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Gastric and sacral electrical stimulation for motility disorders—A clinical perspective

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Abstract

Background: Electrical stimulation of the gut has been investigated in recent decades with a view to treating various gastro-intestinal motility disorders including, among others, gastric electrical stimulation to relieve nausea and vomiting associated with gastroparesis and sacral neuromodulation to treat fecal incontinence and/or constipation. Although their symptomatic efficacy has been ascertained by randomized controlled trials, their mechanisms of action are not fully understood.

Purpose: This review summarizes the past year's literature on the mechanisms of action of gut electrical stimulation therapies, including their impact on the gut-brain axis.

KEYWORDS

constipation-brain gut axis, electrical stimulation, functional bowel disorders-enteric nervous system, gastroparesis-fecal incontinence

1 | INTRODUCTION

Electrical stimulation of the gut has evolved in recent years as an alternative treatment for clinical motility disorders, including gastroparesis, chronic constipation, irritable bowel syndrome (IBS), and fecal incontinence (FI). Gastric electrical stimulation (GES) and sacral neuromodulation (SNM) have received the most attention and are currently used in routine care. Although their efficacy in treating clinical motility disorders has been proven using blinded randomized controlled trials and long-term cohort studies, their mechanisms of action are not fully understood. This review summarizes current knowledge on both methods, including the different stimulation modalities used, their clinical results, and their possible mechanisms of action based on basic, animal, and clinical research.

2 | ELECTRICAL STIMULATION OF THE STOMACH

2.1 | Method

Electrical stimulation of the stomach was first developed as “gastric pacing” for its ability to capture then pace the natural slow waves generated by interstitial cells of Cajal (ICC) in the stomach. However, to stimulate smooth muscle contractions these stimulations require the use of long 100-2000-ms pulse widths at a low frequency close to that of the natural gastric pacemaker, i.e., 3/min¹ (Figure 1). Although such an approach has been shown to increase gastric motility and thus accelerate gastric emptying,² the use of long pulses requires high energy consumption and has slowed the development of long-term implantable stimulators. Canine models

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of gastroparesis, however, have made it possible to identify new parameters using high frequency-low energy GES or simply GES, as opposed to gastric pacing. Shorter pulse GES widths (<0.4ms) delivered at faster frequencies (4 to 5 times higher than the intrinsic rate) have been shown to decrease drug-induced vomiting in dogs.³ This has been corroborated in patients.⁴ These new parameters have entered clinical practice for the treatment of gastroparesis with refractory nausea and vomiting. Unlike gastric pacing, GES is unable to capture gastric slow waves and is thus incapable of entraining the natural gastric pacemaker. Currently, GES standard parameters used in clinical practice involve 330- μ s pulse widths delivered at a frequency of 14Hz and an amplitude of 5mA during 0.1s pulse trains every 5s⁵ (Figure 1). GES devices include a stimulator that is implanted subcutaneously in the abdominal wall and that is connected to a pair of electrodes with leads inserted in the gastric muscularis along the great curvature of the stomach 10cm from the pylorus and 1cm apart.⁶ The battery usually lasts 5 to 10years and can be replaced as needed.⁷

2.2 | Clinical applications

The clinical efficacy of GES was first investigated using open-label studies that mostly involved patients with gastroparesis. Studies on the symptomatic efficacy of GES have reported greater reductions in nausea and vomiting than in the other symptoms of gastroparesis.⁸⁻¹² Symptomatic improvement has been further confirmed by long-term studies showing that GES is clinically efficacious in more than 50% of patients, with an intention-to-treat exceeding 5 and 10years of follow-up.¹³⁻¹⁵ GES has also been shown to reduce hospitalisations, improve nutritional status, lower HbA1c levels,⁵ and decrease health-related costs.¹⁶ This clinical efficacy in treating gastroparesis has been further confirmed by double-blind randomized controlled trials showing that vomiting frequency decreased during active stimulation compared to sham stimulation with the device

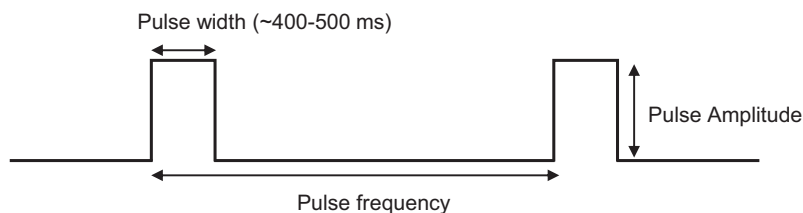
Key points

- Gastric electrical stimulation and sacral neuromodulation have received the most attention and are currently used in routine care.
- Their efficacy in treating clinical motility disorders has been proven using blinded randomized controlled trials and long-term cohort studies.
- Their mechanisms of action are not fully understood.
- Preclinical studies have provided evidence that they involve the gut-brain axis at both the peripheral and central levels.

turned OFF.^{5,17} The symptomatic efficacy of GES has been further corroborated by a recent meta-analysis that pooled short- and mid-term data from randomized controlled trials.¹⁸

However, most cohort studies have shown that neither a decrease in severity nor a normalization of gastric emptying was associated with a better outcome.^{7,19} In addition, the largest recent double-blind randomized controlled trial has shown that neither GES nor sham stimulation accelerated gastric emptying.¹⁷ Interestingly, open-label trials also suggested that GES relieved chronic nausea and vomiting in patients with normal gastric emptying.¹⁴ Such improvements following GES have been further investigated in a recent randomized controlled trial of patients with medically refractory nausea and vomiting associated with normal gastric emptying.¹⁷ The results of this trial indicated that the vomiting frequency score decreased following GES compared with the sham stimulation. Lastly, studies combining pyloromyotomy, which is known to accelerate gastric emptying,^{6,20,21} with GES have shown that the combination provided greater symptomatic improvement than GES alone.^{6,22} Altogether, these studies suggest that clinical GES efficacy is not related to the acceleration of gastric emptying.

(A) Gastric pacing



(B) Gastric electrical stimulation

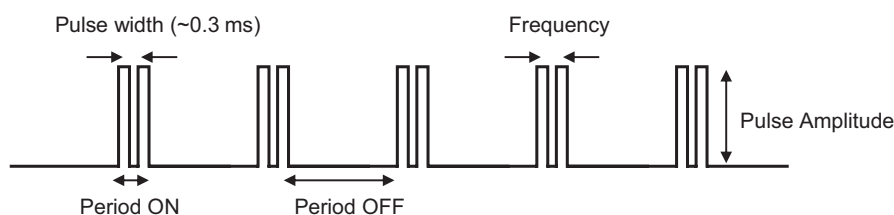


FIGURE 1 Types of electrical stimuli. (A) gastric pacing with long pulse stimulation; (B) gastric electrical stimulation with trains of short pulses.

2.3 | Mechanisms (both animals and humans)

In addition to gastric emptying, the involvement of ICC has been investigated in an attempt to explain the symptomatic efficacy of electrical stimulation of the stomach. Altered gastric myoelectrical activity, which depends upon ICC, has been observed in patients with chronic nausea or vomiting, even in the absence of a delay in gastric emptying.^{23,24} A loss of ICC has been observed in the stomachs of patients with gastroparesis and in patients with chronic nausea and vomiting syndrome,^{25,26} although this has not been replicated by others (PMID: 29052298). In addition, the ICC count was not associated with symptom severity.²⁷ In rodents, both GES and gastric pacing have been shown to repair and protect ICC.^{28,29} In dogs, gastric pacing normalizes vasopressin-induced gastric dysrhythmia but did not improve vasopressin-induced vomiting.³⁰ In contrast, GES prevented vasopressin-induced vomiting but had no effect on slow waves.³⁰ Similar results have been observed with patients, where gastric pacing entrained gastric slow waves and then accelerated gastric emptying, while GES did not.² However, GES has been shown to increase the amplitude and propagation velocity of gastric slow waves,^{8,31} although this effect was independent of the number of gastric ICC counts.³² In addition, discrepant outcomes have been reported following GES in patients with ICC depletion. Indeed, one study has reported that ICC depletion was associated with symptomatic improvement during GES compared to patients with a normal ICC count,³³ while a second study has reported the opposite.³² Given these opposing results, whether the symptomatic efficacy of GES is driven by the modification of ICC activity or not remains to be proven.

A second possibility is that GES acts on gastric sensitivity. In a model of a post-operative ileus in rodents, GES has been shown to decrease hypothalamic neuronal activation, a centre that is involved in gastric motility and meal-related sensation.³⁴ In dogs, GES decreased vasopressin-induced vomiting behavior while this antiemetic effect was lost in vagotomised animals.³⁰ In patients, an increase in gastric relaxation associated with a change in metabolic activity in the thalamic and caudate nuclei as well as a decrease in the sympathovagal balance has been observed following GES, suggesting that the afferent and efferent vagal pathways were both involved.^{35,36} However, GES was also effective in reducing vomiting in patients with post-surgical gastroparesis, most cases of which are related to vagal lesions.^{11,37} Conversely, it has also been proposed that GES increases the discomfort threshold to gastric distension,^{38,39} in rodents and patients. In rodents, GES increased pain thresholds to gastric distension and neuronal activation in the dorsal root ganglia as well as in the dorsal horn of the thoracic spinal cord, which suggests a direct effect of gastric splanchnic afferents.³⁹ Electrophysiologic studies have shown that GES activated thoracic spinal neurons receiving inputs from both the stomach and the duodenum. This involved primary afferent fibers that express transient receptor potential vanilloid receptor-1.⁴⁰ In patients, GES decreased the discomfort induced by gastric distension.³⁸ Likewise, an increase in the discomfort threshold, but not gastric emptying, has been correlated

with symptom improvement after the GES threshold was reached.³⁸ Lastly, the release of gut hormones at the gastric level after GES has been hypothesized via a possible stimulation of enteroendocrine cells, including ghrelin-producing X/A-like cells. Indeed, ghrelin has been shown to increase the gastric pain threshold to gastric distension.⁴¹ However, the plasma and mucosal levels of the different gastro-intestinal hormones, including ghrelin, remained unchanged in patients with the stimulator turned ON unlike in patients with the stimulator turned OFF.⁴²

3 | SACRAL NEUROMODULATION

3.1 | Method

Sacral neuromodulation (SNM) was first developed to treat urinary incontinence due to overactive bladder and urinary retention.⁴³ SNM was subsequently used to treat functional gastrointestinal disorders such as FI, constipation, and, more recently, IBS. The SNM device consists of an electrode probe (Medtronic) that usually unilaterally stimulates the third sacral nerve. It is first connected to an external stimulation device for a temporary peripheral nerve evaluation (PNE). If the PNE is successful (50% improvement in symptoms), the temporary device is replaced by an implantable pulse generator (Interstim™, Medtronic), which is surgically placed in the subcutaneous tissue of the buttocks and which can be programmed using an external controller.⁴⁴ Stimulations are delivered continuously, with the polarity and amplitude adjusted according to an intraoperative motor and post-operative sensory responses while the frequency and pulse width are systematically set at 14 Hz and 210 μs, respectively.⁴⁴

3.2 | Clinical applications

Clinical studies have evaluated the effectiveness of SNM with the stimulation parameters described above. Since the first use of SNM in the mid-1990s, numerous meta-analyses, including randomized controlled and cohort studies, have shown that SNM is effective for the treatment of FI⁴⁵ (Table 1). For an intention-to-treat, the percentage of patients exhibiting an improvement in symptoms of more than 50% has been estimated at 63% for a short-term follow-up, 58% for a medium-term follow-up, and 54% for a long-term follow-up.⁴⁵ When conservative treatments fail, SNM is considered a second-line therapeutic option for FI, as confirmed by the International Continence Society.⁵⁰ SNM has also received FDA approval for treating FI. However, there is currently no sufficiently robust marker that can identify patients with FI who would benefit most from SNM.⁵¹

The clinical data of SNM for treating chronic refractory constipation is less convincing. Although some initial non-controlled data have been promising,⁵² more recent randomized controlled trials have shown poor response rates as well as no difference between sham and active interventions for the primary outcome.^{53,54} A study involving 36 patients with chronic constipation who received

TABLE 1 Meta-analyses on the effects of sacral nerve modulation (SNM) for treating fecal incontinence (FI).

Author	Year	Studies N	Total Patients N	Follow-up	Results	Conclusion
Mowatt G et al. ⁴⁶	2007	2 randomized studies	36	1 to 6 months	Significantly reduced the number of FI episodes compared to the control group in 2/2 trials	Very limited evidence suggested that SNM could improve continence in selected people with FI
Tan et al. ⁴⁷	2011	34 studies comparing SNM with conservative management	665	2 to 35 weeks	Weekly incontinence episodes and incontinence scores were significantly reduced when SNM was increased. Ability to defer defecation was increased. Most SF-36 and FIQL domains improved following SNM	SNM resulted in significant improvements in objective and subjective measures for FI patients
Thaha MA et al. ⁴⁸	2015	4 crossover trials (ON vs. OFF period) and 2 parallel groups (SNM compared to no SNM)	219	2 weeks to 12 months	Parallel groups: Significantly reduced the number of FI episodes compared to the control group in 2/2 trials Crossover trials: Fewer episodes of FI during the ON compared with the OFF period in 3/4 trials	SNM could significantly improve FI in some selected patients
Simillis et al. ⁴⁹	2019	31 trials reporting on 25 different treatments for FI	2381	-	Significantly improved the incontinence score compared to the placebo, NRL001, medical management (antidiarrhoeal medications and laxatives), biofeedback, medical management, transanal irrigation, Permacol, and Bulkamid injections	SNS resulted in isolated improvements in specific outcomes of interest

Note: Blank cells indicate no data available.

a permanent SNM implantation after 3 weeks of a temporary PNE did not show any difference between the active and sham stimulations in the proportion of patients who reported at least three bowel movements per week and/or a more than 50% improvement in symptoms (primary outcome).⁵⁴ Another trial had similar results.⁵³ These findings have mirrored findings from systematic reviews of SNM for constipation.^{48,52} SNM is thus not recommended for treating refractory chronic constipation.⁵⁵ However, SNM could become a valuable therapeutic option if long-term responders with refractory severe constipation could be accurately identified.⁵⁶

More recently, the clinical application of SNM for irritable bowel syndrome (IBS) has been explored. The study showed that IBS-specific symptoms are significantly reduced and that quality of life is improved after permanent implantation.⁵⁷ Moreover, the positive effect of SNM was maintained at the 3-year follow-up.⁵⁸ In a double-blind, placebo-controlled study, the same researchers found that SNM significantly reduces pain and the number of daily bowel movements in 21 patients with predominant diarrhea (IBS-D) or mixed bowel pattern (IBS-M).⁵⁹ However, these preliminary findings need to be confirmed by other larger multi-centre studies before using SNM to manage patients suffering from IBS.

3.3 | Mechanisms (both animals and humans)

Although SNM has been used for more than 20 years, its mechanism of action is not completely understood. This may be due to the fact

that, while many pre-clinical and clinical studies have focused on the mechanisms of action of SNM, the interpretation of the results is difficult due to the low quality of most of the studies (small numbers of patients, cases series, retrospective studies, reproducibility of physiological endpoints, disparate patient groups), the disparity of the methods and, particularly, the diversity of the types of stimulation used (acute or chronic stimulation, under anesthesia or not, choice of stimulation parameters). Based on third sacral root stimulation, SNM may stimulate afferent sensory fibers, autonomic efferent fibers comprising the pelvic nerves that innervate the left colon, the rectum, and the internal anal sphincter via the enteric nervous system, and efferent somatic fibers that innervate the external anal sphincter and the pelvic floor muscles. Electromyographic studies have shown that SNM activates afferences, suggesting that the anal sphincter contractions observed during SNM are the result of an afferent-mediated response.⁶⁰ This has been corroborated by several findings. First, studies on the effect of SNM on rectal sensation in patients with FI or constipation have shown that there is a trend toward the normalization of rectal sensations that is correlated with clinical improvements.⁶¹ Second, recordings of cortical-evoked potentials induced by SNM over the sensory cortex have been reported in both human⁶² and animal studies.⁶³ Third, the observation that levels of mucosal substance P, a neuropeptide that plays a role in immunomodulation, contractility, and afferent signaling in visceral sensation, are elevated in FI and return to normal after SNM, is consistent with this hypothesis.⁶⁴ There is that some evidence that SNM can normalize a sensory dysfunction that may

underlie the clinical improvement observed in patients with FI and defecation urgency⁴⁵ as well as the pain improvement observed in IBS patients.⁵⁹ Contradictory results have been reported regarding the autonomic control of the internal anal sphincter and the somatic control of the external anal sphincter by SNM. However, an increase in basal anal pressure, which reflects internal anal sphincter activity, and squeeze pressure, which reflects the activity of the external anal sphincter, have been described during SNM in some studies.⁶¹ This has not been confirmed in large observational series nor in randomized studies.⁶⁵⁻⁶⁷ SNM also improves continence in FI patients with extensive anal sphincter lesions, suggesting that the mechanism of action is not, or not only, due to its effect on the anal sphincter.⁶⁸ On the contrary, there is some evidence that SNM normalizes colonic motility in patients with FI or constipation.⁶¹ A study assessing the colonic contractility of 11 patients with FI using high-resolution colonic manometry with 2 h of stimulation at a supra-sensory threshold, 2 h of sham stimulation, and 2 h at baseline showed that there is an increase in the frequency of retrograde propagating pressure waves in the left colon during active stimulation compared to baseline and that this change is correlated with a significant improvement in incontinence severity scores.⁶⁹ When the same parameters are used (i.e., frequency 14 Hz, pulse width 300 μsec, intensity supra-sensory threshold) in patients with slow transit constipation, acute SNM appears to increase the frequencies

of antegrade propagating sequences and high amplitude propagating sequences through the distal transverse colon,^{70,71} which are accompanied by an improvement in symptoms.⁷⁰ These results reflect the impact of the stimulus protocol (i.e., the intensity) of the nerve stimulation on the mechanism of action of SNM.⁴⁴ Supra-sensory stimulations may activate autonomic efferent fibers, thereby inducing a response in colonic and internal anal sphincter smooth muscles. Animal studies support this hypothesis. Several concordant studies on a porcine model have demonstrated that bilateral supra-sensory SNM may reduce rectal paracellular permeability⁷² and intestinal epithelial barrier dysfunctions⁷³ and enhance intestinal barrier repair in acute mucosal injury.⁷⁴ The effects of SNM on mucosal barrier functions may help explain the success of SNM reported in patients with IBS in which barrier function disruption has been demonstrated.⁷⁵ As a similar effect on the intestinal barrier occurs during vagal stimulation,⁷⁶ it has been suggested that SNM may exert its effects on the rectal barrier by stimulating the parasympathetic presacral plexus.⁷² However, to date, the mediators responsible for the barrier reinforcing effects of SNM remain to be identified.⁷² In contrast, sub-sensory stimulation fails to directly activate such pathways.⁷¹ Sub-sensory stimulation may act differently by exerting an effect on the central nervous system via pelvic sensory afferent pathways. The cortical effects of SNM have been examined in clinical studies.⁶¹ In addition to the study

TABLE 2 Summary of findings of human and animal studies examining the physiological effects of sacral nerve modulation (SNM).

Target of SNM	Type of Effects	Results of Human Studies	Results of Animal Studies
Afferent system	Recruitment of afferent fibers	-Anal contraction (induced by SNM) secondary to an afferently mediated reflex ⁵⁸ -Recording of sensory evoked potentials during SNM ⁶⁰	Sensory evoked potentials during SNM were recorded during SNM ⁶¹
	Role on afferent neurotransmitter	-Normalization of substance P levels in the rectal mucosa of patients with FI treated with SNM ⁶²	There was a reduction in c-fos protein levels in the dorsal horn during acute SNM ⁷⁵
	Inhibition of abnormal sensory inputs to central nervous system	-Normalization of rectal sensation during SNM ⁵⁹ -Visceral pain improvement with SNM ⁵⁷	There was a reduction in visceral sensitivity following acute SNM ⁷⁵
Efferent system	Motor squeeze pressure enhanced	-Controversial ^{59,63-66}	There was a decrease in colorectal motility via the somatosympathetic reflex ⁷⁶
	Motor resting pressure enhanced	-Controversial ^{59,63-66}	
	Colonic motility modulated	-At the supra-sensory threshold of SNM, there was an increase in the number of retrograde propagating contractions and an alteration in distal colonic propagating contractions in patients with FI ⁶⁷ -At the supra-sensory threshold of SNM, there was an increase in the number of antegrade propagating contractions in constipated patients ^{68,69}	
Brain	Cerebral activity modulated	Inhibitory changes in the motor cortex of patients with FI during SNM ⁷² Activation of the frontal and caudate nucleus area during SNM ⁷³	There was a reduction in c-fos protein expression in the parabrachial and solitary tract nuclei during acute SNM
Intestinal epithelial barrier	Modulation of function		Bilateral supra-sensory stimulation reduced permeability and dysfunction ⁷⁰

Abbreviations: FI, fecal incontinence; SNM, sacral nerve modulation.

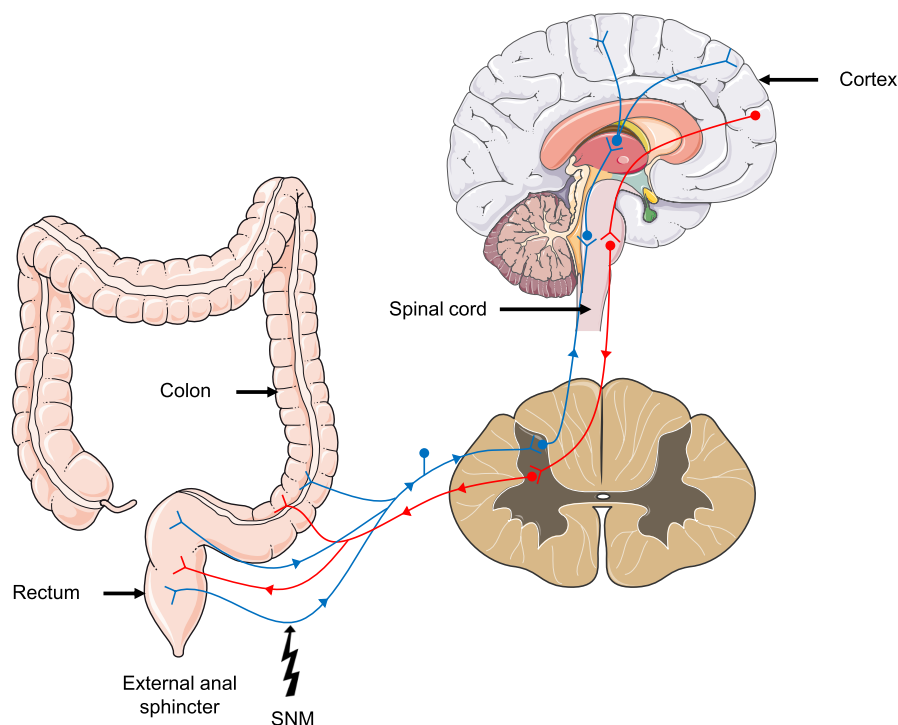


FIGURE 2 Schematic of proposed mechanism of action of sacral nerve modulation. Rectal and pelvic afferents communicate via dorsal horn ganglia and travel via the thalamus to the primary somatosensory cortex and other cerebral areas (frontal cortex, caudate nucleus). Stimulation of these afferents could modulate colorectal motility via autonomic efferent pathways. SNM, Sacral nerve modulation.

mentioned above on cortical evoked potentials,⁶² SNM induces inhibitory changes in the motor cortex to the external anal sphincter pathway of patients with FI.⁷⁷ In addition, acute stimulation activates a region in the frontal cortex that is involved in focused attention and, after 2 weeks of SNM, in parts of the caudate nucleus involved in learning.⁷⁸ Animal studies seem to confirm that SNM has a potential effect on the central nervous system.^{79,80} In one study, visceral colonic mechanosensitivity induced by colorectal distension was assessed in 10 rats that underwent electrode implantation and 2 h of SNM, with the same stimulation parameters as those usually used in clinical studies, and 10 rats that underwent electrode implantation alone.⁸⁰ The authors reported that SNM reduces colonic sensitivity, prevents the colorectal distension-induced rise of c-fos protein (a neuronal proto-oncogene) expression in the dorsal horn of the spinal cord, the parabrachial nucleus, and the solitary tract nucleus, two major relays of sensory information.⁸⁰ Spinal opioid receptors are likely involved in this effect.⁸⁰ The effect of SNM on colonic mechanosensitivity and the recruitment of spinobulbar centres may modify autonomic outflow and, ultimately, colonic motility.⁸⁰ This was corroborated by another study that showed when SNM is applied to the S1 dorsal root in cats it causes an increase in sympathetic outflow, which leads to a drop in colorectal motor activity.⁸¹ This may thus contribute to an improvement in continence and bowel habits and an improvement in the diarrhea-predominant IBS observed during SNM. The main mechanisms of action of neuromodulation according to research in humans and animals are summarized in Table 2.

Although the mechanisms of action of SNM have not been completely elucidated, it appears clear that, with the usual stimulation modalities, it does not act via a simple motor effect on efferent nerves but likely acts in a very complex, multi-synaptic, and

multimodal way to contribute to normalizing impaired colonic and anorectal motility and/or sensitivity (Figure 2).

4 | CONCLUSION

Both GES and SNM have been shown to be efficacious for treating gastrointestinal motility disorders such as FI. Although their mechanisms of action are not fully understood, preclinical studies have provided evidence that they involve the gut-brain axis at both the peripheral and central levels. Further mechanistic studies are needed to decipher their precise mechanisms of action so as to further optimize patient selection and, ultimately, improve their clinical efficacy.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this work.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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