 = interleukin 6, IL-10 = interleukin 10, TNF-α = tumor necrosis factor-alpha, NTS = nucleus tractus solitarius, TRPA1 pathway = transient receptor potential ankyrin 1 pathway, CALCA pathway = calcitonin-related polypeptide alpha pathway, PVH = paraventricular nucleus of hypothalamus, CRH = corticotropin-releasing hormone, ACTH = adrenocorticotropic hormone, DMNV = dorsal motor nucleus of vagus nerve, Ach = acetylcholine, NE = norepinephrine, EP = epinephrine.

stimulation. No studies investigating invasive VNS were deemed appropriate for inclusion due to a lack of comparison with sham stimulation or because they investigated conditions outside of the scope of this search. One study was a post-hoc analysis by Kovacic *et al.* wherein patients with IBS were allocated to either PENFS or sham stimulation.

Patient characteristics

The details of the patient characteristics are presented in Table 2. In total, 644 patients were included in seven trials. Among these patients, 426 had FD, 22 had IBD (10 Crohn's disease, 12 ulcerative colitis), 92 had IBS, and 104 patients had an abdominal pain-related functional gastrointestinal disorder, including IBS (51), FD (26), abdominal migraine (32), functional abdominal pain (1), or functional abdominal pain syndrome (17). The total pediatric population consisted of 176 adolescents aged 10–21 years. No studies were identified that assessed the efficacy of VNS in patients with functional constipation, gastrointestinal reflux disease, and gastroparesis. The review involved 203 men (32%) and 441 women (68%), with a mean age ranging from 15 to 65 years. In addition, participants had a mean disease duration ranging from 9 months to 7 years.

Risk of bias

The overall risk of bias per article is presented in Table 3. Study schemes, devices, and stimulation parameters were comparable across both groups in all studies. While most studies provided adequate information regarding randomization and allocation concealment, blinding methods varied considerably. Four studies implemented blinding for both participants and investigators to reduce bias [24–27], while two studies were single-blinded [28, 29], and one lacked detailed blinding information, resulting in a high risk-of-bias assignment [30]. Deviations from the intended intervention were well described, and most studies sufficiently provided details about the statistical analysis methods used, although some lacked sufficient explanation [28, 30]. Missing outcome data were classified as low across all studies, with adequately described withdrawal reasons. Well-validated tools were used for outcome measurement. Despite this, since outcomes were patient-reported, the participants functioned as the outcome assessors, with a (blinded) interviewer assisting. Some studies used different body locations for taVNS (i.e. cymba conchae of the left ear) and sham stimulation (i.e. middle of the left calf), raising concerns about whether participants were aware of the treatment received, potentially influencing outcome assessment [26, 28, 29]. Additionally, in one randomized cross-over trial, no information was provided about the wash-out period, prompting concerns about possible carryover effects [28]. Overall, all trials were characterized by fairly high placebo responses (i.e. positive responses in the sham treatment), which in itself is not surprising considering that the use of medical devices has been postulated to be associated with high placebo

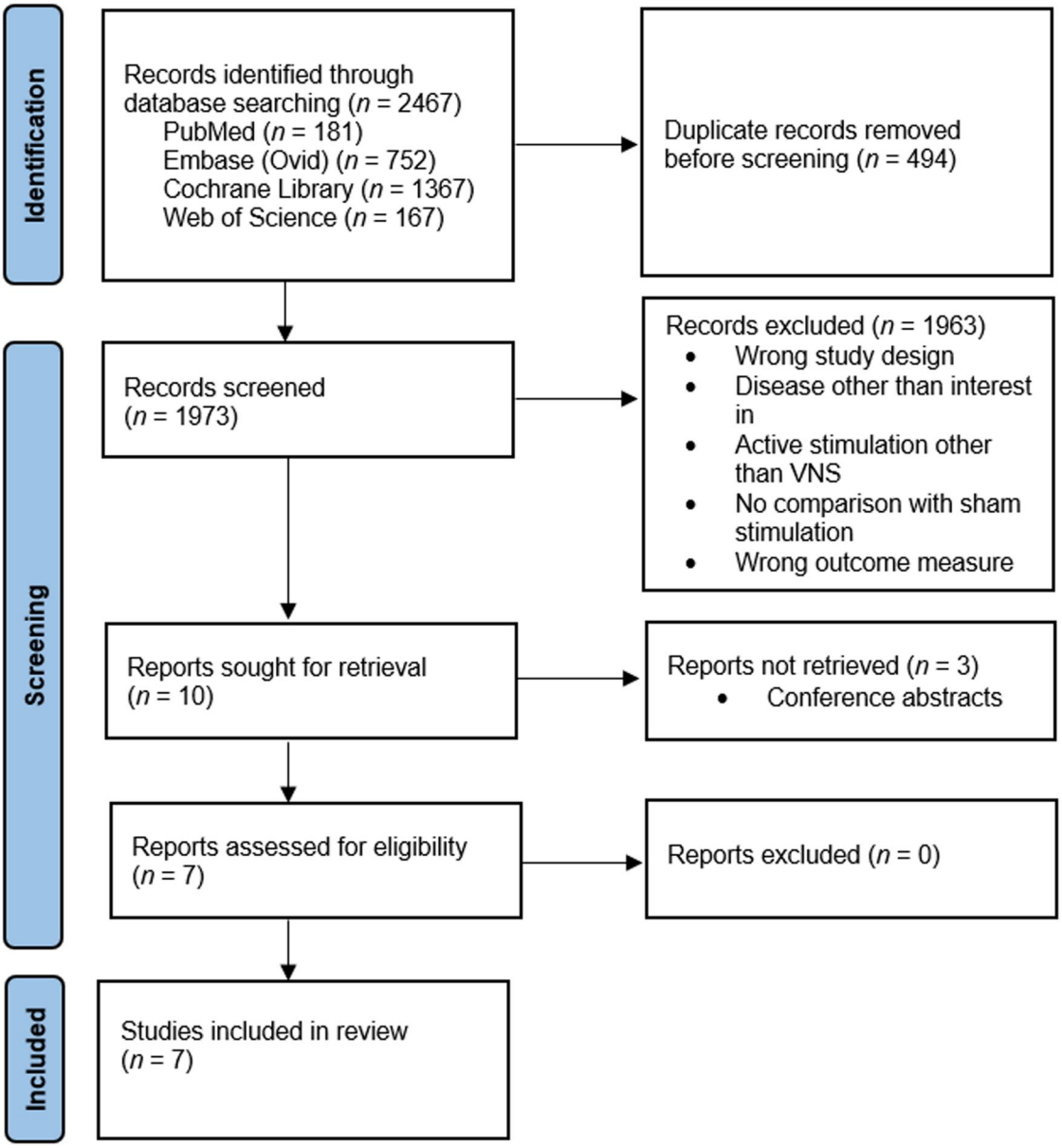

Figure 5. PRISMA flow chart illustrating the selection process. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, VNS = vagus nerve stimulation.

responses and may indeed be related to potential problems with inappropriate blinding [31]. In addition, trials in patients with IBS and FD are also known to be characterized by high placebo responses (up to 40%) [32, 33]. Some included studies lacked a trial protocol, making it difficult to exclude selection bias in the reported results [26, 29]. Consequently, the reported clinical effects, particularly in functional dyspepsia, appear to be exceptionally high, potentially influenced by the selection of chosen endpoints. Moreover, considering the small number of trials identified with largely positive results, publication bias could also have impacted current findings.

Symptom relief

The primary outcome of interest was adequate symptom relief, defined as a clinically significant improvement of complaints, and was measured differently according to the disorder investigated.

Functional dyspepsia

One study examining taVNS in FD patients, with allocation of 300 FD subjects to either 10 Hz (V10) or 25 Hz (V25) taVNS or sham groups, showed higher response rates (81.2% vs. 75.9% vs. 47%, both $P < 0.001$) and adequate relief rates (85.1% vs. 80.8% vs. 67%, both $P < 0.05$) in both the V10 and V25 groups after 4 weeks of treatment, compared with the sham group, with the effect persisting through Weeks 8 and 12 [27]. Nevertheless, there was no significant difference observed between the V10 and V25 groups in terms of response rate and adequate relief rate (both $P > 0.05$). Furthermore, in relation to FD-related symptoms, a significant decrease in stomach pain and bloating was observed in both the V10 and V25 groups compared with the sham group (both $P < 0.05$). The same effect was noted in another study on 2-week taVNS treatment in 36 FD patients ($P = 0.046$ for stomach pain and $P = 0.003$ for bloating, respectively) [26]. Additionally, taVNS enhanced gastric accommodation ($P < 0.008$), increased normal

Table 1. Characteristics of the study included

Authors	Publication year	Country	Study design	Disease	Study population	Intervention	Comparator	Outcome	Duration of follow-up
Kovacic *et al.*	2017	USA	RCT	Abdominal pain-related functional gastrointestinal disorders	115	PENFS	Sham stimulation	Change in abdominal pain score (PFSD scale, $P < 0.05$); global symptom improvement (SRS, $P < 0.05$; FDI, $P > 0.05$; STAI-C, $P > 0.05$).	16 weeks
Krasaelap *et al.*	2020	USA	RCT (post-hoc analysis)	Irritable bowel syndrome	51	PENFS	Sham stimulation	>30% reduction in worst abdominal pain severity ($P < 0.05$); change in composite abdominal pain severity score ($P < 0.05$); change in usual abdominal pain severity score ($P < 0.05$); global symptom improvement (SRS, $P < 0.05$; FDI, $P > 0.05$; STAI-C, $P > 0.05$).	4 weeks
Sahn *et al.*	2023	USA	RCT	Pediatric onset Crohn's disease or ulcerative colitis	22	taVNS	Sham stimulation	Clinical remission (PUCAI/PCDAI score); ≥50% reduction in FC level ($P < 0.05$); heart rate variability	16 weeks
Shi *et al.*	2021	China	RCT	Constipation-predominant irritable bowel syndrome	42	taVNS	Sham stimulation	CSBMs/week ($P < 0.05$); change in abdominal pain score (VAS $P < 0.05$); change in IBS-SSS score ($P < 0.05$) and IBS-QOL score ($P < 0.05$); anorectal motor and sensory function (HRAM, $P < 0.05$); change in cytokines and brain–gut peptides ($P < 0.05$); autonomic function ($P < 0.05$).	4 weeks
Shi *et al.*	2023	China	RCT	Functional dyspepsia	300	10 Hz taVNS, 25 Hz taVNS	Sham stimulation	Response rate ($P < 0.05$), adequate relief rate ($P < 0.05$), elimination rate ($P > 0.05$), modified FDSD ($P < 0.05$), GSRS ($P < 0.05$), SF-NDI ($P < 0.05$), HAMD ($P < 0.05$), HAMA ($P < 0.05$).	12 weeks
Wu *et al.*	2021	China	RCT	Functional dyspepsia	90	taVNS	Sham stimulation	Overall symptom score ($P < 0.05$); FDQOL ($P < 0.05$); HAMA ($P < 0.05$); HAMD ($P < 0.05$); SDS ($P < 0.05$).	12 weeks
Zhu *et al.*	2021	China	RCT	Functional dyspepsia	75	taVNS	Sham stimulation	Gastric accommodation ($P < 0.05$); gastric slow waves ($P < 0.05$); postprandial dyspeptic symptoms ($P < 0.05$ for fullness and $P > 0.05$ for postprandial pain and nausea); autonomic functions ($P < 0.05$); dyspeptic symptoms (DSS, $P < 0.05$); anxiety and depression scores ($P > 0.05$).	2 weeks

PFSD = pain frequency-severity-duration, SRS = Symptom Response Scale, FDI = Functional Disability Inventory, STAI-C = State-Trait Anxiety Inventory for Children, PUCAI = Pediatric Ulcerative Colitis Activity Index, PCDAI = Pediatric Crohn Disease Activity Index, FC = fecal calprotectin, CSBMs/week = complete spontaneous bowel movements per week, VAS = visual analogue scale, IBS-SSS = Irritable Bowel Syndrome Symptom Severity core, IBS-QOL = Irritable Bowel Syndrome Quality of Life score, HRAM = high-resolution anorectal manometry, modified FDSD = modified functional dyspepsia symptom diary score, GSRS = Gastrointestinal Symptom Rating Scale, SF-NDI = Short Form Nepean Dyspepsia Index, HAMD = Hamilton Rating Scale for Depression, HAMA = Hamilton Anxiety Rating Scale, FDQOL = functional dyspepsia-related quality of life questionnaire, SDS = self-rating depression scale, DSS = Dyspeptic Symptom Scale, RCT = randomized controlled trial, PENFS = percutaneous electrical nerve field stimulation, taVNS = transcutaneous auricular vagus nerve stimulation.

Table 2. Characteristics of the patient included

Study	Disease	Population analyzed	Interventions	Population per intervention, *n*	Male/female, *n*/*n*	Average age, years, mean ± SD	Disease duration, years, mean ± SD
Kovacic *et al.*	Abdominal pain-related functional gastrointestinal disorders	104	PENFS	57	6/51	15.3	Not reported
			Sham stimulation	47	4/43	15.6	Not reported
Krasaelap *et al.*	Irritable bowel syndrome	50	PENFS	27	3/24	15.3	Not reported
			Sham stimulation	23	2/21	15.6	Not reported
Sahn *et al.*	Crohn's disease or ulcerative colitis	22	taVNS	10	12/10	15	Not reported
			Sham stimulation	12			
Shi *et al.* (2021)	Constipation-predominant irritable bowel syndrome	42	taVNS	21	4/17	41.5 ± 15.4	0.74 ± 0.71
			Sham stimulation	21	6/15	49.6 ± 15.6	1.11 ± 0.91
Shi *et al.* (2023)	Functional dyspepsia	300	taVNS (V10)	101	40/61	44.5 ± 13.0	3.0
			taVNS (V25)	99	45/54	45.4 ± 11.6	2.0
			Sham stimulation	100	42/58	44.8 ± 11.3	2.0
Wu *et al.*	Functional dyspepsia	90	taVNS	45	16/29	50.58 ± 8.75	4.63 ± 3.29
			Sham stimulation	45	12/33	48.31 ± 9.31	4.51 ± 3.38
Zhu *et al.*	Functional dyspepsia	36	taVNS	18	7/11	44.5 ± 3.7	1.0
			Sham stimulation	18	4/14	43.9 ± 3.4	1.3

PENFS = percutaneous electrical nerve field stimulation, taVNS = transcutaneous auricular vagus nerve stimulation, SD = standard deviation.

Table 3. Overall risk of bias according to the revised Cochrane risk-of-bias tool for randomized trials (RoB2)

Article	Low risk of bias	Some concerns	High risk of bias
Kovacic *et al.*	×		
Krasaelap *et al.*	×		
Sahn *et al.*		×	
Shi *et al.* (2021)		×	
Shi *et al.* (2023)	×		
Wu *et al.*			×
Zhu *et al.*		×	

gastric slow waves during both fasting ($P = 0.010$) and fed states ($P = 0.007$), and augmented vagal activity during fasting ($P = 0.056$) and fed states ($P = 0.026$) compared with sham stimulation. Finally, another study [30] revealed significant reductions in overall symptom scores and FD-related quality of life questionnaire, Hamilton anxiety rating scale, Hamilton rating scale for depression, and self-rating depression scale scores after 4 and 12 weeks of taVNS treatment compared with sham (all $P < 0.05$). The taVNS group exhibited a higher clinical therapeutic effect (91.11%) compared with the sham group (68.89%), with a significant difference observed ($P < 0.05$).

Irritable bowel syndrome

In a post-hoc study [24] of 51 subjects with Rome III-diagnosed IBS, a significant reduction of 30% or more in worst abdominal pain severity was observed after 3 weeks of PENFS therapy compared with sham stimulation ($P = 0.024$), with a number needed to treat of 3. However, extended follow-up (8–12 weeks after the end of therapy) showed no significant difference ($P = 0.33$). Furthermore, significant group differences in composite and usual abdominal pain severity scores were noted after 3 weeks of therapy ($P = 0.026$ and $P = 0.029$, respectively). Similar findings were noted across the entire study cohort of 115 adolescents with abdominal pain-related functional gastrointestinal disorders [25]. Subgroup analysis of IBS subtypes revealed no significant differences in any IBS subtype concerning pain improvement during extended follow-up. Global symptom improvement, defined as an improvement of +2 points or greater on a symptom response scale, was observed in 81% of patients receiving PENFS therapy compared with 26% in the sham stimulation group ($P < 0.001$). Another study [29] involving 42 IBS patients with a constipation-predominant defecation pattern demonstrated significant improvements in VAS (visual analog scale) pain score ($P = 0.001$), quality of life ($P = 0.020$), IBS symptom score ($P = 0.001$), and complete spontaneous bowel movements per week ($P = 0.001$) with taVNS compared with sham stimulation after 4 weeks of treatment.

Inflammatory bowel disease

One study [28] investigated the change in disease activity from baseline in 22 IBD subjects according to the weighted Pediatric Crohn's Disease Activity Index and Pediatric Ulcerative Colitis Activity Index for Crohn's disease (CD) and ulcerative colitis (UC) subjects, respectively. Within the first 2 weeks of active taVNS, four subjects (two CD and two UC) showed clinical response (weighted Pediatric Crohn's Disease Activity Index reduction >12.5 or Pediatric Ulcerative Colitis Activity Index reduction >10). Two subjects (one CD and one UC) responded during sham stimulation initially. Among the 12 subjects with active symptomatic disease indices at baseline, three out of six (50%) with Crohn's disease and two out of six (33%) with ulcerative colitis achieved clinical remission after taVNS treatment by Week 16.

Anti-inflammatory effects

Two studies investigated the anti-inflammatory effects of VNS. One single-blinded randomized cross-over trial [28], involving 22 IBD subjects (10 CD and 12 UC), found that VNS significantly decreased the fecal calprotectin (FC) levels between Weeks 2 and 4, compared with sham stimulation. Specifically, the median FC decreased by 225 μg/g in the VNS group compared with an increase of 308 μg/g in the sham group ($P = 0.016$). Furthermore, 11 out of 17 subjects (64.7%) experienced a >50% reduction in FC at Week 16 (95% CI 38.3%–85.8%), with seven showing a rapid FC response with a 50% reduction after only 2 weeks of taVNS treatment. When analyzed by disease subtype, the median FC in subjects with Crohn's disease decreased from 506 μg/g (interquartile range 255–1976) to 349 μg/g (interquartile range 149–1078) at Week 16 ($P = 0.09$), with a 56% median percent change ($P = 0.12$). Conversely, in subjects with ulcerative colitis, median FC decreased from 994 μg/g (interquartile range 610–2265) to 376 μg/g (interquartile range 83–525), with an 81% median percent change

Table 4. Adverse events

Article	Total study population, *n*	Number of adverse events	Type of adverse events	Group allocation in relation to number of adverse events	*P*-value
Kovacic *et al.*	115	10	I. Ear discomfort ($n=6$) II. Adhesive allergy ($n=3$) III. Syncope ($n=1$)	I. PENFS ($n=3$), sham group ($n=3$) II. PENFS ($n=1$), sham group ($n=2$) III. Sham group ($n=1$)	Not reported
Krasaelap *et al.*	51	1	Adhesive allergy ($n=1$)	taVNS ($n=1$)	Not reported
Sahn *et al.*	22	1	Focal redness and minor break in the skin due to excessive pressure ($n=1$)	taVNS ($n=1$)	Not reported
Shi *et al.* (2021)	42	Not reported	Not reported	Not reported	Not reported
Shi *et al.* (2023)	300	7	I. Tinnitus ($n=3$) II. Palpitation ($n=1$) III. Insomnia ($n=2$) IV. Abdominal pain ($n=1$)	I. V10 group ($n=1$), V25 group ($n=2$) II. V10 group ($n=1$) III. V10 group ($n=1$), sham group ($n=1$) IV. V25 group ($n=1$)	0.509
Wu *et al.*	90	Not reported	Not reported	Not reported	Not reported
Zhu *et al.*	75	1	I. Tinnitus ($n=1$) II. Insomnia ($n=1$)	I. taVNS ($n=1$) II. taVNS ($n=1$)	Not reported

PENFS = percutaneous electrical nerve field stimulation, taVNS = transcutaneous auricular vagus nerve stimulation.

($P=0.10$). Most subjects (18 out of 22) underwent combination therapy alongside tVNS, which included medications such as 5-aminosalicylic acid ($n=8$), methotrexate ($n=4$), adalimumab ($n=3$), and vedolizumab ($n=3$). Another study [29], involving 42 IBS patients with a constipation-predominant defecation pattern randomized to either taVNS or sham stimulation for a 4-week period, investigated the change in inflammatory cytokines from baseline. Results revealed a significant decrease in serum TNF-α and interleukin-6 levels with taVNS compared with baseline ($P=0.001$ and $P=0.037$, respectively). Furthermore, post-taVNS levels were also significantly lower than post-sham stimulation levels ($P<0.001$ and $P=0.0019$, respectively).

Adverse events

Five included studies reported adverse events in both the active treatment group and sham stimulation group. The overall adverse event rate was 3.6% (20 out of 562 participants), with the most reported adverse events being ear discomfort, adhesive allergy, tinnitus, and insomnia. No specific information was provided regarding the duration of side effects. However, Zhu *et al.* [26] reported that tinnitus and insomnia completely disappeared after treatment discontinuation. Most adverse events were reported within the active treatment group (14 in the active treatment group vs. 7 in the sham stimulation group). Only one study [27] reported on statistical testing of adverse events comparing active treatment with sham stimulation, and they did not find a statistically significant difference between the groups. One study [28] documented a *Clostridioides difficile* infection occurring after 3–5 days of taVNS use. However, it was deemed unrelated to this therapy given the patients' history of recurrent *Clostridioides difficile* infection and the noticeably short duration of use. Furthermore, this study reported worsening of disease activity between Weeks 4 and 12 in two subjects with ulcerative colitis, requiring a change in medical therapy. Consequently, the impact of taVNS on disease progression remains uncertain. In total, four patients discontinued study adherence due to side effects, although no serious complications were reported. Further details regarding the adverse events can be found in Table 4.

Discussion

Main findings

This systematic review identified seven randomized controlled trials showing that non-invasive VNS, in the forms of both taVNS and PENFS, effectively provided substantial symptom relief, as evidenced by reductions in abdominal pain, bloating, and overall symptom scores, alongside improvements in disease activity indices and quality of life across various gastrointestinal disorders when compared with sham stimulation. Furthermore, taVNS showed significant reductions in FC levels and serum inflammatory cytokines among children and adolescents with inflammatory gastrointestinal conditions, such as IBD. However, it is important to note that these results were based on a single IBD study with a small sample size and the concomitant use of medication alongside tVNS therapy. Additionally, no significant differences in symptom relief were observed between groups receiving either low- or high-frequency tVNS (i.e. 10 Hz or 25 Hz). The duration of beneficial effects of taVNS in follow-up after cessation of stimulation varied considerably among the studies. No results were obtained regarding these outcome measures with iVNS or tcVNS. The overall adverse event rate, when reported, was low across the studies, and no severe complications were documented.

Mechanism of action underlying the effects of VNS

Previous research indicates that vagal activity is intricately linked with various physiological processes [34], including anti-nociceptive [4, 35] and anti-inflammatory [1] effects, as well as enhancement of gastrointestinal motility [36] and restoration of intestinal barrier function [37]. The significant effects of taVNS on the outcomes discussed in this review are primarily considered anti-nociceptive and anti-inflammatory. First and foremost, taVNS has demonstrated symptom alleviation among individuals experiencing chronic abdominal complaints, such as IBS [24] and FD [27], currently considered as disorders of the gut–brain interaction, where visceral hypersensitivity is assumed to play an important role in symptom generation [25].

Indeed, one study investigated the impact of taVNS on acid-induced esophageal pain in healthy controls and found that it both prevents the onset of and reverses established acid-induced esophageal hypersensitivity [35]. It is generally accepted that the

key neural pathways transmitting pain signals from the digestive tract to the brain encompass afferents from the spinal cord ascending through the dorsal horn to higher brain centers, alongside vagal afferents relaying information to the NTS [5, 6]. More specifically, the spinal afferent neurons, which are in the dorsal root ganglia, ascend to the thalamus and then subsequently project to various brain regions associated with pain perception, referred to as the spinothalamic nociceptive pathway. Simultaneously, the vagus nerve provides information through vagal afferents that project to the NTS, of which the cell bodies are located in the nodose ganglion. In the NTS, primary vagal afferents synapse with the motor efferent vagal nuclei and with "higher" centers, including the hypothalamus, amygdala, parabrachial nucleus, and insular cortex [4]. It is generally believed that splanchnic nerves, which carry spinal afferents, play a primary role in processing pain in the gut, while vagal afferents mediate nonpainful sensations. Therefore, vagal afferents have conventionally been considered to have a more indirect role in pain modulation, although more recent evidence suggests nociceptive information might directly engage vagal pathways, too [38, 39].

The ability of taVNS to directly modulate central viscerosensory processing is further evidenced by functional magnetic resonance imaging studies revealing distinct changes in several brain structures following taVNS, particularly affecting the brainstem, including the NTS and the nucleus spinalis of the trigeminal nerve [40]. Furthermore, it is suggested that the inhibitory antinociceptive effects of taVNS gradually counteract the pronociceptive facilitatory influences as the intensity of stimulation increases [41]. Consequently, the intensity of taVNS may play a critical role in activating different circuits within the brainstem, in particular the NTS [42].

Notably, both in previous research and in the outcomes observed here, the effects of taVNS on brain activity persisted beyond the duration of stimulation itself [43], indicating long-lasting, sustainable effects [42]. This sustained impact was observed not only in enduring anti-nociceptive [25] but also in anti-inflammatory [28, 44] responses following short taVNS stimulation, which can be assumed to be related to neuroplasticity. Additional mechanistic studies in patients would be necessary to establish the exact way in which taVNS can impact visceronociceptive processes.

It has also been hypothesized that VNS leads to a decrease in pro-inflammatory cytokines and an increase in anti-inflammatory cytokines through interaction with three crucial reflex pathways: the anti-inflammatory hypothalamic-pituitary-adrenal axis, the cholinergic anti-inflammatory pathway, and the splenic sympathetic anti-inflammatory pathway [42]. Recent experimental evidence suggests, in addition, that pro- and anti-inflammatory cytokines communicate with distinct populations of vagal neurons to inform the brain of an emerging inflammatory response, thereby implying a pivotal role of the vagus nerve, and in particular the NTS, in orchestrating immune function [21]. Therefore, modulation of the vagus nerve may lead to the suppression of over-inflammation, prevention of tissue injury, and improved survival, particularly in chronic inflammation conditions characterized by an imbalance between pro-inflammatory and anti-inflammatory cytokines, as supported by some results of this review [45]. Yet however tempting it may be to extrapolate such experimentally identified mechanisms to clinical effects of taVNS, drawing such conclusions from a single IBD study including 22 patients should be regarded with caution. Future research will need to establish how the different modalities of VNS can impact the various anti-inflammatory pathways and modulate the immune response, and how this impacts the clinical response.

Important to note is that these putative anti-nociceptive and anti-inflammatory effects of taVNS may have been influenced by factors such as mode of stimulation and variations in stimulation parameters. Specifically, differences in stimulation side, frequency (Hz), and session duration were observed among the studies. It remains to be established, however, whether certain effects of taVNS can be directed based on stimulation parameters and whether this is related to specific neuronal targets within different but distinct signaling pathways. Additionally, achieving suprathreshold stimulation levels in regions innervated by the vagus nerve necessitates relatively strong currents and optimal electrode contact to effectively penetrate the skin barrier [42]. Furthermore, both studies investigating taVNS and PENFS were included in this review. PENFS affects the peripheral cranial neurovascular bundle (V, VII, IX, and X) [16]. However, due to the small size of needle electrodes used with the cymba concha region as the stimulation point, this results in spatially focused stimulating fields that favor precise and specific stimulation of the local afferent auricular branch of the vagus nerve [34]. Conversely, in taVNS, the use of a relatively large surface area of electrodes results in diffuse stimulation fields. This possibly enables the activation of both vagal and non-vagal auricular nerves, the implications of which are still under debate [42]. Therefore, taVNS and PENFS of the external ear may have similar biological effects, but PENFS might be more specific to the vagus nerve, albeit this might not clinically be relevant [34]. In addition, PENFS utilizes needle electrodes, making it more invasive than taVNS and potentially less advantageous as a consequence for practical use.

Potentials and barriers in VNS research

tVNS shows promise in treating various clinical conditions due to its non-invasive nature, patient-friendly use, and affordability [34]. However, while transcutaneous cervical VNS (tcVNS) has gained Food and Drug Administration (FDA) approval solely for the treatment of cluster headache and migraine [46, 47], transcutaneous auricular (taVNS) currently lacks FDA clearance for any disorder [34]. This discrepancy may be attributed to the inconsistency in treatment success among individuals [48], possibly linked to stimulation parameters, physiological state, and anatomical variances, which remain poorly understood. taVNS offers variability in stimulation parameters such as frequency (Hz), current intensity (mA), pulse width (μs), duty cycle (s), and session duration (min). Outcome variability may also be influenced by factors like sham or control stimulation type, stimulation location, and sham electrode placement [34, 48]. Furthermore, inadequate blinding of subjects, assessors, and investigators may substantially impact outcomes, especially considering the reliance on patient-reported measures. As VNS gains wider recognition, maintaining blinding becomes increasingly challenging.

Due to the lack of properly controlled trials, the potential of iVNS and tcVNS as a treatment for gastrointestinal disorders was not explored in this review. Indeed, iVNS has shown promising results in an uncontrolled pilot study of nine patients with moderately active Crohn's disease [49]. This suggests that iVNS merits further investigation for its potential anti-inflammatory effects. However, iVNS, compared with tVNS, may be less appealing for further research due to its invasive nature. Additionally, tcVNS, stimulating both vagal afferents and efferents, may induce more non-selective effects compared with taVNS, which solely affects the auricular vagus, a vagal afferent [48]. Nonetheless, a

comprehensive understanding of how each of these factors affects pathophysiology and clinical outcomes remains incomplete, necessitating further research into taVNS.

Despite the growing interest in taVNS research, a clear consensus is still lacking on the optimal parameters to be adopted in this field. Thoroughly measuring target engagement is crucial for identifying effective stimulation patterns. However, due to the absence of direct measures of local target engagement, studies on taVNS largely depend on stimulation parameters similar to those used for implantable VNS. Nevertheless, differences in electrode design, size, contact area, target fiber type, and fiber orientation affect neural recruitment, potentially leading to differences in physiological effects between taVNS and iVNS. Hence, it is expected that stimulation parameters transferred from iVNS may not reproduce the same physiological effects or fiber recruitment during taVNS [48]. However, having real-time data on neural target engagement would facilitate the refinement of stimulation parameters, electrode configurations, and control mechanisms [50]. According to a systematic analysis determining the most optimal treatment frequencies for taVNS, recommended stimulation parameters may include using a rectangular pulse wave in a biphasic signal form, with an impulse duration of 30 s, followed by an impulse pause (the duration of which may vary depending on the condition), and an impulse frequency between 20 and 30 Hz. Additionally, as in most studies of taVNS, the current should be adjusted to a suprathreshold stimulation intensity [51]. This, however, may pose problems with regard to deblinding in the setting of controlled trials, if the sham condition does not elicit any sensation whereas the active stimulation does. The application of subthreshold stimuli could overcome such limitations, but again, the question is whether this would have the same biological effect. Even more importantly, to establish standardization across studies examining taVNS, methodological details of these studies should be provided sufficiently to facilitate result comparison, study replication, and enhance study participant safety. In response to this necessity, Farmer *et al.* have recently provided an international consensus-based review outlining the minimum reporting standards for research on tVNS, guided by the principle of reproducibility, in order to facilitate further research in the area [34].

Strengths and limitations

The studies included in this review offer valuable insights into the use of tVNS as a therapeutic intervention for a range of gastrointestinal diseases. However, it is important to acknowledge the inherent limitations of both this review and the studies it includes.

Firstly, this review included a limited number of randomized controlled trials performed in patients with a wide range of gastrointestinal disorders, many of which had small sample sizes themselves. Secondly, most of the studies were conducted at single centers, thus limiting their generalizability. Additionally, both pediatric and adult subjects were included in this review, which might have introduced heightened heterogeneity among the studies, potentially affecting the strength of the evidence. Nonetheless, the purpose of this review was to provide a broad insight into the clinical effects and the anti-nociceptive and anti-inflammatory potential of VNS. The clinical impact of anti-inflammatory effects is very preliminary. No well-controlled trials on the efficacy of tVNS in adult subjects with inflammatory gastrointestinal diseases have previously been performed. Only one uncontrolled study regarding iVNS was conducted in adult subjects with IBD, showing promising results [49]. Therefore, it is tempting to assume that the positive effects of tVNS observed in a small study performed in a pediatric population will similarly manifest in adult IBD subjects, albeit this remains to be examined in future studies.

Furthermore, there are concerns about the potential impact of patient awareness of the treatment received due to inadequate blinding or lack of detailed blinding information. Additionally, the follow-up duration among the studies was notably brief, and a longer assessment period would be preferable to account for long-term effects of tVNS. Furthermore, in most of the included trials, tVNS was combined with standard therapy, potentially introducing confounding effects on the results. Most importantly, significant heterogeneity was observed among the studies, primarily due to variations in outcome measures and stimulation parameters, but also the different disorders examined with the inclusion of both pediatric and adult patients. As a consequence of this lack of standardization, comparing results across the studies is challenging, as direct one-to-one comparisons and meta-analysis cannot be performed at this point. Therefore, caution should be used when interpreting these preliminary results.

The strengths of this review include a comprehensive literature search conducted with transparent and reproducible methods. Secondly, only studies with a randomized controlled trial design were included, ensuring a high level of methodological quality and minimizing the risk of bias. Furthermore, all included studies compared tVNS with sham stimulation, allowing for direct comparisons of efficacy and controlling for potential placebo effects. Additionally, the inclusion of different gastrointestinal conditions allows for a broad investigation into the effects and underlying mechanisms of action and applicability in different conditions, thereby revealing its potential as a therapeutic intervention in gastroenterology.

Conclusions

Overall, the results of this review suggest that non-invasive VNS is a promising and safe therapeutic approach for various gastrointestinal disorders. Nevertheless, it is important to note that these findings are based on studies with small sample sizes and only offer preliminary insights. Future research into the underlying mechanisms and long-term efficacy of VNS in large randomized controlled trials with adequate blinding is needed to define the exact position of VNS within the therapeutic arsenal.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Authors' Contributions

F.V. and K.H. collected, analyzed, and interpreted the data. F.V. drafted the manuscript and completed graphics and visualization. D.K. supervised the writing of the manuscript. All authors read and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare that there is no conflict of interests in this study.

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