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Some Non-FDA Approved Uses for Neuromodulation in Treating Autonomic Nervous System Disorders: A Discussion of the Preliminary Support

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Introduction: Neuromodulation, including cavernous nerve stimulation, gastric electrical stimulation, deep brain stimulation, and vagus nerve stimulation, has been used with success in treating several functional disease conditions. The FDA has approved the use of neuromodulation for a few indications. We discuss in our review article the evidence of using neuromodulation for treating some important disorders involving the autonomic nervous system that are not currently FDA approved.

Methods: This was a review article that included a systematic online web search for human clinical studies testing the efficacy of neuromodulation in treating erectile dysfunction, gastroparesis, gastroesophageal reflux disease, obesity, asthma, and heart failure. Our review includes all feasibility studies, nonrandomized clinical trials, and randomized controlled trials.

Results: Our systematic literature search found 3, 4, 5, 4, 1, and 4 clinical studies relating to erectile dysfunction, gastroparesis, gastroesophageal reflux disease, obesity, asthma, and heart failure, respectively.

Conclusion: This review article shows preliminary support based on clinical studies that neuromodulation can be of benefit for patients with important autonomic nervous system disease conditions that are not currently approved by the FDA. All of these investigational uses are encouraging; further studies are necessary and warranted for all indications discussed in this review before achieving FDA approval.

Keywords: Anesthesiology, asthma, autonomic nervous system, erectile dysfunction, functional electrical stimulation, gastroparesis, GERD, heart failure, neuromodulation, obesity

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INTRODUCTION

Since 1967, neuromodulation has been used to successfully treat many chronic pain conditions and has thus far received FDA approval for use in the treatment of chronic pain of the trunk and limbs, complex regional pain syndrome, and intractable low back pain, leg pain, and pain from failed back surgery syndrome (1). Neuromodulation has also been increasingly used in the treatment of painful conditions such as angina pectoris, peripheral vascular disease, migraine headaches and neuropathic pain (2). In this review article, we discuss emerging therapeutic uses of neuromodulation for disorders involving the autonomic nervous system that are not currently FDA approved. These conditions include erectile dysfunction, gastroparesis, gastroesophageal reflux disease, obesity, asthma, and heart failure.

METHODS

In this review article, we performed a systematic web search for human clinical studies testing the efficacy of neuromodulation in treating erectile dysfunction, gastroparesis, gastroesophageal reflux disease, obesity, asthma, and heart failure. Our review includes all feasibility studies, nonrandomized clinical trials, and randomized controlled trials.

Erectile Dysfunction After Pelvic Surgery

A systematic literature search was performed in the PubMed and Cochrane Library databases with the search terms "spinal cord stimulation" and "erectile dysfunction," "neuroprotection," "nerve regeneration," or "cavernous nerves." The same individual completed the two searches, using the exact same search terms in both databases.

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Gastroparesis

A systematic literature search was performed in the PubMed and Cochrane Library databases with the search terms "Spinal Cord Stimulation" and "gastroparesis," "gastric electrostimulation," "neuromodulation," "GES," "vomiting," and "Enterra." Reference lists of studies retrieved via this method were also used to locate other relevant studies. The same individual completed the two searches, using the exact same search terms in both databases.

Gastroesophageal Reflux Disease

A systematic literature search was performed in the PubMed and Cochrane Library databases with the search terms "Spinal Cord Stimulation" and "gastroesophageal reflux disease," "GERD," "electrical stimulation," and "neuromodulation." The same individual completed the two searches, using the exact same search terms in both databases.

Obesity

A systematic literature search was performed in the PubMed and Cochrane Library databases with the search terms "neuromodulation" and "obesity," "stimulation," "DBS," "deep brain stimulation," and "FDA approval." Reference lists of studies retrieved via these searches were also used to locate other relevant studies. The same individual completed the two searches, using the exact same search terms in both databases.

Asthma

A systematic literature search was performed in the PubMed and Cochrane Library databases with the search terms "neuromodulation" and "asthma," "vagal nerve stimulation," "VNS," "stimulation," and "FDA approval." The same individual completed the two searches, using the exact same search terms in both databases.

Heart Failure

A systematic literature search was performed in the PubMed and Cochrane Library databases with the search terms "neuromodulation" and "heart failure," "vagal nerve stimulation," "VNS," and "stimulation." Reference lists of studies retrieved via these searches were also used to locate other relevant studies. The same individual completed the two searches, using the exact same search terms in both databases.

RESULTS

Our search for studies relating to neuromodulation and erectile dysfunction returned two feasibility studies and one clinically controlled trial, further detailed in Table 1. Of these studies in conglomerate, 18/49 (37%) of patients regained at least a measureable increase in erections after prostatectomy. These preliminary studies suggested that it is efficacious to treat erectile dysfunction with neuromodulation.

Twenty-one studies concerning neuromodulation and gastroparesis were identified, with 19 excluded because they were case studies or reviews. Our search returned two clinically controlled trials, further detailed in Table 2. These studies showed that gastric electrical stimulation could significantly improve diabetic gastroparesis, as measured by total symptom scores and gastric retention. Results of idiopathic gastroparesis and postsurgical gastroparesis treated with gastric electrical stimulation did not reach significance.

As outlined in Table 3, our search for studies relating to electrical stimulation and GERD returned two feasibility studies and three clinical trials, outlined in Table 3. These studies showed the potential of using neuromodulation in the treatment of GERD; a significant increase in lower esophageal sphincter pressure and a significant decrease in acid reflux were noted after treatment with an implantable electrical stimulation device.

Our search for studies relating to electrostimulation and obesity returned four ongoing clinical trials, outlined in Table 4. The clinical studies that have thus far been completed showed that this indication for neuromodulation is feasible. We also explained the scientific foundation and justification for further studies to evaluate the efficacy of neuromodulation to treat obesity.

Another investigational use of neuromodulation includes its role in the treatment of asthma. Our search for studies relating to vagal nerve stimulation and asthma returned one feasibility study, as described in Table 5. This study shows that it is feasible to use vagal nerve stimulation as a treatment option for asthma. Our review also includes a brief explanation of the basis for such studies and the ongoing need for further evaluation of this potential indication for neuromodulation.

Our search for studies relating to neuromodulation and heart failure returned four clinical trials that fit our parameters, further detailed in Table 6. These studies showed that vagal nerve stimulation is feasible and may potentially provide significant improvement in the treatment of heart failure.

DISCUSSION

Erectile Dysfunction

Erectile dysfunction is a common complication of radical prostatectomy and various other pelvic surgeries. Despite being a well-recognized adverse consequence of pelvic surgery, erectile dysfunction is ineffectively avoided. It is generally understood to be caused by penile vascular impairment secondary to neuropathic effects of cavernous nerve injury (7). Several clinical treatments, including electrical stimulation, have been proposed as providing neuromodulatory therapeutic effects; electrical stimulation of the cavernous nerves has been shown to elicit penile erection. Lue et al. (8) found that intraoperative electrical stimulation of the cavernous nerves is a feasible method of inducing penile erection; intraoperative electrical stimulation produced erectile responses in 8 out of 16 (50%) men undergoing retropubic radical prostatectomy and in 5 out of 6 (83%) patients undergoing penile surgery for venous leakage. A small clinical trial (9) then reported that such treatment could promote spontaneous erectile function recovery after surgery; this study reported that electrostimulation of the corpus cavernosum led to improved spontaneous erectile function in 4 (19%) and responsiveness to vasoactive drugs in 3 out of 21 (14%) patients with chronic erectile dysfunction nonresponsive to vasoactive therapy. Burnett et al. (10) further studied this technique to determine the feasibility of cavernous nerve electrical stimulation via a chronic implantation device. The authors note that this method leveraged cavernous nerve electrical stimulation beyond its intraoperative purpose to assist in cavernous nerve localization when performing "nerve-sparing" prostatectomy. In this study, the cavernous nerve was stimulated intraoperatively to assess proper placement of the leads, which were then connected temporarily to an external stimulator device. Among the 12 men enrolled in this study, 6 (50%) demonstrated measurable increases in penile circumference in response to implantable device-induced cavernous nerve stimulation (20 Hz frequency, 260 μsec pulse width, 5 mA–60 mA amplitude),

Table 1. Summary of Studies Investigating Electrostimulation for Erectile Dysfunction.

Study	Method	Patient population	Intervention(s)	Outcome(s)	Result(s)	Conclusion(s)
Lu et al. "Intraoperative electrostimulation of the cavernous nerve: technique, results and limitations"	Prospective, nonrandomized, feasibility study	22 males (radical prostatectomy, 16; penile surgery, 6)	Intraoperative electrostimulation of cavernous nerve (applied to both sides of the prostatic apex or hilum of penis in the prostatectomy group and venous surgery group, respectively)	Presence of erection, intracavernous pressure	Visible erection in 8/16 prostatectomy patients, increase in intracavernous pressure in 5/6 venous surgery patients	This feasibility study offers promise and warrants further controlled studies and refinement of technique to be clinically useful
Stief et al. "Functional electromyostimulation of the corpus cavernosum penis—preliminary results of a novel therapeutic option for erectile dysfunction"	Controlled clinical trial	42 males (transcutaneous stimulation, 21; control, 21)	Daily transcutaneous functional electrostimulation of the corpus cavernosum smooth muscles	Spontaneous improvement in erectile function, response to vasoactive drugs after stimulation	4/21 (19%) regained full spontaneous erections, 3/21 (14%) responded to vasoactive drugs after stimulation	This study showed that it is feasible to regain spontaneous erections and responsiveness to vasoactive drugs in chronic nonresponders with stimulation of the corpus cavernosum
Burnett et al. "Intraoperative assessment of an implantable electrode array for cavernous nerve stimulation"	Prospective, nonrandomized, feasibility study	12 males	Temporary surgical placement of cavernous nerve stimulation device	Increase in penile circumference	6/12 (50%) demonstrated measurable increases in penile circumference in response to cavernous nerve stimulation (mean increase of 5.0 mm)	It is feasible to have neuromodulatory effects on the recovery of penile erections after radical prostatectomy via a chronic implantable nerve stimulation system for cavernous nerve stimulation

Table 2. Summary of Studies Investigating Electrostimulation for Gastroparesis.

Study	Method	Patient population	Intervention(s)	Outcome(s)	Result(s)	Conclusion(s)
Abell et al. (3) "Gastric electrical stimulation for medically refractory gastroparesis"	Randomized Control Trial (two months), then Prospective (ten months)	33: Diabetic (17), Idiopathic (16)	Permanently implanted stimulator; high-frequency/low-energy GES	Total symptom severity score, vomiting severity score, nausea severity score, SF-36 physical and mental composite scores, requirement for nutritional support, gastric emptying	Significant reduction in vomiting frequency during blind and unblind portions of study; significant improvement in symptom severity and quality of life at 6 and 12 months; modest acceleration in gastric emptying; five patients had GES explanted or revised due to infection or other complications	"High-frequency/low-energy gastric electrical stimulation significantly decreased vomiting frequency and gastrointestinal symptoms and improved quality of life in patients with severe gastroparesis"
McCallum et al. (4) "Gastric electrical stimulation with enterra therapy improves symptoms from diabetic gastroparesis in a prospective study	Prospective (1.5 months), RCT (six months, then prospective	55: Diabetes (55)	Permanently implanted stimulator; high-frequency, low-energy GES	Total symptom score, weekly vomiting frequency (SVF), gastric emptying, quality of life, length of hospital stay	Mean reduction in weekly vomiting frequency at six weeks was 57%; -no difference in SVF between patients who had the device turned on or off during cross-over period; -significant improvement in total symptom score, gastric emptying, quality of life, median days in hospital	In patients with intractable diabetic gastroparesis, 6 weeks of GES significantly reduced vomiting and gastroparetic symptoms
Abell et al. (5) "A double-masked, randomized, placebo-controlled trial of temporary endoscopic mucosal gastric electrical stimulation for gastroparesis"	Randomized, placebo-controlled, cross-over trial	58: Idiopathic (38), Diabetic (13), Postsurgical (7)	Endoscopically placed, temporary gastric electrical stimulation	Symptoms measured daily, gastric emptying, electrogastrography, quality of life	In session 1, vomiting decreased in both groups, but was greater with stimulation. In session 2, vomiting slightly decreased with stimulation and slightly increased without it	"Although overall treatment effects were not significant, differences in favor of stimulation were suggested. [. . .] Future studies should better define inclusion criteria, use longer washout periods, randomize by etiology and baseline physiological findings, and pursue alternative designs"
McCallum et al. (6) Gastric electrical stimulation with Enterra therapy improves symptoms of idiopathic gastroparesis	Prospective, multicenter, double-blinded, randomized, cross-over study	32: Idiopathic (32)	Permanently implanted stimulator; Enterra gastric electrical stimulation	Daily vomiting, total symptom score, SF-36, hospital stay, adverse events	During the unblended ON period, there was a reduction in weekly vomiting frequency (WVF) from baseline (61.2%, $P < 0.001$); Non-significant reduction in WVF between ON vs. OFF periods; At one year, WVF remained decreased, accompanied by improvements in GP symptoms, gastric emptying and days of hospitalization ($P < 0.05$)	"The first message is that initiation of GES for six weeks caused a rapid and significant reduction of symptoms which was able to be sustained despite a period of up to three months with the device off. Future placebo-controlled research trials must be initiated at the time of surgery"

Table 3. Summary of Studies Investigating Electrostimulation for GERD.

Study	Method	Patient population	Intervention(s)	Outcome(s)	Result(s)	Conclusion(s)
Rodriguez et al. "Short-term electrical stimulation of the lower esophageal sphincter increases sphincter pressure in patients with gastroesophageal reflux disease"	Prospective, nonrandomized, feasibility study	Ten (nine female). All successfully implanted; nine received high frequency, low energy stimulation; four received low frequency, high-energy stimulation	Electrical stimulation of Lower Esophageal Sphincter (LES); temporarily implanted leads with external stimulator	Lower esophageal sphincter pressure (resting and residual), amplitude of esophageal contractions; Symptoms of chest pain, abdominal pain, dysphagia	Both types of stimulation significantly increased resting LES pressure; neither type of stimulation affected amplitude of esophageal peristalsis or residual LES pressure; no complaints of dysphagia	"Short-term stimulation of the LES in patients with GERD significantly increases resting LESP without affecting esophageal peristalsis or LES relaxation. Electrical stimulation of the LES may offer a novel therapy for patients with GERD"
Banerjee et al. "Effect of electrical stimulation of the lower esophageal sphincter using endoscopically implanted temporary stimulation leads in patients with reflux disease"	Prospective, nonrandomized, feasibility study	Six males	Electrical stimulation therapy via temporary endoscopic lead implantation	Pre-, during and post-stimulation LES pressure; Symptoms of heartburn, chest or abdominal pain and dysphagia	All had a significant increase in LES pressure; no effect on swallow-induced LES relaxation; no electrical stimulation therapy-related adverse symptoms	"In patients with GERD, short-term EST delivered using electrodes endoscopically implanted in the LES results in a significant increase in LES pressure without affecting patients' swallow function or causing any adverse symptoms or cardiac rhythm disturbances. EST may offer a novel therapy to patients with GERD"
Rodriguez et al. "Electrical stimulation therapy of the lower esophageal sphincter is successful in treating GERD: final results of open-label prospective trial"	Open-label, single center clinical trial	24 patients: mean age = 53 years, 14 male	Electrical stimulation of LES via permanently implanted LES stimulator	GERD-HRQL, daily symptom and medication diaries, SF-12, esophageal pH, high-resolution manometry	At six month follow-up: 91% (21/23) of patients were off PPI and had significantly better median GERD-HRQL; no unanticipated implantation- or stimulation-related adverse events; No reports of dysphagia; Manometric swallow unaffected	"Electrical stimulation of the LES is safe and effective for treating GERD. There is a significant and sustained improvement in GERD symptoms, esophageal pH, and reduction in PPI usage without any side effects with the therapy"
Rodriguez et al. "Long-term results of electrical stimulation of the lower esophageal sphincter for the treatment of gastroesophageal reflux disease"	Open-label, single center clinical trial	24 patients: mean age = 53 years, 14 male	Electrical stimulation of LES via permanently implanted LES stimulator	GERD-HRQL, daily symptom and medication diaries, SF-12, esophageal pH, high-resolution manometry	At 12 month follow-up: median composite GERD-HRQL score was significantly better than baseline scores both on PPI and off PPI therapy; 69% of patients showed either normalization or >50% improvement in distal esophageal pH; 96% of patients (22/23 were completely off PPI medication	"During the long term follow-up of 12 months, LES-EST was safe and effective for the treatment of GERD. There was a significant and sustained improvement in GERD symptoms, reduction in esophageal acid exposure with elimination of daily PPI usage, and no stimulation-related adverse effects"

Table 3. *Continued*

Study	Method	Patient population	Intervention(s)	Outcome(s)	Result(s)	Conclusion(s)
Rodriguez et al. "Two-year results of intermittent electrical stimulation of the lower esophageal sphincter treatment of gastro-esophageal reflux disease"	Open-label, single center clinical trial	25 patients implanted successfully; 23 patients participated in two year extension trial	Electrical stimulation of LES via permanently implanted LES stimulator	GERD-HRQL, daily symptom and medication diaries, SF-12, esophageal pH, high-resolution manometry	At two years, significant improvement in median GERD-HRQL; median 24 hour distal esophageal acid exposure improved from 10% at baseline to 4%; 71% demonstrated either normalization or a >50% decrease in distal esophageal acid exposure; significant improvement in sleep quality and daily symptoms of heartburn and regurgitation	"LES-EST is safe and effective for treating patients with GERD over a period of two years. LES-EST results in a significant and sustained improvement in GERD symptoms, and esophageal acid exposure and eliminated PPI use in a majority of patients"
Rodriguez et al. "Electrical stimulation therapy of the lower esophageal sphincter is successful in treating GERD: long-term three year results"	Open-label, single center clinical trial	25 patients implanted successfully; 15 patients participated in three year extension trial	Electrical stimulation of LES via permanently implanted LES stimulator	GERD-HRQL, daily symptom and medication diaries, SF-12, esophageal pH, high-resolution manometry	At three years: significant improvement in median GERD-HRQL; Median 24 hour distal esophageal acid exposure was significantly reduced from 10.3% at baseline to 3%; 73% had normalized distal esophageal acid exposure	"LES-EST is safe and effective for treating patients with GERD over long-term, three-year duration. There was a significant and sustained improvement in esophageal acid exposure and reduction in GERD symptoms and PPI use"
Siersema et al. "Electrical stimulation therapy (EST) of the lower esophageal sphincter (LES)—an effective therapy for refractory GERD—interim results of international multicenter trial"	Open-label, multicenter clinical trial	24 patients: 14 men, median age 51. Currently 18 patients have completed three-month follow-up and 14 patients six-month follow-up	LES electrical stimulation therapy via permanently implanted LES stimulator	GERD-HRQL, daily symptom diaries, quality of life scores, esophageal acid exposure	GERD-HRQL improved from baseline score of 31 to 4 at three months and 5 at six months ($P < 0.001$ and $P < 0.01$, respectively); Acid exposure time decreased from 11.3% at baseline to 3.3% at three months and 2.6% at six months	These interim results have shown good efficacy of the treating GERD with esophageal stimulation therapy. Completion of the data up to 24 month follow-up is awaited
Kappelle et al. "Electrical stimulation therapy of the lower oesophageal sphincter for refractory gastro-oesophageal reflux disease—interim results of an international multicenter trial"	Open-label, multicenter clinical trial	44 patients (six month data from 41 patients are available)	LES electrical stimulation therapy	GERD-HRQL, daily symptom diaries, quality of life scores, esophageal acid exposure, and LES resting and residual pressure	GERD-HRQL improved from 31 off-PPI and 16.5 on-PPI to 4 at three-month and 5 at six-month follow-up ($P < 0.0001$); esophageal acid exposure improved from 10.0% to 3.8% at three months and 4.4% at six months ($P < 0.0001$)	"These interim results show an acceptable safety record of LES-EST to date, combined with good short-term efficacy in GERD patients who are partially responsive to PPI therapy. A remarkable reduction in regurgitation symptoms, without the risk of intervention-requiring dysphagia may prove to be an advantage compared with other anti-reflux procedures"

Table 4. Summary of Studies Investigating DBS for Obesity.

Study	Method	Patient population	Intervention(s)	Outcome(s)	Result(s)	Conclusion(s)
Rezai. "Deep Brain stimulation for the treatment of obesity"	Prospective, nonrandomized, clinical trial	5 patients with treatment-refractory obesity	DBS, target unknown	Percentage of excess weight loss after two years	Completion in Jan. 2018	Completion Jan. 2018
Whiting et al. "Lateral hypothalamic area deep brain stimulation for refractory obesity"	Prospective, nonrandomized, clinical trial	3	DBS, targeting lateral hypothalamic area (LHA)	Weight loss after one year, Change in metabolic rate after one week, adverse effects	Completion in Dec. 2015. Preliminary data shows that "no serious adverse effects [. . .] promising weight trends"	Completion Dec. 2015
Gorgulho. "Deep brain stimulation for human morbid obesity (BLESS)"	Prospective, nonrandomized, clinical trial	6	DBS, targeting VMH	Identification of possible adverse events related to stimulation after one year	Completion April 2017	Completion April 2017
Luming. "PINS stimulator system for deep brain stimulation to treat obesity"	Prospective, nonrandomized, clinical trial	8	DBS, target unknown	Body weight after one year	Completion Dec. 2018	Completion Dec. 2018
Damiani. "Deep brain stimulation for the treatment of obesity in patients with Prader-Willi syndrome (DBSPW)"	Prospective, nonrandomized, clinical trial	6	DBS, targeting HA	Waist and mid-upper arm circumference at six months, resting energy expenditure at six months, BMI at six months, adverse events at three and six months	Completion Oct. 2016	Completion Oct. 2016

showing that it is feasible to treat erectile dysfunction secondary to radical prostatectomy with a chronic implantable cavernous nerve stimulation system. A pilot clinical trial is currently underway (to be completed in 2016) to evaluate the safety and tolerability of chronic cavernous nerve stimulation post-radical prostatectomy and to explore the potential efficacy of the stimulation on the return of post-operative erectile function. Research in the field of penile neurogenesis continues to advance, particularly in the context of improved erectile function outcomes post-radical prostatectomy. Great interest exists in furthering the investigation of electrostimulation as a therapeutic option; the continuation of investigation at the preclinical and clinical levels offer promise of this therapy becoming clinically useful for pelvic surgery and potentially other erectile dysfunction disease states as well.

Gastrointestinal Dysmotility

Gastrointestinal motility is regulated by rhythmic myoelectrical activity. Various disorders, including gastroparesis and gastroesophageal reflux disease, can occur when there is impairment in this myoelectrical activity. These disorders are not currently FDA-approved indications for using neuromodulation.

Gastroparesis

Myoelectrical activity is composed of slow waves and spikes. The gastric slow wave, a rhythmic myoelectrical event that controls the frequency and propagation of peristalsis, originates in the proximal one-third of the stomach and propagates toward the pylorus with increasing amplitude and frequency. A lumen-occluded (as in the postprandial state) contraction occurs when the slow wave is superimposed with spikes. Every slow wave is superimposed with spikes in the postprandial state; without a spike, the slow wave does not produce a gastric contraction (11). Gastroparesis is defined as delayed gastric emptying of solids in the absence of mechanical obstruction (12). Different methods of gastric electrical stimulation, typically comprised of a pair of leads implanted in the muscularis propria along the greater curvature of the stomach connected to a subcutaneously implanted or externally placed generator, have been studied for the treatment of gastric motility disorders. The Enterra Therapy method uses a high-frequency-short pulse (Enterra® Therapy, Medtronic, Minneapolis, MN, USA) (13,14). This device has been approved by the FDA for treatment of nausea and vomiting in patients with gastroparesis. Although it was approved based on studies showing that improvement in nausea and vomiting with use of Enterra Therapy was due to central and vagal mechanisms (15), other studies have suggested that this therapeutic effect may involve gastric motility and gastric emptying. Our analysis of these studies demonstrates that high-frequency gastric electrical stimulation may provide significant benefits in the treatment of refractory gastroparesis. High frequency-short pulse stimulation consists of a narrow pulse width on the order of a few hundred microseconds (~300 μsec), with a stimulation frequency (~14 Hz) a few times higher than the 3 cycles per minute physiological frequency of the gastric slow wave. Our review finds that while high-frequency gastric electrical stimulation has consistently shown significant benefits, there is no consensus regarding the mechanism of action by which it treats gastroparesis. A decrease in nausea and vomiting, an improvement in gastric emptying, and a decrease in the requirement for nutritional support are the most frequent benefits to appear in our review. Of the many studies we reviewed, four were clinically controlled trials. These studies have shown promising results with the use of high-frequency gastric electrical stimulation in the treatment of refractory gastroparesis,

Table 5. Summary of Studies Investigating Vagus Nerve Stimulation for Asthma.

Study	Method	Patient population	Intervention(s)	Outcome(s)	Result(s)	Conclusion(s)
Miner et al. "Feasibility of percutaneous vagus nerve stimulation for the treatment of acute asthma exacerbations"	Prospective, nonrandomized, feasibility study	25 patients	Temporarylow voltage, percutaneous vagus nerve stimulation; 25 Hz and 0.2 pulse width, 1–2 volt amplitude	Adverse events, vital signs, FEV1, perceived work of breathing, final disposition	No serious adverse events. One patient with minor bleeding from procedure, one with a hematoma and withdrew prior to VNS. These resolved when VNS ended No significant changes in vital signs FEV1 improved at 15 minutes, 30 minutes, and 60 minutes; Work of breathing improved at 15 minutes, 30 minutes, and 60 minutes	"Percutaneous VNS did not result in serious AEs and was associated with improvements in FEV1 and perceived dyspnea. Percutaneous VNS appears to be feasible for use in the treatment of moderate to severe acute asthma in patients unresponsive to initial standard care treatment"

but additional high quality studies are needed for further evaluation of this treatment option.

Other methods of gastric stimulation show potential for treating gastroparesis as well. Low frequency-long pulse gastric electrical stimulation is commonly called "gastric pacing," which is designed to increase gastric motility by affecting gastric contractions, slow waves and gastric emptying (16–18). Gastric pacing typically includes a wide pulse width on the order of milliseconds (10–600 msec) with a stimulation frequency similar to the physiological frequency of the gastric slow wave. This approach to gastric electrical stimulation has been shown to improve gastric emptying in diabetic mice (17) and to improve gastric dysrhythmias in dogs (19,20), but clinical findings have thus far been limited because of a lack of commercially available devices using low frequency-long pulse stimulation. Our review of high-frequency gastric electrical stimulation shows that increased gastric motility is associated with improved gastroparesis; gastric pacing methods have a strong prokinetic effect on gastric motility and there are thusly strong grounds for further development and evaluation of low frequency-long pulse gastric electrical stimulation in the treatment of gastroparesis.

Gastroesophageal Reflux Disease

The esophagus serves as a passage for ingesting food and water. It consists of a hollow muscular tube that is closed proximally and distally by muscular sphincters (21). The outer muscular coat of the esophagus, called the muscularis propria, consists of an inner layer of circularly oriented muscle fibers and an outer layer of longitudinally oriented fibers. The inner mucosal layer consists of squamous epithelium and an underlying connective tissue that contains a longitudinally oriented muscle layer called the muscularis mucosa. In between these two muscle layers is the myenteric plexus, which controls the motor function of both of these muscles. The primary function of the esophagus is to propel, via peristaltic contraction of circular muscle in the esophageal body, swallowed food or water into the stomach; these peristaltic contractions work in conjunction with relaxation of the upper and lower esophageal sphincters to allow proper passage of the swallowed contents (22–25). The lower esophageal sphincter functions as a barrier that prevents gastric contents from re-entering the esophagus; GERD may occur when the lower esophageal sphincter is loose, leading to the typical "heartburn" symptoms.

The most effective and commonly used treatment of GERD is with proton pump inhibitors to inhibit gastric acid secretion. This method of therapy does not prevent reflux, however. Therapeutic options such as surgically, mechanically or magnetically thickening or tightening the lower esophageal sphincter are also effective in treating GERD, although these methods are complicated by side effects such as dysphagia, gas-bloating, and inability to belch due to impaired relaxation of the lower esophageal sphincter during swallowing (26–28). The first studies analyzing the potential of electrical stimulation in the treatment of GERD were performed in canine models; these studies showed that electrical stimulation of the lower esophageal sphincter led to prolonged contraction of the sphincter complex to prevent GERD (29–31) In the first study of electrical stimulation for treatment of GERD in humans, Rodriguez et al. (32) found that electrical stimulation with both high and low frequency caused an increase in lower esophageal sphincter pressure without affecting sphincter relaxation or residual pressure during swallowing. It was determined that high frequency stimulation was the better option because it requires less energy and thus increases battery life. Banerjee et al. (33) were able to replicate these results with electrical stimulation via temporary stimulation leads implanted during endoscopy. To deliver this stimulation, a

Table 6. Summary of Studies Investigating Vagal Nerve Stimulation for Heart Failure.

Study	Method	Patient population	Intervention(s)	Outcome(s)	Result(s)	Conclusion(s)
De Ferrari et al. "Vagus nerve stimulation: From pre-clinical to clinical application: Challenges and future directions"	Multicenter, open-label phase II, two-staged clinical trial	32 NYHA class II–IV patients (age 56 +/− 11 years, LVEF 23 +/− 8%)	Right cervical VNS with CardioFit (BioControl Medical) implantable system	Adverse events, quality of life, six-minute walk test, LVEF, LV systolicvolumes	26 serious adverse events in 13 of 32 patients (40.6%), including three deaths; Significant improvements in NYHA class quality of life, six-minute walk test, LVEF, and LV systolic volumes	"This open-label study shows that chronic VNS in CHF patients with severe systolic dysfunction may be safe and tolerable and may imiprove quality of life and LV function. A controlled clinical trial appears warranted"
INOVATE-HF	Randomized, controlled, phase III pivotal trial	650 NYHA class III patients (LVEF <40%, LVEDD between 50 and 80 mm). 3:2 ratio of device implantation or optimal medical treatment	Right cervical VNS with CardioFit (BioControl Medical) implantable system	All cause mortality, heart failure hospitalization	Expected completion 2017	Expected completion 2017
NECTAR-HF	Randomized, controlled, phase II clinical trial	96 NYHA class II–III patients (LVEF <35%, LVEDD >55 mm)	Boston Scientific VNS device	Left ventricular end systolic diameter (LVESD), EF, LV volumes, quality of life scores, functional capacity, changes in biomarkers	No significant change in LVESD, LV end diastolic dimension, LV end systolic volume, left ventricular end diastolic volume, LV ejection fraction; significant improvement in quality of life (Minnesota Living with Heart Failure Questionnaire, NYHA class, SF-36 Physical Component)	"Vagal nerve stimulation as delivered in the NECTAR-HF trial failed to demonstrate a significant effect on primary and secondary endpoint measures of cardiac remodeling and functional capacity in symptomatic heart failure patients, but quality-of-life measures showed significant improvement"
ANTHEM-HF	Randomized, controlled, phase I–II clinical trial	60 NYHA class II–III patients (LVEF <40%, LVEDD between 50 and 80 mm): right, 29; left, 31	Autonomic regulation therapy via left or right VNS	LVESV, LVESD, LVEF, adverse effects	After six months: adjusted left-right differences in LVEF, left ventricular end-systolic volume (LVESV), and left ventricular end-systolic diameter (LVESD) were 0.2% (95% CI −4.4 to 4.7), 3.7 mL (95% CI −7.0 to 14.4), and 1.3 mm (95% CI −0.9 to 3.6), respectively	"Chronic open-loop ART via left- or right-side VNS is feasible and well tolerated in HFrEF patients. Safety and efficacy measures are encouraging and warrant further study"

conventional laparoscopic approach is used to implant electrodes in the muscular layer at the anterior aspect of the lower esophageal sphincter. The lead is then advanced through the abdominal wall and secured to a generator that is secured subcutaneously (34).

Thus far, two open-label clinical studies have investigated the efficacy and safety of electrical stimulation therapy of the lower esophageal sphincter using EndoStim LES stimulation. In the first open-label, single center trial, Rodriguez et al. (34) showed significant improvement of symptom scores (GERD-HRQL (35)) soon after activation of the device as well as at six-month follow-up. This study, initially designed with a six-month follow-up period, was extended to allow for two-year and three-year long-term data. Twenty-three of the initial 25 patients completed the two-year extension trial. The median GERD-HRQL symptom score remained significantly lower compared to baseline. Additionally, median acid exposure time decreased even further to 3.3% from baseline ($P < 0.001$) and 64% (14/22) of patients showed normal distal esophageal acid exposure time (pH < 4.0 during $<4\%$ of time). Currently, 21 patients have completed 24 month follow-up and these promising results of esophageal stimulation therapy have persisted; 71% of the patients have shown either a normalized or $>50\%$ reduction in acid exposure time (36,37). The three-year results were recently published electronically ahead of print in October 2015 (38). In this further extension trial, 15 patients completed the study and significant improvement in their median GERD-HRQL scores prevailed. Median 24-hour distal esophageal acid exposure was significantly reduced (10.3% at baseline vs. 3%, $P < 0.001$) and 73% (11/15) of patients had normalized their distal esophageal acid exposure at this point. The remaining four patients had improved acid exposure by 39–48% from baseline. This extension trial has shown promising results of electrical stimulation for the treatment of GERD; this therapy has been safe and effective over long-term, three-year duration.

Two open-label multicenter studies evaluating the use of electrical stimulation for the treat of GERD are ongoing. Siersema et al. (39) have published interim results showing a positive effect on symptoms: GERD-HRQL median score has improved from a baseline of 31 to 4 at three-months and 5 at six-months, respectively with $P < 0.001$ and $P < 0.01$. Acid exposure time has decreased from 11.3% at baseline to 3.3% at three months and 2.6% at six months. Meanwhile, Kappelle et al. (40) have reported interim results showing improved GERD-HRQL scores from 31 at baseline to 16.5 at three month and 5 at six-month follow-up, and improved esophageal acid exposure from 10.0% at baseline to 3.8% at three months. Both of the interim results from these ongoing studies are thus far showing good short-term efficacy of treating GERD with acceptable safety records; long-term data of these studies is awaited.

Our review found that the current data analyzing the potential of esophageal stimulation therapy in the treatment of GERD is promising. The three open-label studies have shown that this therapeutic option is a safe technique and offers significant improvement in both subjective and objective outcomes. However, further studies are needed as no randomized controlled trials have been completed to fully assess this therapy. Additionally, all patients in these studies have used the same settings on their stimulation devices. Future trials are needed to assess whether customized settings will further improve the efficacy of esophageal stimulation therapy for the treatment of GERD.

Obesity

Obesity is now the third leading cause of preventable death in the United States. More than two-thirds of adults in the United States are overweight and over one-third are obese, accounting for over 200,000 deaths annually and nearly 100 billion dollars in health care costs (41–44). Conservative measures to treat obesity are associated with high rates of relapse, so surgical treatment options have been increasingly used, particularly as improvements in bariatric surgery have led to significant weight loss in $>90\%$ of patients (45–47). As knowledge of the neuroanatomic and neuropsychiatric factors in the pathophysiology of obesity continue to increase, neuromodulation as a therapeutic option continues to increase as well. It is well established that the hypothalamus is involved in the neurophysiology of obesity (48,49), and more recently, the brain's reward circuitry has been found to be involved in the pathologic food-seeking behavior typically seen in obese individuals (50,51). The nucleus accumbens is therefore a promising target for neuromodulation (52). Neuromodulation of the brain can be accomplished with deep brain stimulation (DBS), a neurosurgical procedure that involves implantation of a neurostimulator to send electrical impulses via implanted electrodes to specific areas of the brain. DBS is a safe, well-established and effective therapy for several disorders; currently, the FDA has approved the use of DBS in the treatment of essential tremor, Parkinson's disease, dystonia, and treatment-resistant obsessive-compulsive disorder (53,54).

In the first study (55) to investigate the safety and efficacy of DBS for treatment-refractory obesity in a human clinical trial, patients who were at least 24 months post Roux-en-Y gastric bypass surgery without evidence of sustained improvement in BMI after the surgery for at least six months were enrolled to undergo DBS, implanted with stimulation to an unspecified target. The study, which started in 2012, is currently ongoing. In another clinical trial, Whiting et al. (56) have reported preliminary data about DBS of the lateral hypothalamic area for intractable obesity. In this small study, the authors have so far reported that "no serious adverse effects were noted in addition to promising weight loss trends." This study is scheduled to be completed in December 2015. Three other clinical trials (57–59) are ongoing, as summarized in Table 4, and have yet to report data. Data from animal research (60–63), functional imaging studies in humans (64–66), and early results from human pilot studies have demonstrated the potential of DBS in the treatment of obesity. As these clinical trials continue, randomized controlled trials will be necessary to further evaluate the efficacy and safety of DBS in the treatment of obesity in humans.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is currently FDA approved for the treatment of refractory epilepsy and depression. The vagus nerve contains myelinated A and B fibers in addition to unmyelinated C fibers. VNS primarily engages afferent A fibers, and while the exact anticonvulsant and antidepressant mechanisms of VNS are unknown, potential mechanisms include changes in neurotransmitters and neuronal metabolism, an increase in Fos expression, and a desynchronizing effect. Additionally, VNS may provide its therapeutic effects both via its localized electrochemical action and by inducing long-term neuromodulatory effects (67,68). VNS is currently being investigated for its use in functional disease conditions such as asthma and heart failure.

Asthma

Maintenance of airway caliber and control of airway smooth muscle tone is done via two primary mechanisms: neural networks and mediators of inflammation. The parasympathetic nervous system

mediates muscle contraction through the action of Ach on postganglionic cholinergic nerves, while non-adrenergic non-cholinergic nerves mediate muscle relaxation through NO or VIP (69). Muscarinic (M3) receptors on smooth muscle are pro-inflammatory and play an important role in airway constriction and glandular secretion. Epithelial cells, mast cells, invading leukocytes, and airway smooth muscle cells release inflammatory mediators that also activate the parasympathetic drive (70). Asthma is a "common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation (71)." Currently, the mainstay of asthma treatment is inhaled corticosteroid with short-acting β2 agonist (e.g., albuterol) and anticholinergic medications for acute exacerbation (72). VNS has been found to have a bronchodilatory effect. Hoffmann et al. (73) in a mechanistic study on animal subjects, reported that high voltage stimulation induces bronchoconstriction, hypotension, and bradycardia, whereas low voltage stimulation attenuates Ach- or histamine-induced bronchoconstriction. The authors explain that this is likely to occur through an underlying adrenergic mechanism.

These results have led to the investigation of VNS for acute management of clinical asthma exacerbation. In a case series, Steyn et al. (74) reported that three out of four patients who received noninvasive VNS for acute asthma exacerbation were considered treatment successes, as determined by improvement in FEV_1, VAS dyspnea scoring, and the absence of device-related adverse events. In a prospective, nonrandomized feasibility study of 25 patients with acute asthma exacerbation that was nonresponsive to at least one hour of initial standard care therapy, Miner et al. (75) reported that percutaneous VNS led to rapid recovery of FEV_1 within 15 minutes, with progressive improvement during and 60 minutes beyond the stimulation. In this study, physicians experienced with the placement of central venous access lines placed the investigational device. An electrode was placed percutaneously near the right carotid sheath and then removed after stimulation. Further results are outlined in Table 5. Our review finds that current studies have demonstrated the acute bronchodilatory effects of CNS in the treatment of asthma. Continued studies need to be completed to better pinpoint the mechanism of action and to further evaluate the short-term and long-term efficacies of this use of neuromodulation.

Heart Failure

Another investigative use of VNS is for the treatment of heart failure. Right cervical VNS has received clearance in Europe but is not yet FDA approved in the United States. VNS for the treatment of heart failure was first experimented in human patients in a small single-center feasibility study (76). DeFerrari et al. (77) then followed this first stage with a multicenter international extension, increasing the number of patients studied to a total of 32. In this study, patients (mean age 56 +/− 11 years, LVEF 23 +/− 8%) were implanted with a nerve stimulation electrode on the right cervical vagus nerve connected to a Cardiofit stimulator. The authors report that 26 serious adverse events occurred in 13 patients, including three deaths. Of these adverse events, two were clearly device-related while the others were considered expected based on the severity of the underlying disease. Additionally, they reported significant improvements ($P < 0.001$) in NYHA quality of life, six-minute walk test (from 411 ± 76 to 471 ± 111 m), LV ejection fraction (from 22 ± 7% to 29 ± 8) and LV systolic volumes ($P = 0.02$).

Following this pilot study, further clinical investigations have since proceeded, with three randomized controlled clinical trials evaluating VNS in patients with heart failure. The INOVATE-HF study (78) began enrollment in April 2011 and will evaluate the use of vagal nerve stimulation in 650 patients with NYHA class III HF. The primary endpoints will be all-cause mortality or unplanned heart failure hospitalization. This study is scheduled for completion by 2017.

In the NECTAR-HF study (79), published in 2015, the authors reported that vagal nerve stimulation failed to demonstrate a significant effect on primary and secondary endpoint measures of cardiac remodeling and functional capacity in 96 NYHA class II–III patients. They note, however, that quality of life measures showed significant improvement (Minnesota Living with Heart Failure Questionnaire, $P = 0.049$; NYHA class, $P = 0.032$; SF-36 Physical Component, $P = 0.016$).

In another recently completed study, the INOVATE-HF study (80) enrolled and randomized 60 NYHA class II–III patients to either left or right cervical vagal stimulation. The authors of this randomized controlled phase I–II clinical trial report, "Chronic open-loop ART via left- or right-side VNS is feasible and well tolerated in HFrEF patients."

Our review finds that while some studies have shown that VNS for the treatment of heart failure appears to provide both subjective and objective improvement, other studies have not shown a significant benefit. Overall, the investigation of this new use of neuromodulation is encouraging and further studies are warranted.

CONCLUSION

This review article shows preliminary support based on clinical studies that neuromodulation can benefit patients with important disorders of the autonomic nervous system—especially erectile dysfunction, gastroesophageal reflux disease, and obesity—that are not currently approved by the FDA. We have also reviewed the literature for clinical studies evaluating neuromodulation for other potential indications, such as gastroparesis, asthma, and heart failure. For all indications discussed in this article, further randomized controlled clinical trials will be necessary to achieve sufficient evidence for FDA approval before these uses of neuromodulation can be recommended for clinical practice.

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Drs. Lee and Abd-Elsayed contributed to literature search, manuscript writing, and analysis of this review article.

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REFERENCES

1. Ooi YC, Falowski S, Wang D, Jallo J, Ho RT, Sharan A. Simultaneous use of neurostimulators in patients with a preexisting cardiovascular implantable electronic device. *Neuromodulation* 2011;14:20–26.
2. Lee SY, Abd-Elsayed A. Some non-FDA approved uses for neuromodulation: discussing the evidence. *Pain Prac* 2015; e-pub ahead of print. doi: 10.1111/papr.12405.
3. Abell T, McCallum R, Hocking M et al. Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology* 2003;125:421–428.

4. McCallum RW, Snape W, Brody F, Wo J, Parkman HP, Nowak T. Gastric electrical stimulation with enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. *Clin Gastroenterol Hepatol* 2010;8:947–954.
5. 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;74:496–503.e3.
6. McCallum RW, Sarosiek I, Parkman HP et al. Gastric electrical stimulation with Enterra therapy improves symptoms of idiopathic gastroparesis. *Neurogastroenterol Motil* 2013;25:815–e636.
7. Burnett AL, Lue TF. Neuromodulatory therapy to improve erectile function recovery outcomes after pelvic surgery. *J Urol* 2006;176:882–887.
8. Lue TF, Gleason CA, Brock GB, Carroll PR, Tanagho EA. Intraoperative electrostimulation of the cavernous nerve: technique, results and limitations. *J Urol* 1995;154: 1426–1428.
9. Stief CG, Weller G, Noack T et al. Functional electromyostimulation of the corpus cavernosum penis—preliminary results of a novel therapeutic option for erectile dysfunction. *World J Urol* 1995;13:243.
10. Burnett AL, Teloken PE, Briganti A, Whitehurst T, Montorsi F. Intraoperative assessment of an implantable electrode array for cavernous nerve stimulation. *J Sex Med* 2008;5:1949–1954.
11. Chen JD, Pan J, McCallum R. Clinical significance of gastric myoelectrical dysrhythmias. *Dig Dis* 1993;13:275–290.
12. Abell TL, Bernstein RK, Cutts T et al. Treatment of gastroparesis: a multidisciplinary clinical review. *Neurogastroenterol Motil* 2006;18:263–283.
13. Familoni BO, Abell TL, Nemoto D, Voeller G, Johnson B. Efficacy of electrical stimulation at frequencies higher than basal rate in canine stomach. *Dig Dis Sci* 1997;42: 892–897.
14. Abell T, Lou J, Tabbaa M, Batista O, Malinowski S, Al-Juburi A. Gastric electrical stimulation for gastroparesis improves nutritional parameters at short, intermediate, and long-term follow-up. *J Parenter Enteral Nutr* 2003;27:277–281.
15. Yin J, Abell TD, McCallum RW, Chen JD. Gastric neuromodulation with Enterra system for nausea and vomiting in patients with gastroparesis. *Neuromodulation* 2012; 15:224–231.
16. Chen JD et al. Efficiency and efficacy of multi-channel gastric electrical stimulation. *Neurogastroenterol Motil* 2003;17:878–882.
17. Song G et al. Two-channel gastric electrical stimulation accelerates delayed gastric emptying induced by fasopressin. *Dig Dis Sci* 2005;50:662–668.
18. Lin Z, Forster J, Sarosiek I, McCallum RW. Treatment of gastroparesis with electrical stimulation. *Dig Dis Sci* 2003;48:837–848.
19. Liu J, Qiao X, Chen JD. Therapeutic potentials of a novel method of dual-pulse gastric electrical stimulation for gastric dysrhythmia and symptoms of nausea and vomiting. *Am J Surg* 2006;191:255–261.
20. Zhu H, Sallam H, Chen DD, Chen JD. Therapeutic potential of synchronized gastric electrical stimulation for gastroparesis: enhanced gastric motility in dogs. *Am J Physiol Regul Integr Comp Physiol* 2007;293:R1875–R1881.
21. Vantrappen G, Hellemans J. *Diseases of the esophagus*. New York: Springer-Verlag, 1974.
22. Goyal RK, Paterson WG. Esophageal motility. In: Wood JD, ed. *Handbook of physiology: the gastrointestinal system*. Washington, DC: American Physiological Society, 1989:865–908.
23. Goyal RK, Sivarao DV. Functional anatomy and physiology of swallowing and esophageal motility. In: Castell DO, Richter JE, eds. *The esophagus*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1999:1–31.
24. Biancani P, Harnett KM, Behar J. Esophageal motor function. In: Yamada T, ed. *Textbook of gastroenterology*, 3rd ed., vol. 1. Philadelphia: Lippincott Williams & Wilkins, 1999:157–187.
25. Clouse RE, Diamant NE. Esophageal motor and sensory function and motor disorders of the esophagus. In: Feldman M, Friedman LS, Sleisenger MH, eds. *Gastrointestinal and liver disease: pathophysiology, diagnosis, management*, 7th ed., vol. 1. Philadelphia: WBSaunders, 2002:561–598.
26. Perry KA, Pham TH, Spechler SJ, Hunter JG, Melvin WS, Velanovich V. 2014 SSAT state-of-the-art conference: advances in diagnosis and management of gastroesophageal reflux disease. *J Gastrointest Surg* 2015;19:458–466.
27. Straathof JW, Ringers J, Lamers CB, Masclee AA. Provocation of transient lower esophageal sphincter relaxations by gastric distension with air. *Am J Gastroenterol* 2001;96:2317–2323.
28. Broeders JA, Mauritz FA, Ahmed Ali U et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg* 2010;97: 1318–1330.
29. Ellis F, Berne TV, Settevig K. The prevention of experimentally induced reflux by electrical stimulation of the distal esophagus. *Am J Surg* 1968;115:482–487.
30. Sanmiguel CP, Hagiike M, Mintchev MP et al. Effect of electrical stimulation of the LES on LES pressure in a canine model. *Am J Physiol Gastrointest Liver Physiol* 2008; 295:G389–G394.
31. Clarke JO, Jagannath SB, Kalloo AN, Long VR, Beitler DM, Kantsevoy SV. An endoscopically implantable device stimulates the lower esophageal sphincter on demand by remote control: a study using a canine model. *Endoscopy* 2007;39: 72–76.
32. Rodriguez L, Rodriguez P, Neto MG et al. Short-term electrical stimulation of the lower esophageal sphincter increases sphincter pressure in patients with gastroesophageal reflux disease. *Neurogastroenterol Motil* 2012;24:446–450.
33. Banerjee R, Pratap N, Kalpala R, Nageshwar Reddy D. Effect of electrical stimulation of the lower esophageal sphincter using endoscopically implanted temporary stimulation leads in patients with reflux disease. *Surg Endosc* 2014;28: 1003–1009.
34. Rodriguez L, Rodriguez P, Gómez B et al. Electrical stimulation therapy of the lower esophageal sphincter is successful in treating GERD: final results of open-label prospective trial. *Surg Endosc* 2013;27:1083–1092.
35. Velanovich V. The development of the GERD-HRQL symptom severity instrument. *Dis Esophagus* 2007;20:130–134.
36. Rodriguez L, Rodriguez P, Gomez B et al. Long-term results of electrical stimulation of the lower esophageal sphincter for the treatment of gastroesophageal reflux disease. *Endoscopy* 2013;45:595–604.
37. Rodriguez L, Rodriguez P, Gomez B et al. Two-year results of intermittent electrical stimulation of the lower esophageal sphincter treatment of gastroesophageal reflux disease. *Surgery* 2015;157:556–567. Mar;
38. Rodriguez L, Rodriguez P, Gomez B, Netto MG, Crowell MD, Soffer E. Electrical stimulation therapy of the lower esophageal sphincter is successful in treating GERD: long-term 3 year results. *Surg Endosc*. In press 2015.
39. Siersema PD, Smout AJ, Conchillo JM et al. Electrical stimulation therapy (EST) of the lower esophageal sphincter (LES) - an effective therapy for refractory GERD - interim results of an international multicenter trial. *United Eur Gastroenterol J* 2013;1: A411.
40. Kappelle WF, Bredenoord AJ, Conchillo JM et al. Electrical stimulation therapy of the lower oesophageal sphincter for refractory gastro-oesophageal reflux disease – interim results of an international multicenter trial. *Ailment Pharmacol Ther* 2015;42: 614–625.
41. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2014;311:806–814.
42. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA* 2012;307: 491–497.
43. Danaei G, Ding EL, Mozaffarian D et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Med* 2009;6:0.
44. Allison DB, Zannolli R, Narayan KM. The direct health care costs of obesity in the United States. *Am J Public Health* 1999;89:1194–1199.
45. Jeffery RW, Kelly KM, Rothman AJ, Sherwood NE, Boutelle KN. The weight loss experience: a descriptive analysis. *Ann Behav Med* 2004;27:100–106.
46. Li Z, Maglione M, Tu W et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* 2005;142:532–546.
47. Magro DO, Geloneze B, Delfini R, Pareja BC, Callejas F, Pareja JC. Long-term weight regain after gastric bypass: a 5-year prospective study. *Obes Surg* 2008;18: 648–651.
48. van de Sande-Lee S, Pereira FR, Cintra DE et al. Partial reversibility of hypothalamic dysfunction and changes in brain activity after body mass reduction in obese subjects. *Diabetes* 2011;60:1699–1704.
49. Wyrwicka W, Dobrzecka C. Relationship between feeding and satiation centers of the hypothalamus. *Science* 1960;132:805–806.
50. Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. *Arch Gen Psychiatry* 2011;68:808–816.
51. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci* 2010;13:635–641.
52. Knapp CM, Tozier L, Pak A, Ciraulo DA, Kornetsky C. Deep brain stimulation of the nucleus accumbens reduces ethanol consumption in rats. *Pharmacol Biochem Behav* 2009;92:474–479.
53. Hassan A, Okun MS. Emerging subspecialties in neurology: deep brain stimulation and electrical neuro-network modulation. *Neurology* 2013;80:e47–e50.
54. Tagliati M, Krack P, Volkmann J et al. Long-term management of DBS in dystonia: response to stimulation, adverse events, battery changes, and special considerations. *Mov Disord* 2011;26:S54–S62.
55. Rezai A. Deep brain stimulation for the treatment of obesity. *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). Available from: https://clinicaltrials.gov/ct2/show/NCT01512134
56. Whiting DM, Tomycz ND, Bailes J et al. Lateral hypothalamic area deep brain stimulation for refractory obesity: a pilot study with preliminary data on safety, body weight, and energy metabolism. *J Neurosurg* 2013;119:56–63.
57. Gorgulho A. Deep brain stimulation for human morbid obesity (BLESS). *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). Available from: https://clinicaltrials.gov/ct2/show/NCT02232919
58. Luming. PINS Stimulator System for Deep Brain Stimulation to Treat Obesity. In: *Clinical Trials.gov [Internet]*. Bethesda (MD): National Library of Medicine (US). 2000-2015Nov18. Available from: https://clinicaltrials.gov/ct2/show/NCT02254395
59. Damiani D. Deep brain stimulation for the treatment of obesity in patients with Prader-Willi syndrome (DBSPW). *Clinical Trials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). Available from: https://clinicaltrials.gov/ct2/show/NCT02297022
60. Goldstein JM, Siegel J. Suppression of attack behavior in cats by stimulation of ventral tegmental area and nucleus accumbens. *Brain Res* 1980;183:181–192.
61. McCracken CB, Grace AA. High-frequency deep brain stimulation of the nucleus accumbens region suppresses neuronal activity and selectively modulates afferent drive in rat orbitofrontal cortex in vivo. *J Neurosci* 2007;27:12601–12610.
62. Murer MG, Pazo JH. Behavioral responses induced by electrical stimulation of the caudate nucleus in freely moving cats. *Behav Brain Res* 1993;57:9–19.
63. Halpern CH, Tekriwal A, Santollo J et al. Amelioration of binge eating by nucleus accumbens shell deep brain stimulation in mice involves D2 receptor modulation. *J Neurosci* 2013;33:7122–7129.

64. Stice E, Yokum S, Bohon C, Marti N, Smolen A. Reward circuitry responsivity to food predicts future increases in body mass: moderating effects of DRD2 and DRD4. *Neuroimage* 2010;50:1618–1625.
65. O'Doherty JP, Deichmann R, Critchley HD, Dolan RJ. Neural responses during anticipation of a primary taste reward. *Neuron* 2002;33:815–826.
66. Stoeckel LE, Weller RE, Cook EW III, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage* 2008;41:636–647.
67. Haas AM, Benbadis SR, Vale FL. Vagus nerve stimulation for epilepsy. In: *eLS*. Chichester: John Wiley & Sons Ltd; 2014. http://www.els.net. doi: 10.1002/9780470015902.a0020285.pub2
68. Yuan H, Silberstein SD. Vagus nerve and vagus nerve stimulation, a comprehensive review: part III. *Headache*. In press 2015.
69. Undem BJ, Potenzieri C. Autonomic neural control of intrathoracic airways. *Compr Physiol* 2012;2:1241–1267.
70. Kistemaker LEM, Gosens R. Acetylcholine beyond bronchoconstriction: roles in inflammation and remodeling. *Trends Pharmacol Sci* 2015;36:164–171.
71. National Asthma Education and Prevention Program. Expert panel report III: guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051). Available form: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm (Accessed on November 17, 2015).
72. Wasilewski NV, Lougheed MD, Fisher JT. Changing face of b2-adrenergic and muscarinic receptor therapies in asthma. *Curr Opin Pharmacol* 2014;16:148–156.
73. Hoffmann TJ, Simon BJ, Zhang Y, Emala CW. Low voltage vagal nerve stimulation reduces bronchoconstriction in guinea pigs through catecholamine release. *Neuromodulation* 2012;15:527–536.
74. Steyn E, Mohamed Z, Husselman C. Non-invasive vagus nerve stimulation for the treatment of acute asthma exacerbations-results from an initial case series. *Int J Emerg Med* 2013;6:7.
75. Miner JR, Lewis LM, Mosnaim GS, Varon J, Theodoro D, Hoffmann TJ. Feasibility of percutaneous vagus nerve stimulation for the treatment of acute asthma exacerbations. *Acad Emerg Med* 2012;19:421–429.
76. Schwartz PJ, De Ferrari GM, Sanzo A et al. Long term vagal stimulation in patients with advanced heart failure: first experience in man. *Eur J Heart Fail* 2008;10:884–891.
77. De Ferrari GM, Schwartz PJ. Vagus nerve stimulation: from pre-clinical to clinical application: challenges and future directions. *Heart Fail Rev* 2011;16:195–203.
78. Hauptman PJ, Schwartz PJ, Gold MR et al. Rationale and study design of the increase of vagal tone in heart failure study: INOVATE-HF. *Am Heart J* 2012;163:954–962.e1.
79. Zannad F, De Ferrari GM, Tuinenburg AE et al. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. *Eur Heart J* 2015;36:425–433.
80. Premchand RK, Sharma K, Mittal S et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *J Card Fail* 2014;20:808–816.

COMMENTS

The authors provide a summary of a number of non-FDA approved indications for neuromodulation including gastric disorders, sexual dysfunction, asthma and heart failure. Many of these 'indications' do not have class 1 evidential support but the authors present the preliminary work in these fields. This paper reflects the increasing interest in neuromodulation for 'autonomic' disorders and shares many of the early results. It is clear that this field is expanding and as the authors make clear, it is likely to expand much further in the near future.

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This review of several commercially available, non-FDA approved uses of neuromodulatory techniques is both informative and of potential interest to the reader. The authors have provided an accessible systematic review of the available literature and keep the material interesting to the reader.

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Since 2011 the big pharma have disinvested in the development of drugs to treat neurological disorders. This permits the neuromodulation community to fill in this gap for providing treatments for neurological disorders. This manuscript fits in this tendency to provide preliminary support that neuromodulation could potentially be used for the treatment of some autonomic nervous system disorders. However, the provided literature overview should not be considered as evidence but rather as support that further investigation in neuromodulatory approaches for these disorders is worthwhile and needed, as many of these disorders are insufficiently treated by conservative medical management. Furthermore there is no a priori reason why this approach could not be extended to any and every nervous system related disorder, even those that at first sight would not seem amenable to neuromodulation, such as auto-immune disorders. We, as neuromodulation community however have to provide strong evidence, build better neuromodulation devices and use neuromodulation in a pathophysiology based approach if we are to convince non-believers, which is the largest part of the medical field, that neuromodulation can provide benefit to patients who are intractable to conservative medical management. Therefore, collaboration with other medical disciplines is mandatory and essential if neuromodulation is to become an integrated part of routine medicine.

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Comments not included in the Early View version of this paper.

