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Gastric electrical stimulation: Overview and summary

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INTRODUCTION

Gastric electrical stimulation (GES) is a bioelectric therapy[1] first used in humans over 30 years ago.[2] Since its inception, GES, as currently performed, has been used in over 10,000 patients worldwide. This review provides a brief history, methods, indications, mechanisms of action, clinic data, future developments and possible new applications.

BRIEF HISTORY OF GES

Bioelectric therapies like GES have their origin in animal, and some human, studies done in the 1960s through 1980s.[2] The most crucial factor leading to development of GES was interest in and discovery of gastric electrical dysrhythmias in patients with gastrointestinal (GI) motility symptoms such as nausea, vomiting and severe dyspepsia.[1,3] Animal models examining GI electrical function and inducing electrical dysrhythmias began to try ways to "pacing" to normalize the physiologic abnormalities. Work with simulation, now preferably called neuromodulation, showed promise with normalizing abnormal electrical and mechanical function.[4] Encouraged by this animal work, one human was given in February 1992 what was later called low-energy, high-frequency electrical stimulation, which later became, in 1995, an investigational device exemption in the US for more patients.[5] The initial work led to a randomized trial of GES, which was used as the basis for U.S. Food and Drug Administration (FDA) approval of GES as a humanitarian use device (HUD) in 2000. Other work, with higher energies, was also being done in the same time; this approach has not been FDA-approved. This review concerns gastric neuromodulation as approved by the FDA in 2000.

GES METHODS

The current approved system for GES uses leads implanted in the gastric muscle layers from a serosal approach, either by open or laparoscopic procedure as well as a battery and pulse generator unit placed subcutaneously.[6] The techniques are well described and will not be repeated here.[6] The main complications of permanent GES devices are either infection, usually of the device pocket, but sometimes at the incision sites, or lead dislodgement. As permanent GES has been performed longer, these complications are not common and occur in less than 5% of patients.

Several techniques for the placement of temporary GES have been used over the last 30 years, although they are not part of the US FDA approval. These include direct gastric endoscopic placement of leads, placement through a percutaneous endoscopic gastrostomy tube, placement by laparoscopy or other similar techniques.[7] Advantages of temporary GES include being able to try different lead locations, different energy settings, and to evaluate the overall efficacy before of GES before a permanent device is placed.

The most common settings for GI neuromodulation with GES are those provided by the manufacturer (Enterra Medical, Minneapolis, USA). These "factory" settings are 5 milliamps of current, displayed in volts (directed by the impedance as voltage using the equation of Volts = Current × Impedance), 330 microseconds pulse width, 14 Hertz burst

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Access this article online

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DOI: 10.2478/jtim-2022-0056

frequency, with 0.1 seconds on and 5.0 seconds off. These settings were based on both animal work and early human trials and result in low energy, high (er than physiologic) frequency GES and minimized energy use to maximize GES battery longevity. A published algorithm based on empirical observations of the first few years after HUD approval is available.[8]

Other settings for GES are widely used including increasing the current up to a maximum of about 20 milliamps (assuming an impedance of 500 Ohms) and increasing the on time to a maximum of 4 seconds on with 1 seconds off (still providing pulse bursts every 5 seconds). Changes to burst rate and pulse width are usually done as later steps as they will decrease battery life in accordance with how much energy is used. Changes in device settings are often made based on patients' symptoms and sometimes related to gastric emptying or electrogastrogram values at regular intervals. Based on current practice, many patients end up with settings of about 15 milliamps with 2 seconds on and 3 seconds off.[9]

INDICATIONS FOR GES

The FDA approval for GES is for "drug refractory gastroparesis of diabetic or idiopathic origin". The most common upper gastrointestinal symptoms associated with gastroparesis (Gp) include nausea, vomiting and/or abdominal pain, but other patients have additional upper GI complaints of anorexia, early satiety, bloating, and/or distention, often associated with heartburn and sometimes with dysphagia.

The most reported symptoms of Gp used for GES are nausea and/or vomiting. Of the over 500 publications listed on *Wikistim*, the majority describe GES as being used for these two emetic symptoms (www.wiksitim.org). As a result of its FDA labeling, most patients who have received GES have evidence of delayed solid gastric emptying associated with nausea, vomiting and associated symptoms of Gp. Other subtypes of Gp have not been as well studied but some predictors of response to GES, including low BMI and the presence of hindgut symptoms, have recently been described.[9]

Some patients receive GES off-label use of GES for post-surgical Gp symptoms, and who may or may not have delayed solid gastric emptying on testing. Other patients have symptoms of Gp but with non-delayed solid gastric emptying—the so called gastroparesis-like syndrome (GLS) or severe functional dyspepsia (FD)—may receive GES devices, particularly if they respond to a trial of temporary GES. An additional group of patients who may respond to GES are those with chronic unexplained nausea and vomiting (CUNV) who have failed all other medical and, in some cases, endoscopic or surgical approaches.

The advent of pyloric therapies for Gp has opened a spectrum of possibilities for the treatment of some otherwise refractory patients. As with other aspects of this review, a full discussion of pyloric therapies for Gp is beyond the scope of this article. However, many patients who have not responded to pyloric therapies may respond to GES. Likewise, other subgroups of patients may respond to a combination of pyloric therapy and GES.[10]

MECHANISMS OF ACTION OF GES

The mechanism of action (MOA) of GES has been the source of confusion and some controversy. To help understand MOA for any bioelectric therapy, it may be helpful to first mention what is known about the pathophysiology of Gp syndromes. Gp syndromes (GpS) can be related to many different disorders and no one pathophysiology explains all patients with GpS. A full discussion of Gp and GpS is beyond the scope of this review but the topic has been recently reviewed by the ACG Clinical Guidelines for Gp.[11] GES was originally developed in response to the observation that some patients with Gp symptoms have gastric electrical dysrhythmias.[3] Since then, there has been recognition that GES may work by any of several mechanisms, whether they be central, autonomic, enteric, hormonal, anti-inflammatory, and/or other peripheral ways. Some of these mechanisms of action of GES have recently been summarized.[12] Effects of GES have been documented in several areas outside of the stomach including the small bowel/mid-gut and colon/hindgut.[13,14] Systemic effects of GES have been noted including effects on inflammation and hormonal function.[15] Whatever the mechanism(s), GES has had a profound positive impact on many patients, as is discussed below. Figure 1 shows some of the known pathophysiologic areas for gastroparesis syndromes, and thus targets for intervention, as well as possible mechanisms of action/effects of GES so far elucidated.

CLINICAL DATA ON GES

Many of the GES studies listed on *Wikistim* are case reports and open label trials of varying sample sizes. At least 9 controlled trials and at least 5 guidance and meta-analysis of GES currently exist in the published literature with others in preparation.[16–18] These published GES articles have also been discussed in the ACG Guidelines mentioned above. Most of the controlled trials and most of the guidance's/meta-analyses of GES are positive and consistent with other published neuromodulation literature.

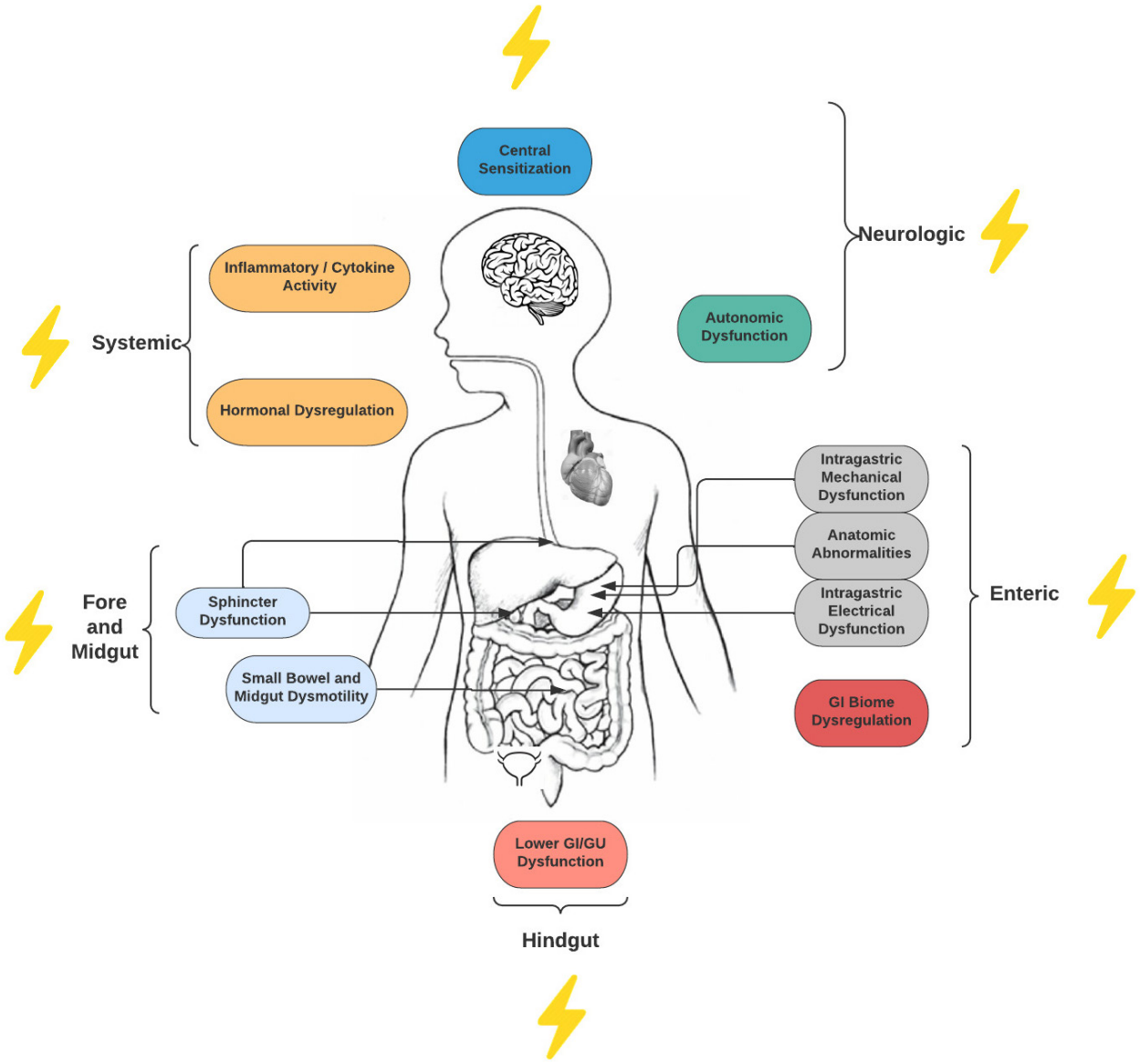

Figure 1: Some of the known pathophysiologic areas for gastroparesis syndromes as well as possible mechanisms of action/effects of GES as noted with the symbol. Adapted from Management of Gastroparesis in 2022.[10] GI: gastrointestinal; GES: gastric electrical stimulation; GU: genitourinary.

FUTURE DEVELOPMENTS AND OTHER APPLICATIONS FOR GES

Future developments for GES may include changes in the current hardware, such as making the device and leads MRI conditionally safe, and new hardware, such as wireless endoscopic devices. These changes may make GES applicable to a greater number of patients with gastroparesis syndromes.

Future applications of GES may include widening the spectrum of patients currently treated with GES in the GI motility arena for other illnesses where GES may be beneficial. This may include not only patients with gastro-pyloric dysfunction described above but those with gastro-esophageal dysfunction and symptoms of both Gp/GpS and GERD. The use of GES in gastro-pyloric and gastro-esophageal dysfunction is now the subject of detailed investigation.

CONCLUSIONS

Gastric electrical stimulation is a proven bioelectric therapy that is FDA-approved for gastroparesis. Gastric electrical stimulation's mechanisms of action are increasingly being determined and validated. The bioelectric therapy of gastric electrical stimulation, which is still evolving, may have the potential for helping more patients with gastroparesis and

other related illnesses in the future.

Acknowledgments

The author would like to thank Catherine McBride for manuscript preparation and Prateek Mathur for figure preparation.

Conflict of Interest

Abell's Main funding is NIH GpCRC and NIH Gastric Dysrhythmias; an Investigator for Censa, Cindome, Vanda, Allergan, Neurogastrx, Prcoessa; a Consultant for Censa, Nuvaira, Takeda, Medtronic and Enterra Medical; a speaker for Takeda and Enterra Medical; a reviewer for UpToDate; the GES editor for Neuromodulation, Wikistim; and the founder of ADEPT-GI which has IP for autonomic/enteric and bioelectric diagnosis and therapies.

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How to cite this article: Abell TL. Gastric electrical stimulation: Overview and summary. J Transl Intern Med 2022; 10: 286-289.