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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.

Keywords

Vagal nerve stimulation; Abdominal pain; Gastrointestinal motility; Inflammation; Brain-gut axis; Gastrointestinal disorders

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

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Conflict of interest

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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 Noninvasive VNS stimulates superficial branches of the vagus nerve 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 μ s 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 vomiting³¹; 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 tVNS 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 $\alpha 7$ 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 $\beta 2$ receptors on splenic T-lymphocytes, leading to TNF- α inhibition through an interaction of ACh and $\alpha 7$ 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-1 β 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-1 β , IL-6, and myeloperoxidase activity.

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; 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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References

- [1]. Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. *Auton Neurosci* 2000;85(1–3):1–17. doi:10.1016/S1566-0702(00)00215-0. [PubMed: 11189015]
- [2]. Bonaz B, Sinniger V, Pellissier S. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. *J Physiol* 2016;594(20):5781–5790. doi:10.1113/JP271539. [PubMed: 27059884]
- [3]. Yuan H, Silberstein SD. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part I. *Headache* 2016;56(1):71–78. doi:10.1111/head.12647. [PubMed: 26364692]
- [4]. Bonaz B, Sinniger V, Pellissier S. Vagus Nerve Stimulation at the Interface of Brain-Gut Interactions. *Cold Spring Harb Perspect Med* 2019;9(8):a034199. doi:10.1101/cshperspect.a034199. [PubMed: 30201788]
- [5]. Prechtl JC, Powley TL. The fiber composition of the abdominal vagus of the rat. *Anat Embryol (Berl)* 1990;181(2):101–115. doi:10.1007/BF00198950. [PubMed: 2327594]
- [6]. Cechetto DF. Central representation of visceral function. *Fed Proc* 1987;46(1):17–23. [PubMed: 3542576]
- [7]. de Lartigue G. Role of the vagus nerve in the development and treatment of diet-induced obesity. *J Physiol* 2016;594(20):5791–5815. doi:10.1113/JP271538. [PubMed: 26959077]
- [8]. Bonaz B. Enteric neuropathy and the vagus nerve: Therapeutic implications. *Neurogastroenterol Motil* 2024;37(8):e14842. doi:10.1111/nmo.14842. [PubMed: 38873822]

- [9]. Bonaz B, Sinniger V, Pellissier S. Vagal tone: effects on sensitivity, motility, and inflammation. *Neurogastroenterol Motil* 2016;28(4):455–462. doi:10.1111/nmo.12817 [PubMed: 27010234]
- [10]. Cunningham KM, Horowitz M, Riddell PS, Maddern GJ, Myers JC, Holloway RH, et al. Relations among autonomic nerve dysfunction, oesophageal motility, and gastric emptying in gastro-oesophageal reflux disease. *Gut* 1991;32(12):1436–1440. doi:10.1136/gut.32.12.1436. [PubMed: 1773945]
- [11]. Zhu Y, Xu F, Lu D, Rong P, Cheng J, Li M, et al. Transcutaneous auricular vagal nerve stimulation improves functional dyspepsia by enhancing vagal efferent activity. *Am J Physiol Gastrointest Liver Physiol* 2021;320(5):G700–G711. doi:10.1152/ajpgi.00426.2020. [PubMed: 33624527]
- [12]. Pellissier S, Dantzer C, Canini F, Mathieu N, Bonaz B. Psychological adjustment and autonomic disturbances in inflammatory bowel diseases and irritable bowel syndrome. *Psychoneuroendocrinology* 2010;35(5):653–662. doi:10.1016/j.psyneuen.2009.10.004. [PubMed: 19910123]
- [13]. Pellissier S, Dantzer C, Mondillon L, Trocme C, Gauchez AS, Ducros V, et al. Relationship between vagal tone, cortisol, TNF-alpha, epinephrine and negative affects in Crohn's disease and irritable bowel syndrome. *PLoS One* 2014;9(9):e105328. doi:10.1371/journal.pone.0105328. [PubMed: 25207649]
- [14]. Farmer AD, Strzelczyk A, Finisguerra A, Gourine AV, Gharabaghi A, Hasan A, et al. International Consensus Based Review and Recommendations for Minimum Reporting Standards in Research on Transcutaneous Vagus Nerve Stimulation (Version 2020). *Front Hum Neurosci* 2020;14:568051. doi:10.3389/fnhum.2020.568051. [PubMed: 33854421]
- [15]. Gottfried-Blackmore A, Habtezion A, Nguyen L. Noninvasive vagal nerve stimulation for gastroenterology pain disorders. *Pain Manag* 2021;11(1):89–96. doi:10.2217/pmt-2020-0067. [PubMed: 33111642]
- [16]. Rong P, Liu J, Wang L, Liu R, Fang J, Zhao J, et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A nonrandomized controlled pilot study. *J Affect Disord* 2016;195:172–179. doi:10.1016/j.jad.2016.02.031. [PubMed: 26896810]
- [17]. Yap JYY, Keatch C, Lambert E, Woods W, Stoddart PR, Kameneva T. Critical Review of Transcutaneous Vagus Nerve Stimulation: Challenges for Translation to Clinical Practice. *Front Neurosci* 2020;14:284. doi:10.3389/fnins.2020.00284. [PubMed: 32410932]
- [18]. Yin J, Chen JD. Noninvasive electrical neuromodulation for gastrointestinal motility disorders. *Expert Rev Gastroenterol Hepatol* 2023; 17(12):1221–1232. doi:10.1080/17474124.2023.2288156. [PubMed: 38018087]
- [19]. Peuker ET, Filler TJ. The nerve supply of the human auricle. *Clin Anat* 2002;15(1):35–37. doi:10.1002/ca.1089. [PubMed: 11835542]
- [20]. Gottfried-Blackmore A, Adler EP, Fernandez-Becker N, Clarke J, Habtezion A, Nguyen L. Open-label pilot study: Non-invasive vagal nerve stimulation improves symptoms and gastric emptying in patients with idiopathic gastroparesis. *Neurogastroenterol Motil* 2020;32(4):e13769. doi:10.1111/nmo.13769. [PubMed: 31802596]
- [21]. Kovacic K, Hainsworth K, Sood M, Chelimsky G, Unteutsch R, Nugent M, et al. Neurostimulation for abdominal pain-related functional gastrointestinal disorders in adolescents: a randomised, double-blind, sham-controlled trial. *Lancet Gastroenterol Hepatol* 2017;2(10):727–737. doi:10.1016/S2468-1253(17)30253-4. [PubMed: 28826627]
- [22]. Bharucha AE, Chakraborty S, Sletten CD. Common Functional Gastroenterological Disorders Associated With Abdominal Pain. *Mayo Clin Proc* 2016;91(8):1118–1132. doi:10.1016/j.mayocp.2016.06.003. [PubMed: 27492916]
- [23]. Enck P, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, et al. Irritable bowel syndrome. *Nat Rev Dis Primers* 2016;2:16014. doi:10.1038/nrdp.2016.14. [PubMed: 27159638]
- [24]. Krasaelap A, Sood MR, Li BUK, Unteutsch R, Yan K, Nugent M, et al. Efficacy of Auricular Neurostimulation in Adolescents With Irritable Bowel Syndrome in a Randomized, Double-Blind Trial. *Clin Gastroenterol Hepatol* 2020;18(9):1987–1994.e2. doi:10.1016/j.cgh.2019.10.012. [PubMed: 31622740]

- [25]. Shi X, Hu Y, Zhang B, Li W, Chen JD, Liu F. Ameliorating effects and mechanisms of transcutaneous auricular vagal nerve stimulation on abdominal pain and constipation. *JCI Insight* 2021;6(14):e150052. doi:10.1172/jci.insight.150052. [PubMed: 34138761]
- [26]. Shi X, Zhao L, Luo H, Deng H, Wang X, Ren G, et al. Transcutaneous Auricular Vagal Nerve Stimulation Is Effective for the Treatment of Functional Dyspepsia: A Multicenter, Randomized Controlled Study. *Am J Gastroenterol* 2024;119(3):521–531. doi:10.14309/ajg.0000000000002548. [PubMed: 37787432]
- [27]. Colombel JF, Shin A, Gibson PR. AGA Clinical Practice Update on Functional Gastrointestinal Symptoms in Patients With Inflammatory Bowel Disease: Expert Review. *Clin Gastroenterol Hepatol* 2019;17(3):380–390.e1. doi:10.1016/j.cgh.2018.08.001. [PubMed: 30099108]
- [28]. McDowell C, Farooq U, Haseeb M. Inflammatory bowel disease. *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2023.
- [29]. Sahn B, Pascuma K, Kohn N, Tracey KJ, Markowitz JF. Transcutaneous auricular vagus nerve stimulation attenuates inflammatory bowel disease in children: a proof-of-concept clinical trial. *Bioelectron Med* 2023;9(1):23. doi:10.1186/s42234-023-00124-3. [PubMed: 37849000]
- [30]. Camilleri M Integrated upper gastrointestinal response to food intake. *Gastroenterology* 2006;131(2):640–658. doi:10.1053/j.gastro.2006.03.023. [PubMed: 16890616]
- [31]. Park SY, Acosta A, Camilleri M, Burton D, Harmsen WS, Fox J, et al. Gastric Motor Dysfunction in Patients With Functional Gastrointestinal Symptoms. *Am J Gastroenterol* 2017;112(11):1689–1699. doi:10.1038/ajg.2017.264. [PubMed: 28895582]
- [32]. Bharucha AE, Lacy BE. Mechanisms, Evaluation, and Management of Chronic Constipation. *Gastroenterology* 2020;158(5):1232–1249.e3. doi:10.1053/j.gastro.2019.12.034. [PubMed: 31945360]
- [33]. Manabe N, Wong BS, Camilleri M, Burton D, McKinzie S, Zinsmeister AR. Lower functional gastrointestinal disorders: evidence of abnormal colonic transit in a 287 patient cohort. *Neurogastroenterol Motil* 2010;22(3):293–e82. doi:10.1111/j.1365-2982.2009.01442.x. [PubMed: 20025692]
- [34]. Huang Y, Liu J, Lv C, Sun C, Meng M, Lowe S, et al. Integrative effects of transcutaneous auricular vagus nerve stimulation on esophageal motility and pharyngeal symptoms via vagal mechanisms in patients with laryngopharyngeal reflux disease. *Front Neurosci* 2024;18:1287809. doi:10.3389/fnins.2024.1287809. [PubMed: 38516311]
- [35]. Drewes AM, Olesen AE, Farmer AD, Szigethy E, Rebours V, Olesen SS. Gastrointestinal pain. *Nat Rev Dis Primers* 2020;6(1):1. doi:10.1038/s41572-019-0135-7. [PubMed: 31907359]
- [36]. Enck P, Azpiroz F, Boeckstaens G, Elsenbruch S, Feinle-Bisset C, Holtmann G, et al. Functional dyspepsia. *Nat Rev Dis Primers* 2017;3:17081. doi:10.1038/nrdp.2017.81. [PubMed: 29099093]
- [37]. Abell TL, Kedar A, Stocker A, Beatty K, McElmurray L, Hughes M, et al. Pathophysiology of Gastroparesis Syndromes Includes Anatomic and Physiologic Abnormalities. *Dig Dis Sci* 2021;66(4):1127–1141. doi:10.1007/s10620-020-06259-6. [PubMed: 32328893]
- [38]. Feng B, La JH, Schwartz ES, Gebhart GF. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. Neural and neuro-immune mechanisms of visceral hypersensitivity in irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol* 2012;302(10):G1085–G1098. doi:10.1152/ajpgi.00542.2011. [PubMed: 22403791]
- [39]. Tack J, Camilleri M. New developments in the treatment of gastroparesis and functional dyspepsia. *Curr Opin Pharmacol* 2018;43:111–117. doi:10.1016/j.coph.2018.08.015. [PubMed: 30245474]
- [40]. Farmer AD, Aziz Q. Mechanisms and management of functional abdominal pain. *J R Soc Med* 2014;107(9):347–354. doi:10.1177/0141076814540880. [PubMed: 25193056]
- [41]. Azpiroz F, Bouin M, Camilleri M, Mayer EA, Poitras P, Serra J, et al. Mechanisms of hypersensitivity in IBS and functional disorders. *Neurogastroenterol Motil* 2007;19(1 Suppl):62–88. doi:10.1111/j.1365-2982.2006.00875.x. [PubMed: 17280586]
- [42]. Boeckstaens G, Camilleri M, Sifrim D, Houghton LA, Elsenbruch S, Lindberg G, et al. Fundamentals of Neurogastroenterology: Physiology/Motility - Sensation. *Gastroenterology* 2016. doi:10.1053/j.gastro.2016.02.030.

- [43]. Tracey KJ. The inflammatory reflex. *Nature* 2002;420(6917):853–859. doi:10.1038/nature01321. [PubMed: 12490958]
- [44]. Cailotto C, Gomez-Pinilla PJ, Costes LM, van der Vliet J, Di Giovangiulio M, Némethova A, et al. Neuro-anatomical evidence indicating indirect modulation of macrophages by vagal efferents in the intestine but not in the spleen. *PLoS One* 2014;9(1):e87785. doi:10.1371/journal.pone.0087785. [PubMed: 24489965]
- [45]. Rosas-Ballina M, Ochani M, Parrish WR, Ochani K, Harris YT, Huston JM, et al. Splenic nerve is required for cholinergic antiinflammatory pathway control of TNF in endotoxemia. *Proc Natl Acad Sci U S A* 2008;105(31):11008–11013. doi:10.1073/pnas.0803237105. [PubMed: 18669662]
- [46]. Hou LW, Fang JL, Zhang JL, Wang L, Wu D, Wang JY, et al. Auricular Vagus Nerve Stimulation Ameliorates Functional Dyspepsia with Depressive-Like Behavior and Inhibits the Hypothalamus-Pituitary-Adrenal Axis in a Rat Model. *Dig Dis Sci* 2022;67(10):4719–4731. doi:10.1007/s10620-021-07332-4. [PubMed: 35064375]
- [47]. Zhou J, Li S, Wang Y, Lei Y, Foreman RD, Yin J, et al. Effects and mechanisms of auricular electroacupuncture on gastric hypersensitivity in a rodent model of functional dyspepsia. *PLoS One* 2017;12(3):e0174568. doi:10.1371/journal.pone.0174568. [PubMed: 28350818]
- [48]. Hou L, Rong P, Yang Y, Fang J, Wang J, Wang Y, et al. Auricular Vagus Nerve Stimulation Improves Visceral Hypersensitivity and Gastric Motility and Depression-like Behaviors via Vago-Vagal Pathway in a Rat Model of Functional Dyspepsia. *Brain Sci* 2023;13(2):253. doi:10.3390/brainsci13020253. [PubMed: 36831796]
- [49]. Jin H, Guo J, Liu J, Lyu B, Foreman RD, Yin J, et al. Anti-inflammatory effects and mechanisms of vagal nerve stimulation combined with electroacupuncture in a rodent model of TNBS-induced colitis. *Am J Physiol Gastrointest Liver Physiol* 2017;313(3):G192–G202. doi:10.1152/ajpgi.00254.2016. [PubMed: 28546285]
- [50]. Li S, Sun C, Rong P, Zhai X, Zhang J, Baker M, et al. Auricular vagus nerve stimulation enhances central serotonergic function and inhibits diabetic neuropathy development in Zucker fatty rats. *Mol Pain* 2018;14:1744806918787368. doi:10.1177/1744806918787368. [PubMed: 29921169]
- [51]. Garcia RG, Lin RL, Lee J, Kim J, Barbieri R, Sclocco R, et al. Modulation of brainstem activity and connectivity by respiratory-gated auricular vagal afferent nerve stimulation in migraine patients. *Pain* 2017;158(8):1461–1472. doi:10.1097/j.pain.0000000000000930. [PubMed: 28541256]
- [52]. Sclocco R, Garcia RG, Kettner NW, Fisher HP, Isenburg K, Makarovskiy M, et al. Stimulus frequency modulates brainstem response to respiratory-gated transcutaneous auricular vagus nerve stimulation. *Brain Stimul* 2020;13(4):970–978. doi:10.1016/j.brs.2020.03.011. [PubMed: 32380448]
- [53]. Zhang Y, Huang Y, Li H, Yan Z, Zhang Y, Liu X, et al. Transcutaneous auricular vagus nerve stimulation (taVNS) for migraine: an fMRI study. *Reg Anesth Pain Med* 2021;46(2):145–150. doi:10.1136/rapm-2020-102088. [PubMed: 33262253]
- [54]. Zhang Y, Lu T, Dong Y, Chen Y, Chen JDZ. Auricular vagal nerve stimulation enhances gastrointestinal motility and improves interstitial cells of Cajal in rats treated with loperamide. *Neurogastroenterol Motil* 2021;33(10):e14163. doi:10.1111/nmo.14163. [PubMed: 33991455]
- [55]. Zhang Y, Lu T, Meng Y, Maisiyiti A, Dong Y, Li S, et al. Auricular Vagal Nerve Stimulation Improves Constipation by Enhancing Colon Motility via the Central-Vagal Efferent Pathway in Opioid-Induced Constipated Rats. *Neuromodulation* 2021;24(7):1258–1268. doi:10.1111/ner.13406. [PubMed: 33887080]
- [56]. Ali MK, Chen JDZ. Roles of Heart Rate Variability in Assessing Autonomic Nervous System in Functional Gastrointestinal Disorders: A Systematic Review. *Diagnostics (Basel)* 2023;13(2):293. doi:10.3390/diagnostics13020293. [PubMed: 36673103]
- [57]. Heremans ERM, Chen AS, Wang X, Cheng J, Xu F, Martinez AE, et al. Artificial Neural Network-Based Automatic Detection of Food Intake for Neuromodulation in Treating Obesity and Diabetes. *Obes Surg* 2020;30(7):2547–2557. doi:10.1007/s11695-020-04511-6. [PubMed: 32103435]

- [58]. Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* 2001;25(5):713–728. doi:10.1016/S0893-133X(01)00271-8. [PubMed: 11682255]
- [59]. Liu J, Dai Q, Qu T, Ma J, Lv C, Wang H, et al. Ameliorating effects of transcutaneous auricular vagus nerve stimulation on a mouse model of constipation-predominant irritable bowel syndrome. *Neurobiol Dis* 2024;193:106440. doi:10.1016/j.nbd.2024.106440. [PubMed: 38369213]
- [60]. Guo Y, Gharibani P. Analgesic Effects of Vagus Nerve Stimulation on Visceral Hypersensitivity: A Direct Comparison Between Invasive and Noninvasive Methods in Rats. *Neuromodulation* 2024;27(2):284–294. doi:10.1016/j.neurom.2023.04.001. [PubMed: 37191611]

tVNS in DGBIs

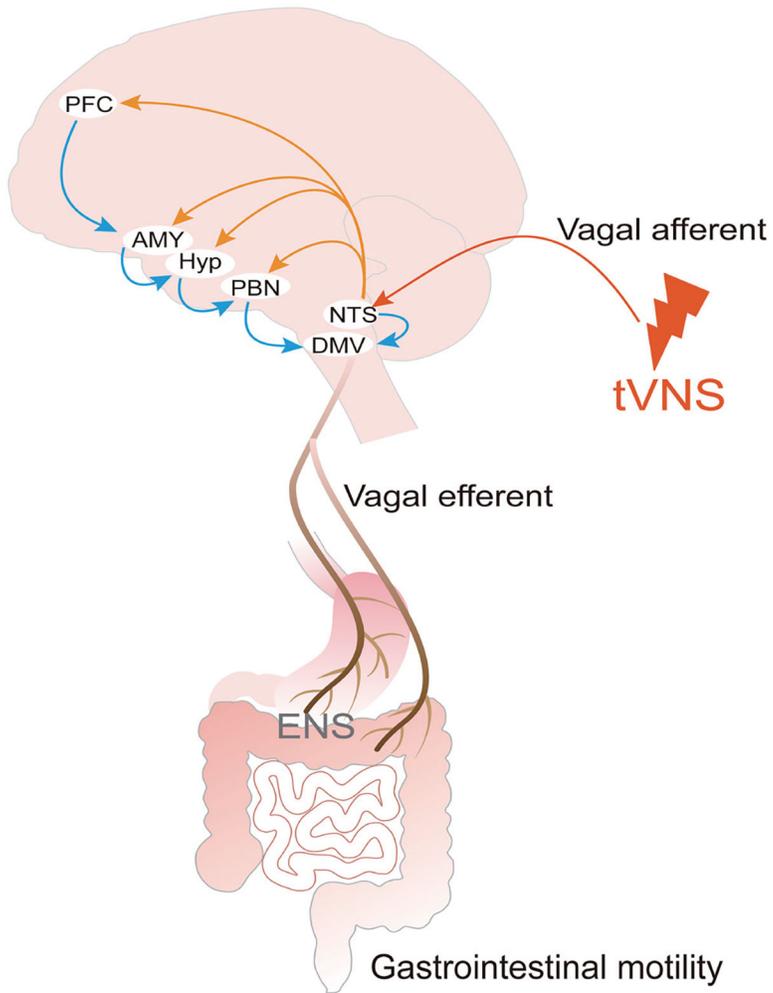


Fig. 1. Mechanisms of tVNS for DGBIs.

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.

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.