Gut Microbiota for Integrative Wellness

REVIEW

Neuromodulation for functional upper gastrointestinal diseases

Jiande Chen*

Division of Gastroenterology and Hepatology, University of Michigan School of Medicine, Ann Arbor, Michigan 48109, United States

ABSTRACT

Neuromodulation has recently received a great deal of attention among academic institutions, government funding agents and industries. This mini-review focuses on methods and applications as well as mechanisms of various neuromodulation methods in treating functional diseases of the upper gastrointestinal tract. First, the methods of various neuromodulation are introduced, including direct electrical stimulation at various peripheral nerves, such as the vagus nerve, sacral nerve and spinal cord, direct gastrointestinal electrical stimulation and noninvasive/transcutaneous electrical stimulation. Then, literature search was performed on the clinical applications of these neuromodulation methods for treating gastroesophageal reflux disease, functional dyspepsia and gastroparesis. Due to nature of the mini-review, the search results are selectively presented based on the expert opinions. Finally, a perspective is provided based on the author's own experience in this field of research.

Key words: electrical stimulation, gastroesophageal reflux, functional dyspepsia, gastroparesis, gastrointestinal motility

INTRODUCTION

While the first modern neuromodulation procedure (deep brain stimulation for chronic pain) was reported more than half a century ago in 1954,[1] the recent development in the field of neuromodulation is dramatic and escalated to a much higher level attributed to the involvement of industries (not only the traditional device companies but also pharmaceutical giants), government agents and academic institutions and universities.

In 2013, *Nature* published an article entitled "a jump to electroceuticals",[2] and the authors stated that "imagine a day when electrical impulses are a mainstay of medical treatment. Your clinician will administer electroceuticals that target individual nerve fibers or specific brain circuits to treat an array of condition". A pharmaceutical giant, GSK sponsored 50 laboratories around the world to work on various novel neuromodulation therapies and announced an award of 1 million USD to someone who was able to build an implantable pulse generator that could be used in a lab research setting and perform closed-loop neuromodulation at a world summit on neuromodulation in New York in 2014. Shortly after that, the Defense Advanced Research Projects Agency (DARPA) announced an Electrical Prescriptions Program and funded seven teams to modulate nerves to treat diseases such as inflammatory bowel diseases.[3] In 2015, National Institutes of Health established a common funds of 240 million USD for a special neuromodulation program called "Stimulating Peripheral Activity to Relieve Conditions".[4] The program was designed to investigate neuroanatomy of the peripheral organ systems, such as the gut and to develop novel neuromodulation therapies for various diseases associated with the peripheral organs. The program has recruited more than 100 leading scientists, engineers and physicians to collaborate on neuromodulation research.

***Corresponding Author:**
Jiande Chen, Division of Gastroenterology and Hepatology, University of Michigan School of Medicine, Ann Arbor, Michigan 48109, United States. Email: Cjiande@umich.edu. https://orcid.org/0000-0002-0191-5697.

Received: 29 April 2022; Revised: 13 April 2023; Accepted: 13 April 2023; Published: 28 April 2023
https://doi.org/10.54844/gmiw.2022.0087

Most recently, the US congress authorized a program in NIH called "Helping to End Addition Long-term (HEAL)".[5] The program was designed to combat the opioid epidemic in USA and to substantially reduce the use of opioids for treating pain. Neuromodulation medical device is a large part of the program as neuromodulation, such as spinal cord stimulation, has been successfully used for treating various pain. The US congress has provided 1 billion USD to the HEAL program in 2019.

"In 1997, the field of neuromodulation was small and well defined. Indications for NIH neuromodulation procedures were largely limited to the treatment of chronic pain, spasticity and tremor," written by Robert Levy, MD, the Editor-in-Chief of an official journal of International Neuromodulation Society "*Neuromodulation* ".[6] The most traditional fields of neuromodulation include neuromodulation of the central nerve systems, such as deep brain stimulation and spinal cord stimulation. The new definition of neuromodulation has expanded to a much broader areas, including vagal nerve stimulation (VNS), sacral nerve stimulation (SNS), peripheral organ stimulation and even noninvasive transcutaneous autonomic nerve stimulation. In addition to the traditionally targeted diseases of Parkinson, epilepsy and chronic neuropathic pain, new treatments include inflammation (rheumatoid arthritis and inflammatory bowel diseases), metabolic diseases (obesity and diabetes), cardiovascular diseases (heart failure and hypertension) and gastrointestinal disorders.[6]

This mini-review focuses on the applications of neuromodulation for treating several functional upper gastrointestinal diseases (FGIDs), including gastroesophageal reflux disease (GERD), functional dyspepsia (FD) and gastroparesis.

METHODS OF NEUROMODULATION

Three different methods of neuromodulation have been applied for treating gastrointestinal diseases: (1) direct nerve stimulation; (2) direct gastrointestinal electrical stimulation and (3) transcutaneous electrical stimulation. The concept and pros/cons of each of these methods are introduced in this section.

Direct nerve stimulation

Direct nerve stimulation that has been used for treating gastrointestinal diseases includes VNS, SNS and spinal cord stimulation (SCS). The advantage of direct nerve stimulation is that the therapy is delivered automatically and chronically and is well suited for treating chronic illness. The major disadvantage of direct nerve stimulation is the requirement of surgical placement of stimulation electrodes and an implantable pulse generator.

Vagal nerve stimulation

VNS is accomplished by chronically implanted stimulation electrodes around the cervical (Figure 1) or abdominal (sub-diaphragmatic) vagus nerve and an implantable pulse generator chronically placed under the skin in the chest area. Typically, VNS is performed *via* the left vagus nerve using intermittent electrical stimulation and has been approved for treating epilepsy, treatment-resistant depression disorder and obesity.[7–9] Cervical VNS has advantage of being simple in surgical placement of electrodes and disadvantage of possible side effects on respiratory and cardiovascular systems.[10] Conversely, abdominal VNS is surgically more challenging but there are potentially less side effects on respiratory or cardiovascular system. Although no device has been approved for treating any gastrointestinal diseases, VNS has been under investigation for treating Crohn's disease with promising preliminary results.[11]

Sacral nerve stimulation

Similar to the vagus nerve, the sacral nerve belongs to parasympathetic nerve that innervates pelvic organs. While the vagus nerve plays an important role in controlling the functions (secretion, sensation and motility) of the esophagus, stomach, small intestine and proximal/middle portion of the colon, the sacral nerve controls the sensory and motility functions of the distal colon, rectum and anal sphincter. SNS has been clinically approved to treat overactive bladder, urinary retention and fecal incontinence.[12–14] SNS is also delivered *via* an implantable pulse generator subcutaneously placed beneath the skin of the buttocks (Figure 1). Its potential applications for treating gastrointestinal diseases are reported in a recent review.[15] Compared with VNS, SNS has advantages of being far away from the heart (and thus no concerns on potential cardiovascular side effects) and ease in electrode placement (the electrode lead can be inserted *via* the sacral foreman under guidance of x-ray.[16]

Spinal cord stimulation

SCS is the most commonly used neuromodulation method in clinical practice, accounting for about 70% of all neuromodulation treatments. It is approved for treating chronic pain from nerve damage in the trunk, arms or legs.[17] About 34,000 patients each year around the world undergo SCS implants and 50%–70% of patients report a 50% reduction in pain.[18] Unlike SNS or VNS, SCS uses multiple electrodes for stimulation in order to target the right nerves that innervate the area of pain. Recent innovations in SCS include various stimulation paradigms such as kilohertz stimulation, burst stimulation and closed-loop stimulation.[19–21] SCS has also been reported to suppress abdominal pain in patients with gastric disorders and chronic

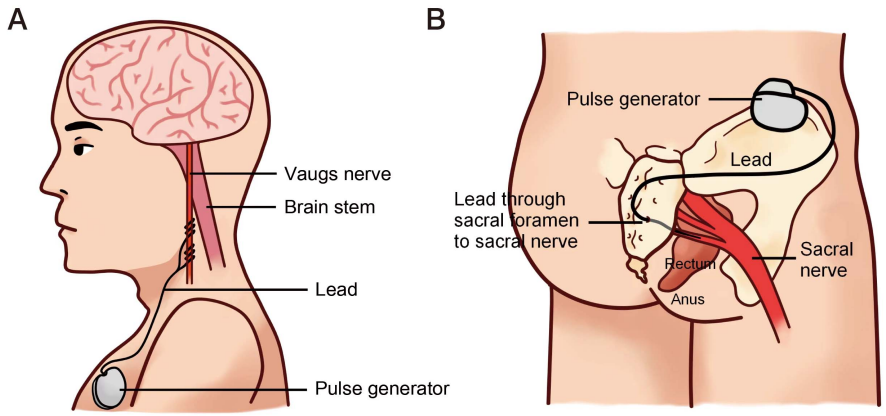

Figure 1. Electrical stimulation of parasympathetic nerves using an implantable pulse generator. A: Vagal nerve stimulation; B: Sacral nerve stimulation.

pancreatitis.[22,23]

Direct gastrointestinal electrical stimulation

Direct electrical stimulation of the gastrointestinal tract is accomplished by chronically implanting stimulation electrodes at the serosal surface of the esophagus, stomach, small intestine and colon.[24] Major variations in gastrointestinal electrical stimulation are in configuration of stimulation parameters, including long pulse stimulation, short pulse stimulation and pulse train stimulation.[25] Based on their effects on gastrointestinal motility, they can be classified as excitatory stimulation and inhibitory stimulation.

Long pulse stimulation (gastrointestinal pacing)

In all methods of direct nerve stimulation, including VNS, SNS and SCS, the stimulation pulse is below 600 microseconds (μs)or 0.6 ms, typically between 100–500 μs. In long pulse gastrointestinal (GI) stimulation that is designed to pace the gut, i.e., altering the intrinsic pace-making activity of the gut, the stimulation pulse width is much wider, ranging from 10,000 μs to 600,000 μs or 10 ms to 600 ms (see Figure 2A). The rationale for the use of such a wide stimulation pulse is due to the characteristic of the smooth muscle of the gut that has a long time constant of about 100ms. Only with such a wide pulse, is the GI stimulation capable of altering the intrinsic pace-making activity of the gut.[26] Another major difference in comparison with direct nerve stimulation is that GI long pulse electrical stimulation uses a stimulation frequency in the vicinity of intrinsic pace-making activity.[27] In the human stomach, the pace-making activity is of a frequency of 0.05 Hz or 3 cycles/min. This is much lower than the stimulation frequency used in nerve stimulation that is typically in the frequency range of 5–100 Hz. If a long pulse GI stimulation is delivered at a frequency slightly higher than the intrinsic pace-making activity, it may be able to successfully pace the gut and improve motility.[28] On the other hand, if the stimulation is performed at a frequency 50% higher than the intrinsic pace-making activity, it may induce dysrhythmia and inhibit gastrointestinal motility.[29] This method of inhibitory stimulation in the stomach has been proposed for treating obesity as it delays gastric emptying and suppresses food intake.[30–32]

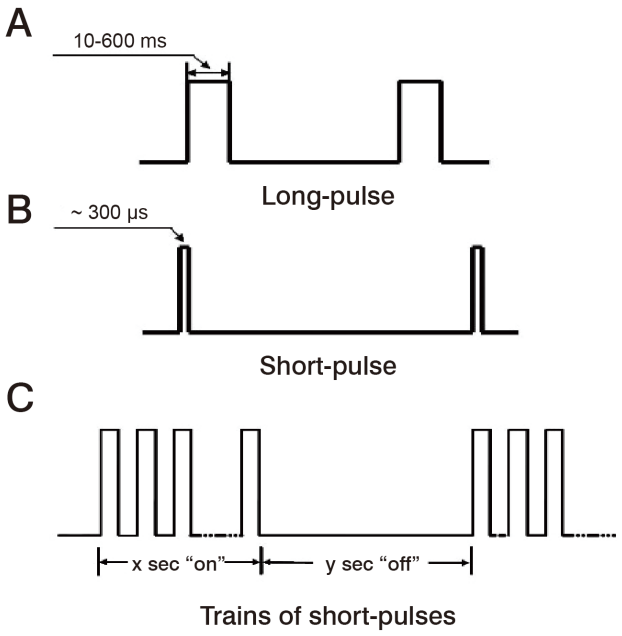

Figure 2. Different stimulation patterns used in gastrointestinal electrical stimulation. A: Long-pulse stimulation with a pulse width in the range of 10-600 ms; B: Short-pulse stimulation with a pulse width in the order of a few hundred microsecond (μs); C: Intermittent stimulation using trains of short-pulses.

Short pulse stimulation

In contrast to long-pulse stimulation, the pulse width in this method is substantially shorter and is in the order of a few hundred μs (Figure 2B). This is commonly used in nerve stimulation. Typically, electrical stimulation of the gut using short pulses does not directly alter GI smooth

muscle functions, but it may alter functions of the autonomic nervous system, central nervous system and enteric nervous system. However, it may not be as effective as direct nerve stimulation because the stimulation electrodes are placed in the gastrointestinal tissues instead of the nerve. The most popularly applied method of gastric electrical stimulation (GES) using short pulses is called the Enterra Therapy[33–35] that has been clinically used for treating nausea and vomiting in patients with gastroparesis. Detailed discussion is provided later in this review.

Pulse train stimulation

In most methods of electrical stimulation, pulses are delivered repetitively and continuously. However, in some cases, pulses are delivered intermittently, *i.e.*, electrical stimulation is delivered for a certain time period, called on-time and paused for a period of time, called off-time (Figure 2C). In this review, we call this method pulse train stimulation; whereas, in some applications, it is termed burst stimulation.[20] This method of stimulation has been used in a number of different areas, including GES, SCS and VNS.[11,20,31,32] In the method of GES for obesity, the train on-time was set at 2 s and off-time at 3 s.[31,32] In the Enterra therapy, the train on-time was set at 0.1 s and off-time at 5 s.[33]

Transcutaneous electrical stimulation

This is a noninvasive but indirect electrical stimulation method. It is appliable to nerves that are superficial and can be stimulated without direct electrode-nerve contact. This review focuses on three noninvasive methods that have been applied for treating gastrointestinal disease: transcutaneous auricular vagal nerve stimulation (taVNS), transcutaneous cervical vagal nerve stimulation (tcVNS) and transcutaneous electrical acustimulation (TEA). These three methods share a common feature and advantage: the therapy can be self-administrated by patients. Due to noninvasiveness and self-administrable features, these methods may have great potentials for treating various gastrointestinal diseases with mild-moderate symptoms.

taVNS

The auricular concha is innervated by the auricular vagus afferent nerve and the innervation of the cymba concha is 100% of vagus origin.[36,37] The auricular branch of the vagus nerve projects to the nucleus tractus solitarius that is further connected to other brain regions.[38,39] Due to superficial innervation of the auricular vagus nerve, taVNS is almost identical to direct auricular vagal nerve stimulation and has been applied for treating various disorders associated with central nervous system, such as epilepsy, migraine, and depression and anxiety.[38,40,42] Recently, taVNS has also been reported to improve gastrointestinal functions. The major technical challenge for taVNS is the development of an easy to use, reliable (good contact between stimulation electrodes and auricular concha) and wearable device.[43]

tcVNS

The tcVNS is accomplished by noninvasively stimulating the cervical vagus nerve using an external device. A small hand-held device called Gammacore has received the US Food and Drug Administration (FDA) clearance for treating and preventing migraine and cluster headache pain.[44] Typically, tcVNS is delivered a few times a day, each lasing a few minutes. While the majority of its applications is associated with central nervous system, it has also been applied for treating gastroparesis.[45,46]

TEA

In this method, electrical stimulation is delivered *via* surface electrodes to certain acupuncture points that are in vicinity of or coincide with peripheral nerves.[47,48] One typical example is the transcutaneous electrical stimulation at ST36 (an acupuncture point below the kneecap) that is in the vicinity of peroneal, sciatic and tibial nerves. The other example is the transcutaneous electrical stimulation at acupuncture point PC6 that coincides with the medial nerve. Since the stimulation is delivered *via* skin surface electrodes, TEA can be self-administered at home. Compared with electroacupuncture that can only be administered by medical professionals or acupuncturists, TEA has several distinct advantages: (1) it is completely noninvasive and does not use medical resources; (2) it can be delivered daily or even a few times daily and could thus be more effective than electroacupuncture that is typically applied only a few times a week; (3) TEA stimulation parameters are carefully chosen to improve physiological functions of a remotely targeted organ *via* the autonomic pathway. TEA at ST36 and PC6 has been reported to treating various FGIDs.[47,48]

RATIONALE OF NEUROMODULATION FOR FUNCTIONAL GI DISEASES

Autonomic dysfunction, sympathetic overactivity and/or parasympathetic hypoactivity, is common in various diseases, such as obesity, diabetes, inflammation, postoperative ileus and FGIDs. Three non-pharmacological methods may be used to improve autonomic dysfunctions: (1) enhancement of parasympathetic activity by directly or indirectly stimulating parasympathetic nerve; (2) inhibition of sympathetic activity by stimulating/blocking sympathetic nerve; and (3) suppression of sympathetic activity by surgically denervating corresponding sympathetic nerves. Due to non-reversal nature and potential side effects, surgical denervation is rarely applied for treating disorders associated with autonomic dysfunctions; whereas, neuromodulation that is reversable and

adjustable has a greater potential in treating various disorders attributed to autonomic dysfunction.

Autonomic dysfunction assessed by the time-domain and frequency-domain analyses of heart rate variability has been reported in patients with FGIDs, including GERD,[49,50] functional dyspepsia, [51,52] irritable bowel syndrome (IBS)[53,54] and constipation.[55] Most commonly reported abnormalities include a reduced parasympathetic activity or vagal tone and increased sympathovagal ratio. Reduced parasympathetic activity is known to result in gastrointestinal hypomotility that is one of major pathophysiological factors in FGIDs. Whereas increased sympathovagal balance or sympathetic overactivity has been reported to play an important role in visceral pain or hypersensitivity[56] that is another major pathophysiological factor of FGIDs. Indirectly, sympathetic overactivity was reported to result in inflammation and lead to visceral hypersensitivity.[57]

Most common pathophysiologies of FGIDs include GI dysmotility, visceral hypersensitivity and dysfunction of central processing of sensory information received from the GI tract. From the above discussion, we know that autonomic dysfunction is associated with most of these pathophysiological factors. Accordingly, direct and indirect autonomic neuromodulation has potentials for treating FGIDs.

NEUROMODULATION FOR GASTROESOPHAGEAL REFLUX DISEASE

GERD is a chronic disorder that the reflux of stomach contents into the esophagus causes troublesome symptoms or complications. It can be classified into non-erosive reflux disease (NERD), erosive esophagitis and Barrett's esophagus.[58] The prevalence of at least weekly GERD symptoms in the US is 20% with 110,000 annual hospital admissions.[59] Major GERD pathophysiologies include: (a) impaired esophageal clearance due to impaired esophageal motility (*e.g.* weak esophageal peristalsis); (b) the esophagogastric junction (EGJ) anti-reflux barrier dysfunction due to hypotensive lower esophageal sphincter (LES), transient LES relaxations (tLESRs), and/or dyssynergia between LES and the crural diaphragm (*e.g.* the presence of hiatal hernia); and c) downstream gastric factors: delayed gastric emptying and gastric acid pocket.[60,61] Treatment of GERD includes lifestyle modifications, medications (*e.g.* proton pump inhibitors and histamine-2 receptor antagonists), and surgical procedures (*e.g.* fundoplication).[62] Neuromodulation methods that have been applied for treating GERD include direct electrical stimulation at the LES and transcutaneous electrical stimulation at acupuncture points and abdominal muscles.

LES electrical stimulation

In this method, electrical stimulation is directly applied to the LES *via* implantable electrodes and pulse generator. In open-label clinical trial, LES electrical stimulation was performed using parameters of 20 Hz, 215 μs, 3–8 mA, 30 min each time and 6–12 times/day in 23 patients with GERD. It resulted in a reduction of acid reflux from 10% to 4% and normalization of acid reflux in 71% of the patients after 24-month treatment.[63] However, another open-label study in 17 patients with GERD and ineffective esophageal motility, the same method of electrical stimulation at LES failed to demonstrate normalization or significant improvement of acid exposure in the distal esophagus although patients satisfaction was improved.[64] It remains to be determined whether this novel LES electrical stimulation method will gain regulatory approval for treating GERD. Mechanistically, it is unclear whether such a stimulation alters the function of the vagus nerve or the function of the LES. Based on the parameters (pulse width of 215 μs) used in clinical studies, this method of stimulation may not have a direct effect on the smooth muscle of the LES. Further mechanistic studies may be needed to improve the therapy efficacy.

Transcutaneous electrical acustimulation

Several clinical studies have reported the ameliorating effects and autonomic mechanisms of TEA at acupuncture points ST36 alone or ST36 plus PC6 using a special set of parameters (2s-on, 3s-off, 25 Hz, 0.5 ms) known to improve gastrointestinal motility and vagal activity.[47,48]

In an earlier comparative study, TEA at both ST36 and PC6 (30 min twice daily for 2 weeks) plus proton pump inhibitor (PPI) was reported to increase LES pressure and reduce the number of weak acid reflux episode, which was not seen in patients treated with PPI + sham stimulation or PPI + domperidone.[65] The increase in LES pressure was also reported in an acute study in 40 patients with GERD in which TEA was performed *via* bilateral ST36 points and the patients were asked to breath in synchronization with the stimulation (12 breaths per minute), a method called synchronized TEA or STEA;[55] in addition, STEA but not sham-TEA reduced the pooled number of ineffective esophageal motility among the treated patients ($P = 0.021$). A typical example showing the effects of TEA on LES pressure and distal esophageal motility is presented in Figure 3. The increase in LES pressure (pressure zone in between 30–35 cm) is shown by the change in the color from green (low pressure) to red (high pressure). Similarly, the enhancement of distal esophageal peristalsis is also shown by the change in the color from green to red. Concurrently, the acute STEA increased vagal activity and reduced the sympathovagal ratio assessed by the

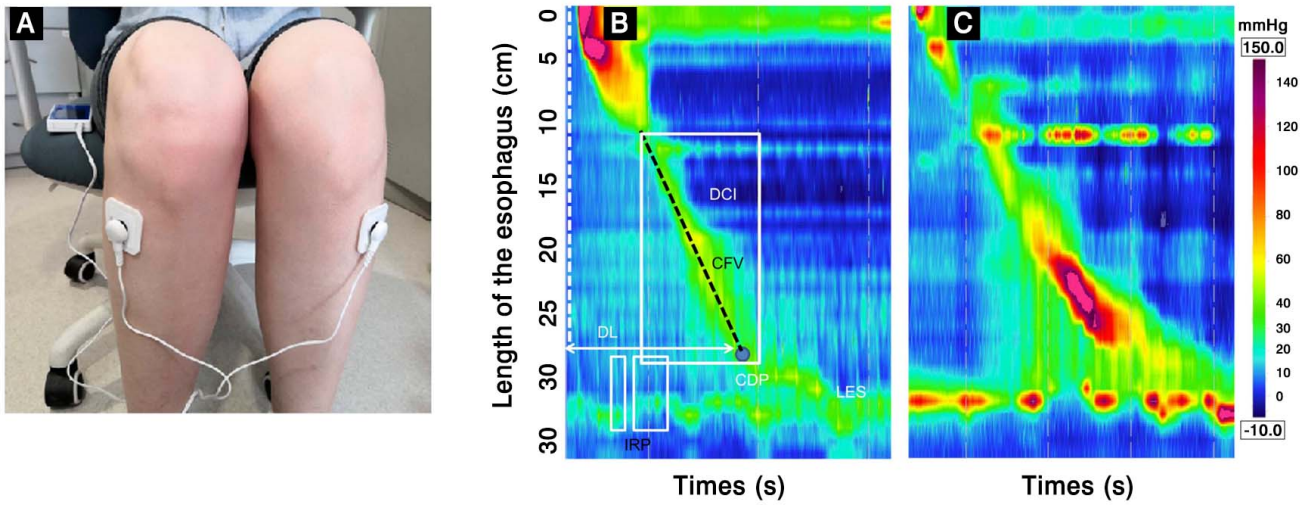

Figure 3. STEA at bilateral ST36 in patients with GERD. A: Placement of stimulation electrodes at bilateral ST36 points. Right: high resolution esophageal motility before (B) and after 30-min STEA (C) in a GERD patient. An increase in LES pressure and distal esophageal motility can be clearly appreciated. STEA: synchronized transcutaneous electrical acustimulation; GERD: gastroesophageal reflux disease; LES: lower esophageal sphincter.

spectral analysis of heart rate variability (HRV), suggesting a vagally mediated mechanism.[66]

In addition to hypotensive LES pressure and ineffective esophageal motility, impaired gastric accommodation and delayed gastric emptying also play important role in the pathophysiology of GERD. Acute TEA at bilateral ST36 and bilateral PC6 was reported to improve gastric accommodation and gastric pace-making activity and reduced postprandial dyspepsia symptoms in patients with GERD.[67] A 4-week TEA at bilateral ST36 and bilateral PC6 in patients with GERD improved reflux-related symptoms, increases distal esophageal motility, reduced the incidence of ineffective esophageal contractions during wet swallows, and improved gastric accommodation and pace-making activity.[68] It was concluded that the improvement in GERD symptoms was attributed to the integrative effects of TEA on these gastroesophageal functions mediated *via* the vagal mechanism.

In another study, TEA at ST36 and PC6 was performed in combination with deep breathing training in patients with GERD.[69] A 4-week treatment using this combined method was reported to reduce acid reflux and GERD symptoms with concurrent increase in LES pressure and vagal activity, and decrease in serum nitric oxide.

Transcutaneous abdominal electrical stimulation

Recently, a transcutaneous electrical stimulation device was developed to stimulate abdominal muscle in synchronization with the subject's breathing phase (active during inhalation). Although its mechanism is unclear, it seems that the stimulation aims to induce abdominal muscle contractions and thereby enhancing the LES pressure. It is known that the LES pressure measured by esophageal manometry results from the combined pressure of the LES and crural diaphragm. Such a stimulation might increase the pressure of crural diaphragm. However, no data is available to support the hypothesis. In a pilot open-label study, the transcutaneous abdominal electrical stimulation reduced acid exposure time and the DeMeester score by more than 50% in GERD patients who were refractory to standard proton pump inhibitor therapy A.[70]

NEUROMODULATION FOR GASTROPARESIS

Gastroparesis is the second most common functional disorders of the upper gastrointestinal tract. Gastroparesis is defined by characteristic symptoms of nausea, vomiting, early satiety, abdominal pain and weight loss in the absence of mechanical gastric outlet obstruction and with evidence of an objective delay in gastric emptying.[71] A 4-hour solid gastric scintigraphy is generally considered the most valid means of defining delayed gastric emptying.[72] Currently prokinetic therapies are limited and elicit serious side effects.[73–75] Pathophysiology of gastroparesis includes delayed gastric emptying, impaired gastric accommodation, visceral hypersensitivity and gastric dysrhythmia.[76] There are several cellular pathological alterations in gastroparesis, including loss of interstitial cells of Cajal, fibrosis of muscular layers, inflammatory cell infiltration around myenteric neurons and neuronal abnormalities.[76]

Neuromodulation methods that have been applied for treating gastroparesis include GES with short pulses, GES with long pulses, TEA, and tcVNS.

GES with short pulses (Enterra Therapy) for nausea and vomiting

This is most published method of neuromodulation used in patients with gastroparesis because the therapy received FDA approval for humanitarian use and there are very limited treatment options for gastroparesis. The therapy is accomplished by chronically and surgically implanting stimulation electrodes in the gastric serosa and an implantable pulse generator underneath the skin in the abdomen. The typical stimulation parameter setting is as follows: two pulses with a width of a few hundred μs and frequency of 14 Hz or an interval of 71.4 ms between the two pulses repeated every 5 sec. The stimulation is continuous.

The Enterra therapy is mostly used for treating nausea and vomiting (two major symptoms of gastroparesis) in patients with gastroparesis with a general efficacy of 60%–70%.[33,35,77,79] However, possible placebo effects could not be ruled out. A recent systematic review and meta-analysis revealed following results: five controlled studies from 1990–2014 showed no difference in total symptom severity score of gastroparesis between periods of stimulation-on vs. stimulation-off; whereas, 16 open-label GES studies showed a significant decrease in total symptom severity score. It was concluded that independent of the treatment modality, baseline symptom severity impacted treatment results in gastroparesis.[80] The GES effects on symptoms of gastroparesis might be comprised by its controversial findings on gastric emptying: few studies indicated improvement in gastric emptying but most of other studies showed no acceleration in gastric emptying.[35]

Based on the setting of stimulation parameters (short pulses), the Enterra therapy is unlikely to alter smooth muscle functions directly. However, enhancement of vagal activity has been reported with this method of GES in several previous studies.[81,82] Furthermore, increased vagal responses to stimulation were reported to be correlated with significant decrease in total symptom score in patients with idiopathic and type 1 diabetic gastroparesis.[83] In an animal model of vomiting, vagotomy was noted to block its anti-emetic effect of the GES in dogs[81] and denervation of the vagal afferent nerve abolished its enhancive effect on vagal efferent.[84] These findings suggest a vagal-vagal pathway of GES with the Enterra parameters.

GES with long pulses (gastric pacing) for gastroparesis

As stated earlier, gastric pacing can be accomplished with the use of long pulses delivered at a frequency in the vicinity of the intrinsic frequency of the gastric slow wave. Similar to cardiac pacing, such a GES method (gastric pacing) is capable of altering intrinsic gastric pace-making activity.[26,85] Normalization of gastric dysrhythmia with gastric pacing was reported in patients with gastroparesis and animals with glucagon- and vasopressin-induced gastric dysrhythmia with concurrent acceleration in gastric emptying.[28,81,86]

To the best of my knowledge, none of current commercially available implantable pulse generators is capable of delivering long pulses and therefore gastric pacing has been applied in only few clinical studies with the use of custom-made device. In one study, gastric pacing was performed daily for 4 weeks using repetitive long pulses (about 300 ms, 1000 times higher than that used in most neuromodulation devices) *via* an external device in 9 patients with gastroparesis.[28] Gastric slow waves were entrained in all patients and tachygastria observed at baseline in 2 patients was normalized with gastric pacing. Both symptoms of gastroparesis and delayed gastric emptying were improved at the end of the treatment. In another clinical study, sequential gastric pacing was delivered at two longitudinal locations in the stomach *via* an external multi-channel stimulator for a period of 2 weeks in 19 patients with gastroparesis.[87] Similar improvement was reported on gastroparetic symptoms and gastric emptying. In addition, two-channel sequential pacing was found to outperform single channel gastric pacing.

Compared with short pulse GES, GES with long pulses exerts direct effects on gastric pace-making activity and gastric emptying. It is therefore capable of improving both symptoms of gastroparesis and gastric motility. However, due to the lack of any regulatorily approved device, its clinical applications have been limited.

Transcutaneous electrical acustimulation for gastroparesis

To investigate potential effects of TEA on nausea in gastroparesis, Sarosiek *et al.* performed acute TEA at both ST36 and PC6 in 11 nauseated patients with diabetic gastroparesis.[88] TEA was reported to significantly reduce visual stimulation-induced nausea score and improve gastric slow waves. The electroencephalography revealed a change of dominance from right to left inferior lobe activity, suggesting a central mechanism involved in the anti-nauseated effect of TEA. Similar effects on nausea and gastric slow waves were reported in patients with idiopathic gastroparesis with TEA in synchronization with breathing.[89]

In a placebo-controlled crossover clinical study in 18 patients with diabetic gastroparesis, daily treatment of TEA at ST36 and PC6 for a period of 4 weeks improved major symptoms of gastroparesis, including nausea, vomiting, abdominal pain, bloating and retching. None of the symptom improvement was noted during the period of sham-TEA treatment.[90] Physiologically, the

TEA treatment resulted in a significant improvement in gastric pace-making activity in both fasting and postprandial states, suggesting an enhancement of gastric motility.

Transcutaneous cervical vagal nerve stimulation for gastroparesis

tcVNS was applied in treating gastroparesis. In a pilot open-label clinical study in 17 patients with idiopathic gastroparesis, tcVNS was performed twice daily for a period of 4 weeks. Each stimulation was delivered for 2 min over the left and right cervical vagus nerve using a hand-held stimulator.[45] Mild-moderate but significant improvement was noted at the end of the treatment in nausea/vomiting, fluuness/satiety and bloating/pain; the effects were sustained during the follow-up period without treatment. Currently the gastric emptying half-time was marginally (P = 0.053) reduced after the treatment.

The tcVNS is attractive since it is easy to implement. However, placebo-controlled clinical studies are needed to confirm the above-mentioned improvement in gastroparesis. It is also important to prove whether such a stimulation method indeed activates vagal nerve. The other issue is compliance with the delivery of the therapy. As reported in an initial study with tcVNS in patients with drug-refractory gastroparesis, only 23 of 35 patients were compliant with the study and only 7 patients continued the treatment beyond 3 weeks.[46]

NEUROMODULATION FOR FUNCTIONAL DYSPEPSIA

FD is the most prevalent functional disorders of the upper gastrointestinal tract. It affects up to 16% of general population.[91–93] FD is one of the most common reasons for primary care visits, negatively impacts productivity at the workplace, and has annual costs in the United States exceeding 18 billion USD.[94,92] Symptoms of FD are similar to those of gastroparesis but to a lesser degree, especially nausea and vomiting. However, a recent multi-center study suggested that FD and gastroparesis in tertiary care are interchangeable syndromes with common clinical and pathologic features.[95] Pathophysiology of FD is multi-factorial, including impaired gastric accommodation, gastroduodenal dysmotility, gastroduodenal hypersensitivity, gastroduodenal inflammation, intestinal dysbiosis, dysfunction of the brain-gut axis, and psychological factors and central mechanisms.[96] Conventional treatment options include H. pylori eradication, dietary modifications, medications and other therapies, such as psychotherapy and complementary and integrative therapies.[96]

Neuromodulation therapies applied to FD are exclusively noninvasive, including TEA,[97–99] taVNS[100] and transcutaneous electrical stimulation using vacuum interferential current.[101]

Transcutaneous electrical acustimulation for FD

Several clinical studies have demonstrated the feasibility and efficacy of TEA at ST36 and PC6 for treating FD. Most importantly, findings of these studies suggested that TEA ameliorates dyspeptic symptoms by improving several major pathophysiological factors of FD mediated *via* the vagal mechanism.

In one study, 27 patients with FD were treated with TEA at acupuncture points ST36 and PC6 or sham-TEA (stimulation delivered at non-acupoints) twice daily for 2 weeks using a TENS unit.[97] The TEA treatment resulted in a 55% reduction in the total symptom score of FD compared with the baseline score and the improvement was significantly higher than the sham treatment. Mechanistically, both acute and chronic TEA was reported to enhance vagal efferent activity assessed by the spectral analysis of HRV derived from the electrocardiograph (ECG) signal. Meanwhile, the chronic TEA treatment also increased the plasma level of neuropeptide Y.[97] In another study, TEA at ST36 and PC6 and TEA at sham points were performed in a crossover design twice daily in 28 patients with FD using a wearable watch-sized stimulator.[98] The TEA at the acupoints not the sham points reduced the total dyspeptic symptom by 35%. Physiologically, chronic TEA improved several pathophysiological factors of FD, including gastric accommodation, gastric slow waves and gastric emptying.[98] Similar improvement in gastric accommodation, gastric slow waves and vagal activity was also reported with acute TEA in patients with FD.[99]

Transcutaneous auricular vagal nerve stimulation for FD

taVNS is typically used for treating disorders of the central nervous system due to its central effect *via* the vagal afferent pathway. Recently, taVNS has also been applied for treating gastrointestinal disorders, such as FD,[100] irritable bowel syndrome[102,103] and constipation.[103]

In a recent clinical study, 36 patients with FD were randomized to receive 2-week bilateral taVNS or sham-ES (stimulation *via* points at elbow), 30min twice daily with parameters (2s-on, 3s-off, 25 Hz and 0.5 ms) known to enhance vagal activity when applied at ST36.[47,48] Significant improvement in total dyspeptic symptoms was reported with the chronic TEA treatment but not sham-EA. TEA but not sham-ES also reduced the symptom scores of bloating, abdominal pain, depression and anxiety (Figure 4). Physiologically, TEA

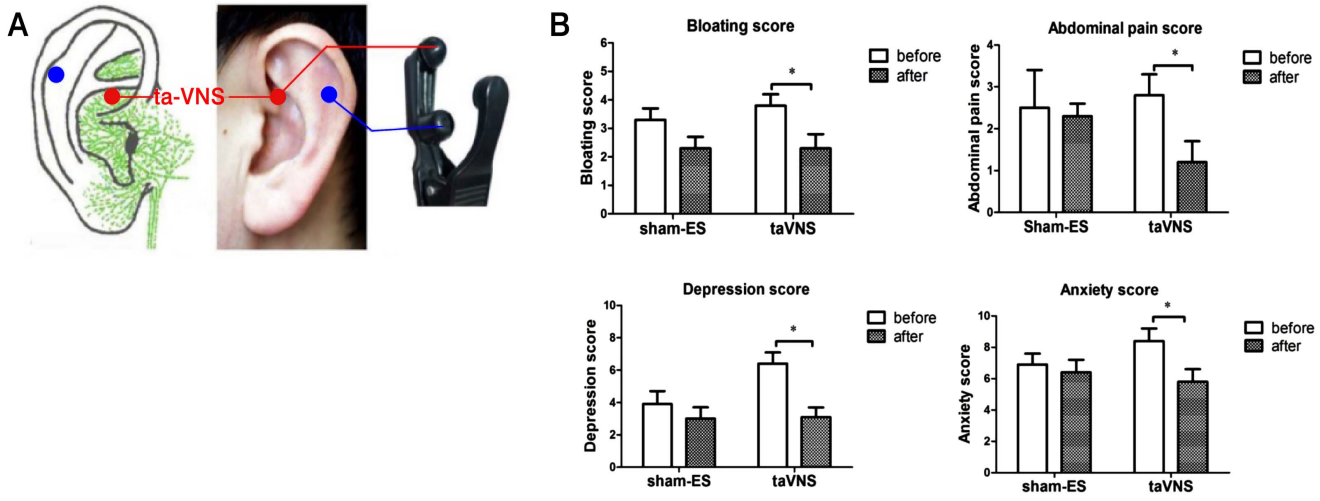

Figure 4. The taVNS in patients with functional dyspepsia. A: Placement of stimulation electrodes. B: Effects of chronic taVNS on abdominal bloating, abdominal pain, depression and anxiety. $^{*}P < 0.05$ *vs.* before, sham-ES and taVNS ($n = 18$). taVNS: transcutaneous auricular vagal nerve stimulation.

improved gastric accommodation, gastric slow waves and vagal activity.

CONCLUSIONS

Both invasive and noninvasive neuromodulation methods have been clinically applied for treating GERD, FD and gastroparesis. While this review is limited to their applications for upper GI disorders, some of these neuromodulation methods have also been applied for treating functional disorders of the lower GI tract, such as irritable bowel syndrome and constipation.[24,104]

Invasive neuromodulation methods are attractive for treating refractory chronic diseases. GES with the Enterra parameters is most widely used method in treating nausea and vomiting in patients with gastroparesis with several hundred publications. Although the therapy is effective in more than 50% of patients, possible placebo effects cannot be ruled out. Apparently, methodological improvement, such as optimization of stimulation parameters and treatment regimens is needed before the therapy is fully approved by regulatory authority. In addition, a better understanding on the mechanisms involved in the anti-emetic effect of the GES-Enterra method is needed in order to refine the method and improve the efficacy of the therapy. Gastric pacing using long pulses is attractive for treating gastroparesis since it improves both symptoms and gastric emptying. Unfortunately, no implantable device is commercially available at present and therefore the progress in clinical research and applications has been slow. Electrical stimulation at LES for GERD is an innovative method. However, more clinical studies are needed to demonstrate its efficacy in reducing acid reflux and symptoms of GERD. Moreover, it remains unclear whether and how LES stimulation may enhance LES pressure.

The noninvasive methods of TEA, tcVNS and taVNS have been used for treating GERD, FD and gastroparesis with promising results. Most of studies presented in this review were randomized and controlled. These methods have great therapeutic potentials for treating patients with mild-moderate symptoms. Major challenges with the widespread applications of these transcutaneous methods include patient compliance and mechanisms of action. Unlike the use of an implantable device with which the patient does not have to do anything or the use of medications with which the patient only needs to take the pill once or twice daily, the noninvasive neuromodulation therapy is dependent on full commitment of the patient. Each day, the patient has to wear the device and deliver the therapy that could be tedious and bothersome. Accordingly, advanced technologies should be used to make the transcutaneous devices easy and reliable to use. Moreover, it is necessary to make the devise resemble to an entertainment apparatus so that the patient can deliver the therapy in public or working environment.

DECLARATIONS

Author contributions

Jiande Chen: Responsible for all work associated this review article.

Funding

This work was partially funded by the National Institutes of Health (DK107754; DK100212; UG3NS115108).

Informed consent

The author certified that he obtained all appropriate experimenters' consent forms. In the forms, the experimenters have given their consents for their images to be published in the journal.

Ethical approval
Not applicable.

Conflict of interest
Jiande Chen is the Editor-in-Chief of the journal. The article was subject to the journal's standard procedures, with peer review handled independent of the editor and the affiliated research groups.

Data sharing
No additional data is available.

REFERENCES

1. Heath RG. *Studies in schizophrenia*. Harvard University Press; 1954.
2. Famm K, Litt B, Tracey KJ, Boyden ES, Slaoui M. Drug discovery: a jump-start for electroceuticals. *Nature*. 2013;496(7444):159–161.
3. Wang B. DARPA funds seven teams to modulate nerves to treat disease. NextBigFuture. Published October 06, 2015. Accessed 18 April, 2023. https://www.nextbigfuture.com/2015/10/darpa-funds-seven-teams-to-modulate.html
4. The NIH Common Fund. Stimulating Peripheral Activity to Relieve Conditions (SPARC). Common Fund. Updated October 26, 2022. Accessed 18 April, 2023. https://commonfund.nih.gov/sparc
5. NIH HEAL. The Helping to End Addiction Long-term® Initiative. Accessed 18 April, 2023. https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative
6. Levy RM. The evolving definition of neuromodulation. *Neuromodulation*. 2014;17(3):207–210.
7. Herman ST, Pedley TA. New options for the treatment of epilepsy. *JAMA*. 1998;280(8):693–694.
8. Schlaepfer TE, Frick C, Zobel A, *et al*. Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med*. 2008;38(5):651–661.
9. Shikora SA, Wolfe BM, Apovian CM, *et al*. Sustained Weight Loss with Vagal Nerve Blockade but Not with Sham: 18-Month Results of the ReCharge Trial. *J Obes*. 2015;2015:2015365604.
10. Ben-Menachem E, Revesz D, Simon BJ, Silberstein S. Surgically implanted and non-invasive vagus nerve stimulation: a review of efficacy, safety and tolerability. *Eur J Neurol*. 2015;22(9):1260–1268.
11. Bonaz B. Is-there a place for vagus nerve stimulation in inflammatory bowel diseases? *Bioelectron Med*. 2018;4:4.
12. Nazema Y Siddiqui, Jennifer M Wu, Cindy L Amundsen. Efficacy and adverse events of sacral nerve stimulation for overactive bladder: A systematic review. *Neurourol Urodyn*. 2010;29:S18–S23.
13. Yang, Yong Xu, Genyi Qu, Yulong Zhang. Refractory overactive bladder patients who chose sacral neuromodulation therapy after failed OnabotulinumtoxinA treatment: A systematic review and meta-analysis. *PLoS One*. 2020;15(3):e0230355.
14. Huang Y, Koh CE. Sacral nerve stimulation for bowel dysfunction following low anterior resection: a systematic review and meta-analysis. *Colorectal Dis*. 2019;21(11):1240–1248.
15. Wang X, Chen JDZ. Sacral Nerve Stimulation for Gastrointestinal Disorders. In: Thakor NV, eds. *Handbook of Neuroengineering*. Singapore: Springer; 2022.
16. Whitney K Hendrickson, Cindy L Amundsen. Sacral neuromodulation: sacral anatomy and optimal lead placement. *Int Urogynecol J*. 2021;32(9):2545–2547.
17. E L Simpson, A Duenas, M W Holmes, D Papaioannou, J Chilcott. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess*. 2009;13(17):1–154.
18. Thomson S. Spinal cord stimulation: its role in managing chronic disease symptoms. Published December 2019. Accessed April 18, 2023. https://www.neuromodulation.com/assets/documents/Fact_Sheets/fact_sheet_spinal_cord_stimulation.pdf
19. Al-Kaisy A, Palmisani S, Pang D, *et al*. Prospective, Randomized, Sham-Control, Double Blind, Crossover Trial of Subthreshold Spinal Cord Stimulation at Various Kilohertz Frequencies in Subjects Suffering From Failed Back Surgery Syndrome (SCS Frequency Study). *Neuromodulation*. 2018;21(5):457–465.
20. Kirketeig, Carsten Schultheis, Xander Zuidema, Corey W Hunter, Timothy Deer. Burst Spinal Cord Stimulation: A Clinical Review. *Pain Med*. 2019;20(Suppl 1):S31–S40.
21. Mekhail N, Levy RM, Deer TR, *et al*. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. *Lancet Neurol*. 2020;19(2):123–134.
22. Ratnayake CB, Bunn A, Pandanaboyana S, Windsor JA. Spinal Cord Stimulation for Management of Pain in Chronic Pancreatitis: A Systematic Review of Efficacy and Complications. *Neuromodulation*. 2020;23(1):19–25.
23. Kapural L, Brown BK, Harandi S, Rejeski J, Koch K. Effects of Spinal Cord Stimulation in Patients with Chronic Nausea, Vomiting, and Refractory Abdominal Pain. *Dig Dis Sci*. 2022;67(2):598–605.
24. Chen JD, Yin J, Wei W. Electrical therapies for gastrointestinal motility disorders. *Expert Rev Gastroenterol Hepatol*. 2017;11(5):407–418.
25. Yin, Jiande D Z Chen. Implantable gastric electrical stimulation: ready for prime time? *Gastroenterology*. 2008;134(3):665–667.
26. Z Y Lin, R W McCallum, B D Schirmer, J D Chen. Effects of pacing parameters on entrainment of gastric slow waves in patients with gastroparesis. *Am J Physiol*. 1998;274(1):G186–G191.
27. Sun, Geng-Qing Song, Jieyun Yin, Yong Lei, Jiande D Z Chen. Effects and mechanisms of gastrointestinal electrical stimulation on slow waves: a systematic canine study. *Am J Physiol Regul Integr Comp Physiol*. 2009;297(5):R1392–R1399.
28. McCallum RW, Chen JD, Lin Z, Schirmer BD, Williams RD, Ross RA. Gastric pacing improves emptying and symptoms in patients with gastroparesis. *Gastroenterology*. 1998;114(3):456–461.
29. Ouyang H, Xing J, Chen JD. Tachygastria induced by gastric electrical stimulation is mediated. *via*. alpha- and beta-adrenergic pathway and inhibits antral motility in dogs. *Neurogastroenterol Motil*. 2005;17(6):846-853.
30. Maisiyiti A, Chen JD. Systematic review on gastric electrical stimulation in obesity treatment. *Expert Rev Med Devices*. 2019;16(10):855–861.
31. Zhang J, Tang M, Chen JD. Gastric electrical stimulation for obesity: the need for a new device using wider pulses. *Obesity (Silver Spring, Md.)*. 2009;17(3):474–480.
32. Song GQ, Zhu H, Lei Y, *et al*. Gastric electrical stimulation optimized to inhibit gastric motility reduces food intake in dogs. *Obes Surg*. 2015;25(6):1047–1055.
33. Abell T, McCallum R, Hocking M, *et al*. Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology*. 2003;125(2):421–428.
34. Soffer E, Abell T, Lin Z, *et al*. Review article: gastric electrical stimulation for gastroparesis--physiological foundations, technical aspects and clinical implications. *Aliment Pharmacol Ther*. 2009;30(7):681–694.
35. Yin, Thomas D Abell, Richard W McCallum, Jiande D Z Chen. Gastric neuromodulation with Enterra system for nausea and vomiting in patients with gastroparesis. *Neuromodulation*. 2012;15(3):224–231.
36. Kaniusas E, Kampusch S, Tittgemeyer M, *et al*. Current Directions in the Auricular Vagus Nerve Stimulation I - A Physiological Perspective. *Front Neurosci*. 2019;13:854.
37. Peuker ET, Filler TJ. The nerve supply of the human auricle. *Clinical anatomy (New York, N.Y.)*. 2002;15(1):35–37.
38. Kong J, Fang J, Park J, Li S, Rong P. Treating Depression with

Transcutaneous Auricular Vagus Nerve Stimulation: State of the Art and Future Perspectives. *Front Psychiatry*. 2018;9:20.

39. Chun-Hong Liu, Guang-Zhong Zhang, Bin Li, *et al*. Role of inflammation in depression relapse. *J Neuroinflammation*. 2019;16(1):90.
40. Sabers A, Aumüller-Wagner S, Christensen LR, *et al*. Feasibility of transcutaneous auricular vagus nerve stimulation in treatment of drug resistant epilepsy: A multicenter prospective study. *Epilepsy Res*. 2021;177:106776.
41. Thompson SL, O'Leary GH, Austelle CW, *et al*. A Review of Parameter Settings for Invasive and Non-invasive Vagus Nerve Stimulation (VNS) Applied in Neurological and Psychiatric Disorders. *Front Neurosci*. 2021;15:709436.
42. Straube A, Eren O. tVNS in the management of headache and pain. *Autonomic neuroscience : basic & clinical*. 2021;236:102875.
43. Lei Wang, Yu Wang, Yifei Wang, *et al*. Transcutaneous auricular vagus nerve stimulators: a review of past, present, and future devices. *Expert Rev Med Devices*. 2022;19(1):43–61.
44. Nesbitt AD, Marin JC, Tompkins E, Ruttledge MH, Goadsby PJ. Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. *Neurology*. 2015;84(12):1249–1253.
45. 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.
46. Paulon E, Nastou D, Jaboli F, Marin J, Liebler E, Epstein O. Proof of concept: short-term non-invasive cervical vagus nerve stimulation in patients with drug-refractory gastroparesis. *Frontline Gastroenterol*. 2017;8(4):325–330.
47. Chen JDZ, Ni M, Yin J. Electroacupuncture treatments for gut motility disorders. *Neurogastroenterol Motil*. 2018;30(7):e13393.
48. Zhang B, Xu F, Hu P, *et al*. Needleless Transcutaneous Electrical Acustimulation: A Pilot Study Evaluating Improvement in Post-Operative Recovery. *Am J Gastroenterol*. 2018;113(7):1026–1035.
49. Branislav Milovanovic, Branka Filipovic, Slavica Mutavdzin, *et al*. Cardiac autonomic dysfunction in patients with gastroesophageal reflux disease. *World J Gastroenterol*. 2015;21(22):6982–6989.
50. Djeddi DD, Kongolo G, Stéphan-Blanchard E, *et al*. Involvement of autonomic nervous activity changes in gastroesophageal reflux in neonates during sleep and wakefulness. *PLoS One*. 2013;8(12):e83464.
51. Dal K, Deveci OS, Kucukazman M, *et al*. Decreased parasympathetic activity in patients with functional dyspepsia. *Eur J Gastroenterol Hepatol*. 2014;26(7):748–752.
52. Vargas-Luna FM, Huerta-Franco MR, Schurman JV, *et al*. Electrogastrographic and autonomic nervous system responses to solid and liquid meals in youth with functional dyspepsia. *Neurogastroenterol Motil*. 2020;32(4):e13785.
53. Mazurak N, Seredyuk N, Sauer H, Teufel M, Enck P. Heart rate variability in the irritable bowel syndrome: a review of the literature. *Neurogastroenterol Motil*. 2012;24(3):206–216.
54. Cain KC, Jarrett ME, Burr RL, Hertig VL, Heitkemper MM. Heart rate variability is related to pain severity and predominant bowel pattern in women with irritable bowel syndrome. *Neurogastroenterol Motil*. 2007;19(2):110–118.
55. Heitkemper M, Jarrett M, Cain KC, *et al*. Autonomic nervous system function in women with irritable bowel syndrome. *Dig Dis Sci*. 2001;46(6):1276–1284.
56. Gil DW, Wang J, Gu C, Donello JE, Cabrera S, Al-Chaer ED. Role of sympathetic nervous system in rat model of chronic visceral pain. *Neurogastroenterol Motil*. 2016;28(3):423–431.
57. John H Winston, Sushil K Sarna. Enhanced sympathetic nerve activity induced by neonatal colon inflammation induces gastric hypersensitivity and anxiety-like behavior in adult rats. *Am J Physiol Gastrointest Liver Physiol*. 2016;311(1):G32–G39.
58. Katzka DA, Pandolfino JE, Kahrilas PJ. Phenotypes of Gastroesophageal Reflux Disease: Where Rome, Lyon, and Montreal Meet. *Clin Gastroenterol Hepatol*. 2020;18(4):767–776.
59. Thukkani N, Sonnenberg A. The influence of environmental risk factors in hospitalization for gastro-oesophageal reflux disease-related diagnoses in the United States. *Aliment Pharmacol Ther*. 2010;31(8):852–861.
60. C P Gyawali, S Roman, A J Bredenoord, *et al*. Classification of esophageal motor findings in gastro-esophageal reflux disease: Conclusions from an international consensus group. *Neurogastroenterol Motil*. 2017;29(12):10.
61. Tack J, Pandolfino JE. Pathophysiology of Gastroesophageal Reflux Disease. *Gastroenterology*. 2018;154(2):277–288.
62. Zerbib F, Bredenoord AJ, Fass R, *et al*. ESNM/ANMS consensus paper: Diagnosis and management of refractory gastro-esophageal reflux disease. *Neurogastroenterol Motil*. 2021;33(4):e14075.
63. Rodríguez L, Rodriguez P, Gómez B, *et al*. Two-year results of intermittent electrical stimulation of the lower esophageal sphincter treatment of gastroesophageal reflux disease. *Surgery*. 2015;157(3):556–567.
64. Paireder M, Kristo I, Asari R, *et al*. Effect of electrical stimulation therapy of the lower esophageal sphincter in GERD patients with ineffective esophageal motility. *Surg Endosc*. 2021;35(11):6101–6107.
65. Meng LN, Chen S, Chen JD, Jin HF, Lu B. Effects of Transcutaneous Electrical Acustimulation on Refractory Gastroesophageal Reflux Disease. *Evid Based Complement Alternat Med*. 2016;2016:8246171.
66. Liu Z, Lu D, Guo J, *et al*. Elevation of Lower Esophageal Sphincter Pressure With Acute Transcutaneous Electrical Acustimulation Synchronized With Inspiration. *Neuromodulation*. 2019;22(5):586–592.
67. Hu Y, Zhang B, Shi X, *et al*. Ameliorating Effects and Autonomic Mechanisms of Transcutaneous Electrical Acustimulation in Patients With Gastroesophageal Reflux Disease. *Neuromodulation*. 2020;23(8):1207–1214.
68. Zhang B, Hu Y, Shi X, *et al*. Integrative Effects and Vagal Mechanisms of Transcutaneous Electrical Acustimulation on Gastroesophageal Motility in Patients With Gastroesophageal Reflux Disease. *Am J Gastroenterol*. 2021;116(7):1495–1505.
69. Yu Y, Wei R, Liu Z, Xu J, Xu C, Chen JDZ. Ameliorating Effects of Transcutaneous Electrical Acustimulation Combined With Deep Breathing Training on Refractory Gastroesophageal Reflux Disease Mediated. *via*. the Autonomic Pathway. *Neuromodulation*. 2019;22(6):751-757.
70. Dickman R, Levy S, Perets TT, *et al*. Effect of the transcutaneous electrical stimulation system on esophageal-acid exposure in patients non-responsive to once-daily proton-pump inhibitor: proof-of-concept study. *Gastroenterol Rep (Oxf)*. 2021;9(4):323–328.
71. Camilleri, Henry P Parkman, Mehnaz A Shafi, Thomas L Abell, Lauren Gerson, American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol*. 2013;108(1):18–38.
72. Tougas G, Eaker EY, Abell TL, *et al*. Assessment of gastric emptying using a low fat meal: establishment of international control values. *Am J Gastroenterol*. 2000;95(6):1456–1462.
73. Tack J, Camilleri M. New developments in the treatment of gastroparesis and functional dyspepsia. *Curr Opin Pharmacol*. 2018;43:111–117.
74. Hasler WL. Emerging drugs for the treatment of gastroparesis. *Expert Opin Emerg Drugs*. 2014;19(2):261–279.
75. Pasricha PJ. Future directions in the treatment of gastroparesis. *Gastroenterol Clin North Am*. 2015;44(1):185–189.
76. Chen JD, Cheng J. Updates on pathophysiology and treatment of functional dyspepsia and gastroparesis. *Chinese J Dig*. 2021;41(1):3–15.
77. Abell TL, Johnson WD, Kedar A, *et al*. A double-masked, randomized, placebo-controlled trial of temporary endoscopic mucosal gastric electrical stimulation for gastroparesis. *Gastrointest Endosc*. 2011;74(3):496–503.

78. McCallum RW, Lin Z, Forster J, Roeser K, Hou Q, Sarosiek I. Gastric electrical stimulation improves outcomes of patients with gastroparesis for up to 10 years. *Clin Gastroenterol Hepatol*. 2011;9(4):314–319.
79. Richard W McCallum, William Snape, Fredrick Brody, John Wo, Henry P Parkman, Thomas Nowak. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. *Clin Gastroenterol Hepatol*. 2010;8(11):947–e116.
80. Levinthal DJ, Bielefeldt K. Systematic review and meta-analysis: Gastric electrical stimulation for gastroparesis. *Autonomic neuroscience : basic & clinical*. 2017;202:45–55.
81. Chen JD, Qian L, Ouyang H, Yin J. Gastric electrical stimulation with short pulses reduces vomiting but not dysrhythmias in dogs. *Gastroenterology*. 2003;124(2):401–409.
82. R W McCallum, R W Dusing, I Sarosiek, J Cocjin, J Forster, Z Lin. Mechanisms of symptomatic improvement after gastric electrical stimulation in gastroparetic patients. *Neurogastroenterol Motil*. 2010;22(2):161–e51.
83. Ward MP, Gupta A, Wo JM, *et al*. An emerging method to noninvasively measure and identify vagal response markers to enable bioelectronic control of gastroparesis symptoms with gastric electrical stimulation. *J Neurosci Methods*. 2020;336:108631.
84. Liu J, Qiao X, Chen JD. Vagal afferent is involved in short-pulse gastric electrical stimulation in rats. *Dig Dis Sci*. 2004;49(5):729–737.
85. Kelly KA, La Force RC. Pacing the canine stomach with electric stimulation. *The American journal of physiology*. 1972;222(3):588–594.
86. Xu J, Ross RA, McCallum RW, Chen JD. Two-channel gastric pacing with a novel implantable gastric pacemaker accelerates glucagon-induced delayed gastric emptying in dogs. *Am J Surg*. 2008;195(1):122–129.
87. Lin Z, Sarosiek I, Forster J, Ross RA, Chen JD, McCallum RW. Two-channel gastric pacing in patients with diabetic gastroparesis. *Neurogastroenterol Motil*. 2011;23(10):912–e396.
88. Sarosiek I, Song G, Sun Y, *et al*. Central and Peripheral Effects of Transcutaneous Acupuncture Treatment for Nausea in Patients with Diabetic Gastroparesis. *J Neurogastroenterol Motil*. 2017;23(2):245–253.
89. Song G, Sun Y, Bashashati M, *et al*. Efficacy of needleless transcutaneous electroacupuncture in synchronization with breathing for symptomatic idiopathic gastroparesis: A blinded and controlled acute treatment trial. *Neurogastroenterol Motil*. 2018;30(9):e13361.
90. Chen J, Sarosiek I, McCallum R, Abell T, Sun Y, Moody N, *et al*. Chronic transcutaneous electroacupuncture ameliorates dyspeptic symptoms in patients with diabetic gastroparesis: a placebo-controlled multicenter clinical trial using a newly developed microstimulator. *Neurogastroenterol Motil*. 2012;24:170–170. (Abstract)
91. Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. *Gut*. 2015;64(7):1049–1057.
92. Alexander C Ford, Avantika Marwaha, Allen Lim, Paul Moayyedi. What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia? *Clin Gastroenterol Hepatol*. 2010;8(10):830–837.
93. Nicholas J Talley, Alexander C Ford. Functional Dyspepsia. *N Engl J Med*. 2015;373(19):1853–1863.
94. Guilherme Becker Sander, Luiz Edmundo Mazzoleni, Carlos Ferrnando de Magalhães Francesconi, *et al*. Influence of organic and functional dyspepsia on work productivity: the HEROES-DIP study. *Value Health*. 2011;14(5 Suppl 1):S126–S129.
95. Pasricha PJ, Grover M, Yates KP, *et al*. Functional Dyspepsia and Gastroparesis in Tertiary Care are Interchangeable Syndromes With Common Clinical and Pathologic Features. *Gastroenterology*. 2021;160(6):2006–2017.
96. Enck P, Azpiroz F, Boeckxstaens G, *et al*. Functional dyspepsia. *Nat Rev Dis Primers*. 2017;3:17081.
97. Liu S, Peng S, Hou X, Ke M, Chen JD. Transcutaneous electroacupuncture improves dyspeptic symptoms and increases high frequency heart rate variability in patients with functional dyspepsia. *Neurogastroenterol Motil*. 2008;20(11):1204–1211.
98. Ji T, Li X, Lin L, *et al*. An alternative to current therapies of functional dyspepsia: self-administrated transcutaneous electroacupuncture improves dyspeptic symptoms. *Evid Based Complement Alternat Med*. 2014;2014:832523.
99. Xu F, Tan Y, Huang Z, Zhang N, Xu Y, Yin J. Ameliorating Effect of Transcutaneous Electroacupuncture on Impaired Gastric Accommodation in Patients with Postprandial Distress Syndrome-Predominant Functional Dyspepsia: A Pilot Study. *Evid Based Complement Alternat Med*. 2015;2015:168252.
100. Ying Zhu, Feng Xu, Dewen Lu, *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.
101. Köklü S, Köklü G, Ozgüçlü E, Kayani GU, Akbal E, Hasçelik Z. Clinical trial: interferential electric stimulation in functional dyspepsia patients - a prospective randomized study. *Aliment Pharmacol Ther*. 2010;31(9):961–968.
102. Krasaelap A, Sood MR, Li BUK, *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.
103. 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.
104. Huang Z, Lin Z, Lin C, *et al*. Transcutaneous Electrical Acustimulation Improves Irritable Bowel Syndrome With Constipation by Accelerating Colon Transit and Reducing Rectal Sensation Using Autonomic Mechanisms. *Am J Gastroenterol*. 2022;117(9):1491–1501.