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Mini Review

Transcutaneous Vagal Nerve Stimulation for Gastrointestinal Disorders

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Abstract

Imbalanced autonomic function has been reported in gastrointestinal (GI) disorders. The vagus nerve is a major component in the regulation of upper GI motility. Vagal nerve stimulation (VNS) has been shown to improve symptoms of various GI disorders by enhancing parasympathetic activity. This review aims to summarize the clinical efficacy of transcutaneous VNS for GI disorders, focusing on abdominal pain, other GI symptoms, and GI motility, and to discuss the mechanisms of action of transcutaneous VNS. Randomized clinical trials investigating transcutaneous VNS in several major GI disorders, including functional dyspepsia, gastroparesis, constipation, irritable bowel syndrome, and inflammatory bowel disease, were reviewed and discussed. The forms of transcutaneous VNS covered in this review include transcutaneous auricular VNS, transcutaneous cervical VNS, and percutaneous electrical nerve field stimulation. Transcutaneous VNS has been shown to relieve abdominal pain, improve GI symptoms, and accelerate GI motility by enhancing vagal activity in patients with various GI disorders. Transcutaneous VNS is an innovative, effective, and safe therapy for patients with GI disorders; however, large-scale clinical trials are necessary to establish optimal treatment modalities and efficacy.

Introduction

The vagus nerve, a major branch of the parasympathetic system, is a key component of the autonomic nervous system. It is the longest cranial nerve, traveling from the brainstem to the colon, predominantly innervating thoracic and abdominal organs, especially those in the gastrointestinal (GI) tract.[1–3] The vagus nerve is a mixed nerve composed of 80% afferent and 20% efferent fibers.[4,5] It communicates bidirectionally between the central nervous system and the enteric nervous system through both vagal afferent and efferent signaling. Vagal afferent fibers originate from the mucosa to the muscle layer of the digestive tract; their sensory cell bodies reside in the nodose ganglia and relay information to the nucleus tractus solitarius (NTS) and the area postrema.[2,6] The NTS is closely connected with the dorsal motor nucleus of the vagus (DMV) in the hindbrain, which is the origin of the vagal efferent fibers. Together with the DMV and the area postrema, the NTS forms the dorsal vagal complex, which mediates vago-vagal reflexes regulating GI functions such as motility, acid secretion, early satiety, and food intake.[4,7] The NTS also relays vagal afferent signals to multiple brain regions of the central autonomic network to integrate and initiate cognitive, behavioral, endocrine, and autonomic reflexes.[8]

Imbalanced autonomic function, characterized by sympathetic hyperactivity and/or reduced vagal activity, has been reported in several GI motility disorders.[9] An early clinical study identified parasympathetic nerve dysfunction in patients with gastroesophageal reflux disease, which was associated with delayed esophageal transit and abnormal peristalsis.[10] Increased fullness, impaired gastric accommodation, and disturbed gastric slow waves were observed in patients with functional dyspepsia (FD) compared to healthy controls, attributed to lower vagal activity assessed by heart rate variability (HRV).[11] These clinical findings suggest that low vagal tone correlates with reduced GI motility. Reduced vagal tone has also been reported in patients with irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD).[12,13] Thus, enhancing vagal tone to restore parasympathetic balance through vagal nerve stimulation (VNS) may provide prokinetic, anti-inflammatory, and anti-nociceptive benefits to improve symptoms arising from dysmotility, inflammation, and visceral hypersensitivity in disorders of gut-brain interaction (DGBIs).

VNS therapy can be classified into two main types: invasive and non-invasive. Invasive VNS involves implanting electrodes on the cervical or subdiaphragmatic vagus nerve to deliver electrical pulses that generate firing potentials.[7] However, invasive VNS is costly, requires surgery, and may induce side effects.[14] Non-invasive VNS stimulates superficial branches of the vagus nerve

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through the skin using electrical pulses; it is less expensive, more patient-friendly, and thus has been explored for treating various diseases.[14–18]

Three non-invasive VNS methods are commonly used: *1) Transcutaneous auricular vagal nerve stimulation (taVNS),* administered via surface electrodes placed on vagally-innervated regions of the outer ear—most commonly the cymba concha, which is 100% innervated by the auricular vagus nerve.[19] *2) Transcutaneous cervical vagal nerve stimulation (tcVNS)*, where surface electrodes are placed over the sternocleidomastoid muscle with a handheld device that stimulates the vagus nerve within the cervical carotid sheath.[14,20] *3) Percutaneous electrical nerve field stimulation (PENFS)*, which uses miniature needle electrodes that penetrate the skin in the vagally-innervated ear region. Due to the smaller size of the electrodes, stimulation can be precisely targeted to local auricular vagal afferent endings.[14,21]

This review aims to evaluate the clinical effects of non-invasive VNS for GI disorders, including abdominal pain, GI inflammation, and dysmotility, and to discuss the underlying mechanisms of VNS. The PubMed database was searched from January 1990 to July 2025 for relevant articles in English. Clinical trials using noninvasive VNS for DGBIs were included, as well as animal studies exploring mechanisms of non-invasive VNS in GI disorders.

Noninvasive VNS for abdominal pain in DGBIs

Chronic abdominal pain is one of the most common symptoms in DGBIs, including FD, gastroparesis, and IBS, affecting approximately one in four people in the United States.[22] The pathophysiology of abdominal pain in functional GI disorders is not fully understood; pain may develop directly from sensitization of visceral afferents or secondarily due to impaired GI motility.[22,23]

There have been six clinical trials using noninvasive VNS for abdominal pain in DGBIs.[11,20,21,24–26] taVNS has been shown to relieve abdominal pain in patients with FD and constipation-predominant IBS (IBS-C).[11,25] In a multicenter, randomized controlled clinical trial, taVNS or sham treatment was administered twice daily for 30 m over four weeks in 330 patients with FD.[26] It was found that taVNS at either 10 Hz or 25 Hz resulted in a more pronounced reduction in stomach pain compared with sham treatment ($P < 0.05$), with stomach pain relief reported in 75–82.8% of patients receiving taVNS versus 61.5% in the sham group.[26] In addition to abdominal pain, other FD-related symptoms, including bloating and fullness, also improved after four weeks of taVNS treatment.[26] Similar findings were reported in a smaller clinical trial of patients with FD.[11] One study reported that daily four-week taVNS improved both constipation and abdominal pain in patients with IBS-C compared with sham stimulation.[25] The number of complete spontaneous bowel movements per week tripled with taVNS compared to sham treatment, and abdominal pain scores were reduced by 64% after four weeks of taVNS (3.1 ± 2.2 vs. 1.1 ± 1.1, $P = 0.001$).[25] In an open-label clinical trial involving 15 patients with gastroparesis, bilateral tcVNS was applied twice daily for 2 m using a handheld vagal nerve stimulator (gammaCore) for a minimum of four weeks.[20] Responders showed significant improvement in the Patient-Reported Outcomes Measurement Information System GI and pain symptom subscales ($P < 0.01$). However, tcVNS did not normalize autonomic dysfunction during cardiovascular challenge testing, nor did it improve symptoms associated with autonomic function.[20] PENFS has been reported to reduce functional abdominal pain associated with IBS in adolescents. In a randomized, double-blind, sham-controlled trial, three weeks of PENFS (60 patients in the active treatment group) resulted in a greater reduction in worst pain compared with sham treatment (55 patients), with effects sustained for over nine weeks.[21] In another study of 50 adolescents with IBS, more than 30% reduction in abdominal pain was observed with PENFS compared to sham treatment, along with improved overall wellbeing.[24]

Noninvasive VNS for IBD

IBD is a chronic inflammatory disease of the GI tract, divided into Crohn's disease (CD) and ulcerative colitis (UC). UC most often affects the recto-colon region, while CD can affect any part of the digestive tract, predominantly the terminal ileum and colon.[27,28] One small clinical trial investigated the effects of taVNS in IBD.[29] The study enrolled 22 subjects aged 10–21 years with mild or moderate CD (10 participants) or UC (12 participants). taVNS was performed using a commercial transcutaneous electrical nerve stimulator and sensor probe with a pulse width of 300 μs and frequency of 20 Hz, while sham treatment was delivered to the middle of the left calf. The study had two phases. In phase 1, subjects were randomized to receive either taVNS or sham stimulation for two weeks, then crossed over to the alternate treatment for the next two weeks. Phase 2 began at week 4, when all subjects received active taVNS for 5 m twice daily until week 16.

The primary study endpoints were clinical remission, defined as Crohn's Disease Activity Index score < 12.5 or Pediatric Ulcerative Colitis Activity Index score < 10, and a ≥50% reduction in fecal calprotectin levels, a non-invasive marker of intestinal inflammation, from baseline to week 16. Clinical remission was achieved in 50% of CD patients and 33% of UC patients at week 16 following taVNS treatment. Fecal calprotectin levels were reduced by ≥50% in 64.7% of subjects, suggesting an anti-inflammatory effect and potential disease-modifying impact of taVNS in IBD.[29] However, the small sample size, lack of a sham control group during phase 2, and the short daily treatment duration limited the generalizability and applicability of taVNS for IBD.

Noninvasive VNS for GI Motility

GI dysmotility includes impaired peristalsis, delayed gastric emptying or intestinal transit, myoelectrical dysrhythmias, altered contractions and accommodation, disordered sphincters, and other dysfunctions. Disordered GI motility may contribute to GI symptoms. For example, impaired gastric accommodation can lead to postprandial symptoms such as fullness or early satiety in FD[22,30]; delayed gastric emptying may cause nausea or vomiting[31]; and delayed colonic transit is present in 23% of patients with functional constipation or IBS-C.[32,33]

Three clinical trials have investigated taVNS for GI motility.[11,25,34] In a single-blind small clinical trial of 44 subjects diagnosed with laryngopharyngeal reflux disease, bilateral taVNS was performed twice daily for two weeks, with each session lasting 30 m.[34] Esophageal motility was analyzed using high-resolution esophageal manometry. taVNS significantly enhanced upper esophageal sphincter pressure ($P < 0.001$) and lower esophageal sphincter pressure ($P = 0.01$) compared to sham treatment.[34] Two randomized, double-blind, sham-controlled clinical trials investigated the prokinetic effects of taVNS on GI motility in patients with FD and IBS-C.[11,25] In 36 FD patients, a two-week taVNS treatment increased the maximum tolerable gastric volume from 797.1 ± 40.3 mL to 901.2 ± 39.6 mL compared to sham treatment ($P < 0.001$),

indicating improved gastric accommodation. The normal percentage of gastric slow waves, correlated with gastric contractions and emptying, also increased with taVNS treatment.[11] In 42 patients with IBS-C, anorectal motor and sensory function was assessed using high-resolution anorectal manometry. Four-week taVNS improved the rectoanal inhibitory reflex ($P = 0.014$) and enhanced rectal sensation ($P < 0.04$). Moreover, taVNS decreased proinflammatory cytokines tumor necrosis factor α (TNF-α) and interleukin (IL)-6 compared to sham treatment.[25] Enhanced vagal activity assessed by HRV was demonstrated in all three clinical studies. In an open-label clinical study, gastric emptying rate assessed by gastric emptying breath test was accelerated in 15 patients with gastroparesis after four weeks of tcVNS treatment; however, the therapy did not correct autonomic function abnormalities.[20]

Mechanisms of action

Abdominal pain in GI disorders is associated with increased visceral sensitivity or visceral hypersensitivity, which may develop directly due to inflammation-induced peripheral sensitization or secondarily due to impaired GI motility.[22,35,36] Peripheral sensitization is primarily caused by low-grade mucosal inflammation, evidenced by elevated levels of pro-inflammatory cytokines such as TNF-α and IL-6, and plays a key role in the pathogenesis of abdominal pain in several DGBIs, including gastroparesis, FD, and IBS.[23,36–39] During chronic abdominal pain, peripheral sensitization gradually leads to central sensitization in the spinal cord and brainstem.[22,23,36,38] Central pain perception from the GI tract involves two afferent pathways: 1) The spinal afferent pathway, with sensory neurons located in the dorsal root ganglia, ascending via the dorsal horn to the thalamus and projecting to various brain regions involved in pain perception.[15,40] 2) The vagal afferent pathway from the GI tract to the NTS in the brainstem, which communicates with brain regions involved in visceral pain perception, including the hypothalamus, insular cortex, amygdala, and parabrachial nucleus (Fig. 1).[9,15,41,42] In addition, GI dysmotility plays a key role in the pathogenesis of abdominal pain in DGBIs; impaired gastric accommodation and delayed gastric emptying can lead to postprandial bloating and abdominal pain.[22,39]

The vagus nerve exerts anti-inflammatory effects both through its afferent fibers, by activating the hypothalamic-pituitary-adrenal axis, and efferent fibers via the cholinergic anti-inflammatory pathway, maintaining homeostasis.[2,4] The cholinergic anti-inflammatory pathway is mediated by acetylcholine (ACh) release, which binds to α7 nicotinic ACh receptors on macrophages, inhibiting the release of pro-inflammatory cytokines such as TNF-α.[4,43] In the gut, the vagus nerve interacts not directly with macrophages but with nNOS–VIP–ACh enteric neurons.[4,44] A vago-sympathetic pathway via the spleen has also been proposed, wherein the vagus nerve interacts with the splenic sympathetic nerve, which releases norepinephrine binding to β2 receptors on splenic T-lymphocytes, leading to TNF-α inhibition through an interaction of ACh and α7 nicotinic ACh receptors.[4,45]

The anti-nociceptive and anti-inflammatory properties of auricular vagal nerve stimulation (aVNS) have been demonstrated in preclinical studies. aVNS at 100 Hz improved visceral hypersensitivity,[46,47] accelerated gastric emptying, and suppressed serum TNF-α, IL-6, and IL-1β in a rodent model of gastric hyperalgesia.[48] The anti-inflammatory effects of aVNS were also reported in a rodent model of TNBS-induced colitis,[49] where low-frequency aVNS (5 Hz) ameliorated colon mucosal damage and suppressed plasma levels of TNF-α, IL-1β, IL-6, and myeloperoxidase activity.

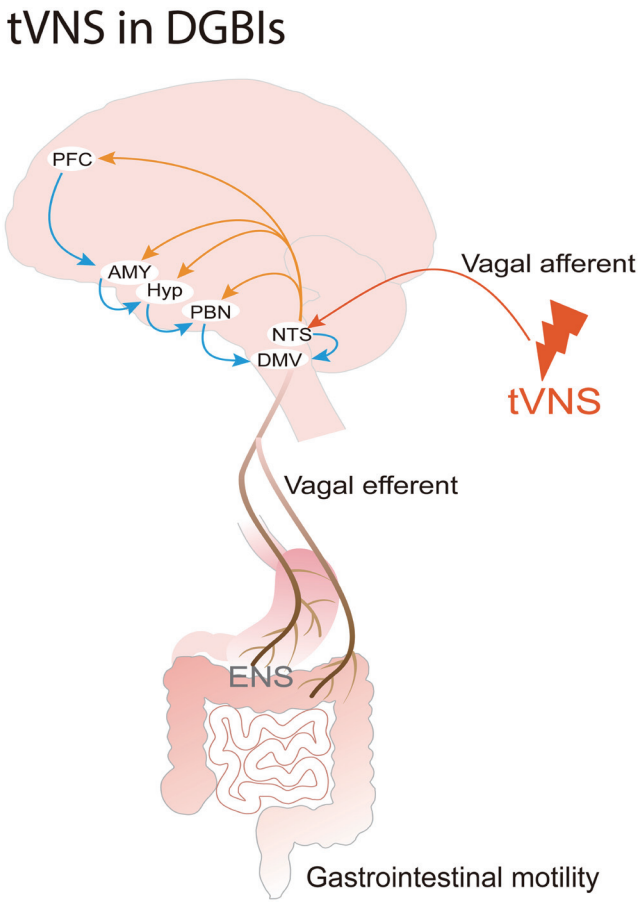

Fig. 1. Mechanisms of tVNS for DGBIs. This figure was made in Adobe Illustrator. AMY, amygdala; DGBIs, disorders of gut-brain interaction; DMV, dorsal motor nucleus of the vagus; ENS, enteric nervous system; Hyp, hypothalamus; NTS, nucleus tractus solitarius; PBN, parabrachial nucleus; PFC, prefrontal cortex; tVNS, transcutaneous vagal nerve stimulation.

Central mechanisms of aVNS have been explored in recent preclinical and clinical studies. Li *et al*.[50] reported that aVNS (2/15 Hz) effectively inhibited the development of nociceptive hypersensitivity in Zucker diabetic fatty rats, assessed by thermal hyperalgesia and mechanical allodynia in the hindpaw; this effect was linked to upregulated expression of 5-HT receptor type 1A in the hypothalamus. Hou *et al*.[46] found that aVNS (100 Hz) improved gastric motility and hypersensitivity and inhibited the hyperactivation of the hypothalamic-pituitary-adrenal axis in a rat model of FD, suggesting prokinetic and analgesic effects mediated via vago-vagal pathways. Imaging techniques such as functional magnetic resonance imaging have been applied to investigate the central mechanisms of taVNS in migraine patients. taVNS was shown to activate the NTS and increase its connectivity to brain areas involved in pain regulation.[51] A recent study comparing different stimulation frequencies found that taVNS at 100 Hz evoked the most robust activation in the ipsilateral NTS.[52] In a single-blinded, placebo-controlled clinical study, taVNS relieved headache symptoms and increased functional connectivity between the motor thalamus and anterior cingulate cortex/medial prefrontal cortex, while decreasing connectivity between the occipital thalamus and postcentral gyrus.[53] To date, no functional magnetic resonance imaging studies have been conducted on taVNS in GI disorders;

Table 1. Clinical trials using transcutaneous vagal nerve stimulation for DGBIs

Disease	Intervention	Stimulation parameters	Major results	
			Symptoms	Mechanisms
Laryngopharyngeal reflux disease	taVNS[34]	25Hz, 2s on, 3s off, 0.5ms	Reduced reflux symptoms index scores; reduced anxiety and depression scores	Enhanced both upper and lower esophageal sphincter pressure. Enhanced vagal activities.
Functional dyspepsia	taVNS[11]	25Hz, 2s on, 3s off, 0.5ms	Improved overall dyspeptic symptoms, decreased scores of anxiety and depression, reduced abdominal pain	Improved gastric accommodation. Enhanced vagal efferent activity.
	taVNS[26]	10Hz or 25Hz, 30s on, 30s off, 0.5ms	Reduced symptom scores of stomach pain, bloating, and fullness	Not studied
Gastroparesis	tcVNS[20]	Not reported	Improved major symptoms of gastroparesis, including nausea, vomiting, fullness, early satiety, and bloating; reduced abdominal pain	Accelerated gastric emptying
Constipation-predominant irritable bowel syndrome (IBS-C).	taVNS[25]	25Hz, 2s on, 3s off, 0.5ms	Improved the weekly number of complete spontaneous bowel movements, abdominal pain, IBS symptoms, and quality of life	Improved rectal sensation. Decreased proinflammatory cytokines. Enhanced vagal activity.
Abdominal pain-related functional GI disorders in adolescents	PENFS[21]	Alternating frequencies (1ms pulses of 1 and 10Hz), 2 h on, 2 h off for 120 h.	Had greater reduction in worst pain compared with sham treatment; the effects were sustained for an extended period.	Not studied
IBS in adolescents	PENFS[24]	Alternating frequencies (1ms pulses of 1 and 10Hz), 2 h on, 2 h off for 120 h.	Reduced 30% or more in worst abdominal pain; improved global symptoms	Not studied
Inflammatory bowel disease (IBD) in children	taVNS[29]	20Hz, 0.3ms	Clinical remission, represented by wPCDAI or PUCAI score, was achieved in 50% with CD and 33% with UC	Reduced fecal calprotectin. Enhanced vagal activity.

CD, Crohn's disease; DGBIs, disorders of gut-brain interaction; GI, gastrointestinal; PENFS, percutaneous electrical nerve field stimulation; PUCAI, pediatric ulcerative colitis activity index; taVNS, transcutaneous auricular vagal nerve stimulation; tcVNS, transcutaneous cervical vagal nerve stimulation; UC, ulcerative colitis; wPCDAI, weighted pediatric Crohn's disease activity index.

however, findings from migraine research may guide future investigations into central mechanisms of taVNS on pain, inflammation, and GI motility.

Prokinetic effects of aVNS/taVNS have been reported in both preclinical and clinical studies.[11,25,46,54,55] The autonomic pathways involved have been evidenced by enhanced vagal efferent activity assessed by HRV analysis.[11,25,46,54,55] The high-frequency band of the HRV power spectrum reflects parasympathetic activity, while the low-frequency band mainly reflects sympathetic activity.[56,57] aVNS has been shown to improve or normalize impaired GI slow waves and accelerate upper GI and colonic transit in a rodent model of opioid-induced constipation,[54,58] mediated via vagal afferent and efferent pathways demonstrated by activation of central sensory nuclei in the NTS and DMV.[54,55] In a mouse model of IBS-C, taVNS improved fecal pellet number, fecal water content, GI transit, and relieved visceral hyperalgesia by restoring gut microbiota and increasing interstitial cells of Cajal.[59] In clinical studies, taVNS improved GI symptoms and dysmotility via enhanced parasympathetic activity in patients with FD and IBS, with high-frequency HRV correlating with clinical symptoms and the percentage of normal gastric slow waves.[11,25] These findings suggest that improvement of GI dysmotility is a key factor in relieving abdominal pain in DGBIs.

Limitations and future directions

A summary of the included clinical trials is presented in Table 1.[11,20,21,24-26,29,34] Despite its efficacy and novelty, only a limited number of randomized clinical trials using transcutaneous VNS for DGBIs have been reported in the literature, possibly due to the indirect connection of the vagus nerve to the GI tract and the lack of an optimized stimulation method. Various stimulation parameters have been used in these clinical trials, but no consensus on the optimal settings for treating GI disorders has been established. Low-frequency stimulation (10–25 Hz) has been reported to reduce abdominal pain and improve GI symptoms and motility in most of the included clinical trials. No clinical trials using transcutaneous VNS at frequencies higher than 30 Hz have been reported for GI disorders, except for GammaCore. In preclinical studies, VNS at 100 Hz was reported to improve visceral hypersensitivity in rodent models of FD,[46,47,60] with evidence suggesting that 100 Hz may be

more effective than 25 Hz.[47,60] Conversely, aVNS at 25 Hz was shown to accelerate GI motility, including increasing the percentage of normal GI slow waves and accelerating gastric emptying and small bowel transit in rats treated with loperamide.[54] taVNS at 25 Hz also improved constipation symptoms and increased GI transit in a mouse model of IBS-C.[59] However, these findings do not imply that a specific set of parameters is established for treating visceral hypersensitivity or GI motility, as they have yet to be translated into clinical studies. Additionally, aVNS at 100 Hz has also been shown to accelerate gastric emptying, and aVNS at 25 Hz was reported to relieve visceral hypersensitivity in preclinical studies.[48,59] Therefore, further preclinical and clinical research is necessary to optimize transcutaneous VNS parameters for DGBIs. Beyond stimulation frequency, other factors such as stimulation site (left ear, right ear, or bilateral), treatment regimens, and patient compliance must be carefully considered.

Conclusions

Transcutaneous VNS appears to be an emerging, effective, low-cost, and safe therapy for GI disorders. However, in-depth research is needed to elucidate the mechanisms of action, especially the central mechanisms underlying the anti-nociceptive, anti-inflammatory, and prokinetic effects of VNS in GI disorders. Furthermore, most clinical studies reviewed here involved small sample sizes; therefore, large randomized, multicenter, double-blinded, sham-controlled clinical trials are necessary to establish the clinical efficacy of transcutaneous VNS for treating various GI disorders.

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Conflict of interest

JY is an employee of Transtimulation Research Inc. and has no conflicts of interest related to this publication.

Author contributions

JY is the sole author of the manuscript. The author has approved the final version and publication of the manuscript.

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