HTA

TECHNOLOGY ASSESSMENT REPORT

GASTRIC ELECTRICAL STIMULATION (ENTERRA™ THERAPY SYSTEM) FOR THE TREATMENT OF GASTROPARESIS

AHFMR ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

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EXECUTIVE SUMMARY

Background

Gastroparesis (GP) is a disorder manifested by delayed gastric emptying in the absence of mechanical obstruction. Clinically, GP may be associated with severe nausea, vomiting, and malnutrition. The principal diagnostic test for delayed gastric empting is nuclear scintigraphy. GP and delayed gastric emptying may accompany and also mimic other diseases or in some cases may be asymptomatic, thus the difficulty in diagnosing, treating, and monitoring this disorder.

Gastric electrical stimulation (GES) is considered a treatment option for patients with severe symptoms associated with GP. The Enterra™ Therapy system is a GES system that is implanted subcutaneously in the abdominal wall and provides high-frequency, low-energy stimulation to the muscle wall of the stomach via a pair of electrodes/leads. The treatment is reversible. The Enterra™ Therapy system may be turned off by the physician at any time or may be removed. The Enterra™ Therapy system had licensure approval from Health Canada as a Class 3 device for the treatment of chronic intractable nausea and vomiting.

Objectives

The aim of this paper is to present the current evidence on the efficacy/effectiveness, safety, and efficiency of GES (Enterra™ Therapy system) used for the treatment of patients with severe GP.

Methodology

A systematic search of PubMed, EMBASE, HealthStar, The Cochrane Library, Science Citation Index, and the websites of various health technology assessment agencies, research registers, and guideline sites from 2000 onward was performed. The analysis was limited to studies published in the English language. Position papers and guidance reports, along with the regulatory status of the Enterra™ Therapy system, are also included.

Results

One two-month, multicentre, crossover, blinded, randomized, placebo-controlled study; one comparative prospective study that compared GES therapy with medication treatment; and eight case series met the inclusion criteria. Four of 10 studies reported results from patients who were previously presented in past publications. The studies were generally of weak methodological design and average quality. Results on long-term follow-up were not available from all patients initially included in the studies.

Overall, the results from studies that reported on patients who were not part of another published study indicated symptomatic improvement after GES. In the randomized crossover study with results measured at one month of follow-up for stimulation ON and OFF with the GES device, the weekly vomiting frequency and total symptom score (TSS) for severity measured separately for diabetic and idiopathic patients showed an improvement compared with baseline values. The differences between the stimulation ON and OFF period were not statistically significant.

The case-series studies reported outcome results mainly at 6 months and 12 months of follow-up. In four studies, the reduction in the frequency and/or severity of vomiting and/or nausea was found to be statistically significant at 6 and 12 months of follow-up. Statistically significant improvement of gastrointestinal TSS of severity and/or frequency was indicated in two studies at 6 and 12 months of follow-up. Improvement of nutritional status measured by patient weight was found to be statistically significant in two studies at 6 and 12 months and in one study at 20 months of follow-up. Statistically significant improvement of quality of life was reported in two studies at 6 and 12 months of follow-up. A reduction in supplementary enteral and parenteral feeding (four studies) and a reduction in reliance on drugs to alleviate symptoms (three studies) were also noted, statistical significance not having been reported, at 12 months of follow-up.

However, these improvements were not associated with improvement of gastric emptying. GES apparently does not cause the muscle of the stomach to contract and only has a modest improvement in gastric emptying. The mechanism of action of the GES system is still unclear.

Overall, these results need to be cautiously interpreted, as many authors noted that the effects of benefits may be placebo attributed.

The use of GES, as with any implanted device, is not without risk. The most common adverse events reported were infection at the pocket site of the impulse generator or erosion, either of which required the removal of the system, and electrode dislodgement, which required reintervention.

There is insufficient information to determine the efficiency of GES. In Canada, the device itself costs approximately Cdn $10,685.

Conclusions

Candidates for GES treatment are a select group of patients aged 18 to 70 years who do not respond to drug therapies and sometimes have severe associated comorbidities (depletion of electrolytes, malnutrition, and a depressed immune system). GES is used more often for symptom control rather than treatment of the motility disorder.

The current evidence, based on an average of 12 months of follow-up on the safety and efficacy of GES for patients with idiopathic GP or GP associated with diabetes or

surgery who tolerated the implanted device, is not adequate to support the routine use of this procedure. It would, however, be considered a last-resort treatment after all conventional treatment regimes had failed to control symptoms of nausea and vomiting. The research on GES for GP associated with other conditions has yet to be done.

Because of possible risks associated with the implantation of this device, the implantation should be provided by trained professionals and the use of the device should be restricted to those patients who have severe symptoms and are refractory to another less invasive and risky approach such as drug therapy and diet. A continuous follow-up of the patients is necessary to identify possible adverse events and effects related to the condition and to treatment, as well as to assess the costs and quality of life experienced by patients.

Controlled studies are ongoing or have been planned and after this research is published, this technology should be reviewed again to determine if the cumulative research adds to the knowledge of efficacy/effectiveness.

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- Dr. Thomas Abell, Professor of Medicine/Gastroenterology, the University of Mississippi Medical Center, Jackson, Mississippi, USA.
- Dr. Louis W.C. Liu, Assistant Professor, McMaster University, Hamilton, Ontario, Canada.

The following individual(s) are acknowledged for provision of the information regarding the local context or published studies:

- Dr. Richard W. McCallum, Professor, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas, USA

In preparing this report, the manufacturer of the Enterra™ Therapy system was contacted for technical and costing information:

- Mr. Thomas Koszegi, Territory Manager, Medtronic of Canada Ltd., Calgary, Alberta, Canada
- Mr. Karl Kriz, Marketing Manager Gastro/Uro Division, Medtronic of Canada Ltd. Mississauga, Ontario, Canada

All information and input is appreciated. The views expressed in the final report are those of the Foundation.

Information Services Support

Literature search for the review was undertaken by Ms. Liz Dennett, Research Librarian, Alberta Heritage Foundation for Medical Research, Edmonton, Alberta, Canada.

COMPETING INTEREST

Only the referees who were paid honoraria were asked to sign a declaration of competing interest. All others who provided general information were exempt.

Competing interest is considered to be financial interest or non-financial interest, either direct or indirect that would be affected by the research contained in this report, or creation of a situation where a person's judgement could be unduly influenced by a secondary interest such as personal advancement.

Based on the statement above, the following person(s) declared potential competing interest:

Dr. Thomas Abell was the recipient of research grants and honoraria for publications from the Division of Medicine, University of Mississippi. Also, Dr. Abell has acted as a consultant to Medtronic Inc., this activity consisted in reviewing studies. The Enterra™ Therapy system uses a technology licensed by the University of Tennessee where Dr. Abell is a former faculty member. He is not involved in patents or any Medtronic stock.

Dr. Louis W.C. Liu declared no competing interest.

One reviewer who provided information and comments on the draft report, declared no competing interest, and requested to remain anonymous.

ABBREVIATIONS

AHFMR: Alberta Heritage Foundation for Medical Research

BMI: body mass index

CUESS: Compassionate Use of Electrical Stimulation Study

FDA: Food and Drug Administration

GEMS: Gastric Electro-Mechanical Stimulation

GES: gastric electrical stimulation

GET: gastric emptying

GI: gastrointestinal

GP: gastroparesis

HbA1c: hemoglobin A1c

HDE: Humanitarian Device Exemption

HFS: high-frequency, low-energy stimulation

IDIOMS: investigator-derived independent outcome measure score

ITT: intention to treat

LFS: low-frequency, high-energy stimulation

LOCF: last observation carried forward

MCS: mental composite score

N, n: number of patients

NS: not significant

NSS: not statistically significant

PCS: physical composite score

PEG: percutaneous endoscopic gastrostomy

PMA: Premarket Approval

SE: standard error

SEM: standard error of the mean

SS: statistical significance

TSS: total symptom score

WAVESS: Worldwide Antivomiting Electrical Stimulation Study

WVF: weekly vomiting frequency

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Tables

SCOPE OF THE REPORT

This report is a systematic review and critical appraisal of the published evidence on the use of gastric electrical stimulation (GES; Enterra™ Therapy) for the treatment of patients with severe gastroparesis (GP) refractory to medication. Its purpose is to provide information to Alberta Advisory Committee on Health Technologies and Alberta Health & Wellness regarding the available evidence on the efficacy/effectiveness, efficiency, and safety of GES (Enterra™ Therapy) for GP.

The search strategy included research published from 2000 onward and English language only (Appendix A: Search and Methodology). Ten studies were included: one RCT, one comparative study, and eight case series (see Appendix B). A critical quality appraisal of the case series was undertaken (see Appendix C). Guidelines, policies, and conclusions by other health technology assessment reports, along with the regulatory status of the Enterra™ Therapy system, are also presented. The manufacturer of the Enterra™ Therapy system, Medtronic Canada Ltd., was contacted for technical and costing information.

BACKGROUND

The stomach is characterized by complex electrical activity that plays an important role in gastric motor function.[1] Normal gastric muscle contractions have a maximal frequency of three cycles per minute.[2] Patients with gastric motor disorders have various kinds of gastric dysmotility (gastric dysrhythmias), including delayed gastric emptying (gastroparesis; GP).[3]

There is no standard definition for GP,[4] but the term broadly refers to a disorder manifested by delayed gastric emptying in the absence of mechanical obstruction.[3-11] Patients with severe GP have frequent hospital admissions and experience a poor quality of life.[4,9]

There are many causes of GP. The disorder is often associated with diabetes.[4,11-16] In patients with diabetic GP, hyperglycemia may be both the cause and the result of poor gastric emptying.[17] [16] GP may also occur after surgical procedures such as partial gastric resection and vagotomy or postbariatric surgery, or may accompany gastrointestinal disorders such as gastrointestinal motor disorders, achalasia, gastric ulcer, atrophic gastritis, functional dyspepsia, and celiac disease.[3,15] There also is an overlap between the symptoms of GP and functional dyspepsia.[3,5] Idiopathic GP may be one of the causes of functional dyspepsia.[3]

Also, GP and delayed gastric emptying can be associated with non-gastrointestinal disorders, albeit less commonly. These disorders may include eating disorders (anorexia), connective tissue disorders (scleroderma, systemic lupus erythematosus), central nervous system disorders (cerebrovascular accident, tumour, Parkinson disease), endocrine and metabolic disorders (thyroid and parathyroid dysfunctions, chronic renal insufficiency), gastric infection, chronic mesenteric ischemia, and tumours (paraneoplastic).[3,15] Patients diagnosed with idiopathic GP in the absence of any apparent cause[14,17-19] may represent the most common form of GP.[3]

Delayed gastric emptying may also accompany digestive and non-digestive disorders, including partial small bowel obstructions, constipation, and depression.[14] Medications (such as narcotic pain medication, calcium channel blockers, and antidepressant medications) may cause delayed gastric emptying, mimicking the symptoms of GP.[13]

Symptoms associated with GP are non-specific and include nausea, vomiting, epigastric pain and distress, abdominal fullness or bloating, early satiety, heartburn, and loss of appetite.[1-3,6-8,10,11,20] A frequently quoted[5-7] study[21] noted that the symptom distribution in 146 patients with GP was nausea in 92%, vomiting in 84%, abdominal bloating in 75%, and early satiety in 60% of the patients. In general, symptoms develop one hour or more after solid food ingestion. Liquids are tolerated relatively well.[10]

In severe and chronic cases, nausea and vomiting may cause weight loss, dehydration, electrolyte disturbances, and poor glycemic control in diabetic patients.[20] Delayed gastric emptying and GP may also be detected in asymptomatic persons such as patients with diabetes mellitus.[4,14]

DIAGNOSIS OF GASTROPARESIS

GP is diagnosed by demonstrating delayed gastric emptying in a symptomatic individual after the exclusion of other potential causes of symptoms such as ulcer disease, mechanical small bowel obstruction, gastric cancer, pancreatic or biliary disorders, gastroesophageal reflux disease with regurgitation, self-induced vomiting, and cyclical vomiting syndrome.[3,4]

Scintigraphy of a solid-phase meal (using a ^{99m}Technetium sulphur colloid-labelled egg sandwich) is considered the gold standard for the diagnosis of GP.[3,4,18,20] Nuclear scintigraphic evaluation is useful to establish the presence of dysmotility, but the clinical diagnosis is difficult because the patient's presenting clinical signs and symptoms are often vague and may overlap with other conditions. Scintigraphy is also useful to evaluate the effectiveness of medical therapy.[15] There is no standard scintigraphic technique with variation among different centres, particularly with respect to the choice of test meal, the period of observation, and the calculation of gastric emptying rates.[4] Conventionally, the test is performed for 2 hours after ingestion of a radiolabelled meal.[3,5] Retention of 10% of the meal in the stomach at 4 hours is considered abnormal, as stated in the guideline published by the Society of Nuclear Medicine in the United States.[22] Gastric emptying measurements have coefficients of variation of almost 15%; thus, only unequivocal results are considered clinically important, and persistent symptoms may be an indication for repeated testing before excluding a motility disorder (consensus opinion published after consultancy with peers at meetings of the American Motility Society and the American Gastroenterological Association).[23]

Other diagnostic tests include upper gastrointestinal endoscopy or barium (used for excluding diagnosis of mechanical obstruction), ultrasound examination, breath tests using the non-radioactive isotope ^{13}C incorporated within a solid meal, magnetic resonance imaging, single-photon emission computed tomography, and satiety testing.[3] Electrogastography is an adjuvant test that can help detect abnormalities in gastric electrical rhythm and gastroduodenal manometry is used to determine motor dysfunction.[3,18,20]

PREVALENCE OF GASTROPARESIS

The prevalence of GP is difficult to estimate because of the incomplete correlation of symptoms with gastric emptying.[3] Women appear to be disproportionately susceptible to GP that results from any cause.[3,6,7]

Prevalence rates reported by several papers from around the world estimate that delayed gastric emptying is observed in 20% to 50% of patients who suffer from type 1 diabetes mellitus, probably as a result of neuropathy of the vagus and other nerves that control the musculature of the gastrointestinal system.[3,5,11,14,18-20] Delayed gastric emptying has also been described in approximately 30% of patients with type 2 diabetes mellitus.[3,14] However, highly variable rates of gastric emptying, including acceleration of transit, were reported in type 1 and type 2 diabetes mellitus, suggesting that development of GP is not universal or inevitable.[3,15]

According to the American Gastrointestinal Association, approximately 5% of patients undergoing vagotomy with antral resection and gastrojejunostomy may develop severe post-surgical GP.[3]

There are inconsistencies in the prevalence rates for severe GP reported by various groups and authors. It was stated in a Medtronic news release that approximately 100,000 people in the United States suffer from a severe form of GP and that the standard medication fails to relieve symptoms adequately in approximately 30,000 of these patients (Medtronic Inc., News release, 2000).[24] Using these estimates with a population base of 282,192,162 in the United States on July 1, 2000,[25] the prevalence rate for severe GP would be 0.035% (35 cases per 100,000 people) and of this group approximately one third (12 cases per 100,000 people) would be refractory to medication.

Another publication by Abell and Minocha in 2002 estimated that the prevalence of severe, symptomatic, and medically refractory GP in the United States population was 50,000.[18] This value would represent 0.017% or 17 cases per 100,000 people, for a population base of 287,941,220 on July 1, 2002.[25]

The prevalence of GP in the Canadian population is unknown. Results from an international study[26] (DIGEST) conducted in 1999 used a representative population sample of 1036 Canadians. The authors found that 153 of the Canadian participants surveyed reported having substantial chronic gastrointestinal symptoms for more than three months. From this group, 84 reported dysmotility-like symptoms, including early satiety, nausea, vomiting, postprandial fullness, diffuse upper abdominal discomfort, regurgitation, belching, and distension as predominant symptoms. However, only 49 participants who reported chronic symptomatology stated that they were diagnosed by a physician with diagnoses such as hiatus hernia, gallstones, peptic ulcer, and esophagitis, or reflux disease. Only 37 of 153 participants with chronic symptoms were

prescribed medication for their gastrointestinal symptoms. A weakness of this study is that the authors focused on dysmotility-like symptoms reported by the participants and not an established diagnosis by physicians; in addition, there was no mention of patients with GP.

The focus of this report is on the subgroup of patients with severe GP that are refractory to medication (2 of 3 classes of drugs). No study was found that addressed the prevalence rate of severe GP in the North American population.

TREATMENT OPTIONS

Traditional management of GP has involved the use of low-fat, low-fibre, soft diets with frequent small meals and high-caloric liquid supplements, as well as the administration of prokinetic and antiemetic medication.[2,4,6,7,10,14,16,17,20] Prokinetic agents stimulate gastric motility and co-ordinate gastric-duodenal motor activity, whereas antiemetics are used to treat nausea. Palliative surgical therapies such as tube gastrostomy or jejunal feeding tube (jejunostomy or j-tube) and partial or total gastric resection (gastrectomy) are used when patients have an inadequate response to dietary and drug therapy.[3,4,14] The role of surgery is neither well defined nor well studied.[2,6,7,10,16,20,27]

The American Gastroenterological Association Clinical Practice Committee in 2004 endorsed a technical review on the diagnosis and treatment of GP.[3] In their review, the general principles for the treatment of symptomatic GP included the correction of fluid, electrolyte, and nutritional deficiencies; identification and rectification of the underlying cause of GP if possible; and reduction of symptoms.[3] There is no consensus regarding the management of patients with GP who do not respond to simple antiemetic or prokinetic therapy or who develop severe medication-induced side effects.[3]

GASTRIC ELECTRICAL STIMULATION

Gastric electrical stimulation (GES) was developed for the treatment of patients with chronic intractable (drug-refractory) nausea and vomiting secondary to GP. GES works by stimulating the gastric wall with electrical pulses. Two types of stimulus parameters are mainly used in the treatment of chronic GP: low-frequency, high-energy stimulation (LFS) and high-frequency, low-energy stimulation (HFS).

LFS (gastric pacing) is able to entrain the gastric slow wave (LFS three cycles per minute with a pulse width of 330 ms), and improve gastric emptying and dyspeptic symptoms in patients with refractory GP.[11] However, LFS requires more electrical energy compared with HFS treatment and is currently limited to devices in which the generator is external to the body, usually connected to the stomach by sewn-in electrodes that protrude through the abdominal wall.[18]

The Enterra™ Therapy system (Medtronic, Minneapolis, MN) is an implantable neurostimulator that works with HFS.[11,12,28] The stimulation frequency used in HFS is much higher than the intrinsic frequency of the gastric slow wave (HFS 12 cycles per minute and a pulse width of 330 μs).[9] The pulse generator (Medtronic ITREL 3 Model 7425G and 3116 Neurostimulator) is a battery-powered device, approximately 2.5 inches (60 mm) long, 2 inches (50 mm) wide, and 0.5 inches (12 mm) thick,[29] implanted subcutaneously in the abdominal wall by laparoscopy or laparotomy.[28,30-32] Also, two stimulating electrodes/leads (Model 4351) are implanted one centimetre apart into the muscle wall of the stomach. The electrodes are secured proximally with an anchor and distally using a small silicone disc and sutures. The connector of each lead is attached to the stimulator.[28,31] The electrical stimulation of the gastric tissue can be adjusted with an external programmer system (Model 7432 Physician Programmer and Model 7457 MemoryMod Software Cartilage) placed on the skin over the implanted pulse generator.[31,32]

The pulse generator is programmed to be ON for 0.1 seconds and then OFF for 5 seconds.[2] The pulse generator's battery has a life span from 5 to 10 years, depending on how strong the stimulation must be for controlling the symptoms. The functioning of the neurostimulator should be checked by a physician about once every 6 months. When the battery needs to be replaced, the implantable pulse generator must be replaced by another surgical procedure.[29] If the leads are still in place and functional, the battery alone may be replaced in a simple surgical procedure under local anaesthesia (personal communication representative Medtronic of Canada Ltd. December 16, 2005). The usual intensity of the stimulating current is 5 mA. In a case series by Mason et al.,[33] at each follow-up visit the neurostimulation was checked, adjusted, and incrementally increased by 1 mA per day, if necessary, until the symptoms were relieved. In this study, the median maximum stimulating current required for controlling patients' symptoms was 7.75 mA (range 4.30 mA to 10 mA).

The Enterra™ Therapy system cannot restore normal gastric emptying but seems to reduce symptoms of nausea and vomiting.[3,9,11,12,18] The mechanism of action is not well known.[10] The treatment is reversible. The Enterra™ Therapy system may be turned off by the physician at any time or may be removed.[32]

Prior to prescribing the device for the first time, physicians should receive appropriate training by specialists in the surgical and/or implantation techniques, operational characteristics, and functions of the Enterra™ Therapy system. Programming of the device is provided by or under the supervision of a physician or by other experienced medical personnel familiar with the use of the programing software.[31]

In a study published by Ayinala et al.[34], the electrodes were temporality implanted via endoscopy (orally) or percutaneous endoscopic gastrostomy (PEG; a less invasive procedure as an alternative to laparotomy), followed by permanent GES. The comment of the authors was that PEG electrodes remained functional for a longer period of time, up to one month, and the placement of the electrodes was considered technically easier compared with endoscopic (oral) placement. The authors considered that it might be preferable to use PEG-placed electrodes in patients with a pre-existing gastrostomy because of longer duration of the temporary electrode placement. In the authors' opinion, temporary GES stimulation appears to be predictive of the long-term outcome of permanent stimulation and may be used to select patients who might benefit from the permanent device, especially if the efficacy of the device is uncertain or if the indication (such as postsurgical disorder) has not been fully studied.

ADVERSE EVENTS AND CONTRAINDICATIONS

Use of the gastric neurostimulator is not without risks. The risks associated with the Enterra™ Therapy system are similar to those for other implanted neurostimulation/ pacemaker systems.[31] The Enterra™ Therapy system is contraindicated in patients who are not deemed as appropriate candidates for surgery and/or anaesthesia because of physical or mental conditions.[29,32] The safety and efficacy of the system has not been evaluated for patients under the age 18 years or over the age of 70.[29]

Patients with severe GP, especially those with diabetes, are usually at high risk for infection[11] because of malnutrition, skin contamination from enteral tubes and ostomies, and immunologic effects. The device is a foreign body and once infected it may be impossible to eradicate the infection without removal of the device.[11]

Although symptoms may be resolved in some patients (such as those with idiopathic GP) after a relatively short period of time, the majority of patients with GP would remain dependent on the device. Another surgery intervention for the replacement of the neurostimulator at appropriate time intervals would be required in the group of patients with persistent symptoms.[29]

The adverse events related to the device and reported by the manufacturer include device infections, erosion, migration, and stomach wall perforation. Other potential technical failures include undesirable change in stimulation, shifts in lead position, and loose electrical connections or lead fractures.[29,31] The most common clinical adverse event is infection at the pocket site of the impulse generator, reported to occur in approximately 5% to 10% of cases, which requires device removal.[3] Other possible clinical complications are hemorrhage, hematoma, gastrointestinal complications resulting from the surgical procedure needed to implant the neurostimulator and leads,[2] persistent pain at the neurostimulator site, seroma at the neurostimulator site, allergenic or immune system response to implanted materials, and loss of therapeutic effect.[29,31]

Adverse events data collected on 51 patients with drug-refractory GP of diabetic or idiopathic etiologies during two multicentre clinical studies conducted in the United States, Canada, and Europe are presented in Appendix D, Table D.1.[32]

HEALTHCARE COSTS

The American Gastroenterological Association Technical Review on the diagnosis and treatment of GP[3] quoted an unpublished study of patients with severe GP that estimated healthcare costs to be an average of US $6972 per patient per month. Most expenditures were attributed to requirements for hospitalization and temporary or long-term use of intravenous alimentation (parenteral nutrition).[3] In addition, diagnostic tests for patients with presumed GP are associated with significant costs, especially for endoscopy and gastric emptying scintigraphy tests.[3]

The cost of implanting the Enterra™ Therapy system in the United States is approximately US $30,000, and is covered by Medicare as well as some private health insurance companies (*The Clarion-Ledger Mississippi News,* 2004).[35] In the United Kingdom, the overall cost, including device and hospital costs, is about £15,000 to £16,000.[36]

Information about the cost of the Enterra™ Therapy system was received from a representative of Medtronic Canada Ltd. (Table 1). The total cost of the device per patient is approximately Cdn $10,685. In addition, other costs, such as those for diagnostic tests, surgical intervention (laparoscopy or laparotomy) to implant the device and its replacement when appropriate, hospitalization, and training, should be considered, as well as the costs for the removal of the device, and treatment of adverse events in those patients who cannot tolerate it.

Table 1: Costing information for the Enterra™ Therapy system*

Model	Component Description	Cost (Cdn $)
3116	Implantable pulse generator	6695
4351-35	Intramuscular lead Each patient requires two leads	1995 X 2 = 3990
Total cost with device implanted in one patient		***10,685***
8840	N'Vision Physician Programmer	3000
8870	N'Vision application card	600
8527	N'Vision portable printer	1295

*Information was obtained from Medtronic Canada Ltd. and is based on a product price list that was effective May 15, 2005.

ENTERRA™ THERAPY SYSTEM APPROVAL IN CANADA AND IN THE UNITED STATES

Health Canada approved the Enterra™ Therapy system (Medtronic Inc.) (date of issue October 2002) as a Class 3 device for use in the treatment of chronic intractable (drug refractory) nausea and vomiting.[37]

Health Canada's approval process for marketing a Class 3 device relies upon information submitted mainly by the manufacturer and consists of background information, device specific information, summary of the safety and efficacy studies, and conclusions drawn from these studies by the manufacturer, and compliance with quality systems requirements (ISO 13485-98).[38] The focus of the clinical assessment is on the summarized data provided by the manufacturer to determine if the new device is superior to its alternative. Raw data submission is not a requirement. Furthermore, safety concerns require the manufacturer to demonstrate biological compatibility according to international standards. Health Canada also searches for any medical alerts regarding device's safety profile.

The Enterra™ Therapy system has been implanted in 12 patients in Canada (five cases in Quebec, five in Ontario, and two in British Columbia). Some of these patients were participants in the two multicentre studies[8,39] (personal communication representative Medtronic of Canada Ltd. September 2, 2005). A survey of provincial health ministries on the coverage status of the Enterra™ Therapy system, conducted among the provinces and territories in Canada in the fall of 2005, revealed that the procedure is not covered by any public plan in hospitals or surgical clinics. Four provinces/territories did not respond to this question (Appendix E, Table E.1).

The Food and Drug Administration (FDA) in the United States approved the Enterra™ Therapy system (GES system) on March 31, 2000,[24,32] under the Humanitarian Device Exemption (HDE) for the treatment of chronic intractable (drug refractory) nausea and vomiting secondary to diabetic and idiopathic GP.[3,6,32,40]

The HDE approval is limited to rare conditions that affect or are manifested in fewer than 4000 individuals per year in the United States for which there is no other comparable device, other than another humanitarian use device approved under the HDE regulation or a device being studied under an approved investigational device exemption available to treat the condition.[41] The HDE approval does not require the manufacturer to submit evidence on effectiveness that would be necessary to support a Premarket Approval (PMA) Application.[12,41] The Center for Devices and Radiological Health of the FDA, on the basis of data submitted in the HDE application, issued the approval for the Enterra™ Therapy system on the premise that it will not expose patients to an unreasonable or significant risk of illness or injury; the probable health benefit from using the device outweighs the risk of illness or injury.[32]

The manufacturer with an HDE approval is required to report periodically to the FDA, with information such as the number of devices sold; a summarization of any changes made to the device; safety information; and adverse reactions and events, including casualties, serious injury, or malfunctioning.[32]

A white paper/petition by the Gastroparesis and Dysmotilities Association, which represents patients from across Canada and the United States, was sent to the FDA in February 2004 to request the transfer of the Enterra™ Therapy system from an HDE approval status to a PMA.[42] This request was denied by the FDA in November 2004 on the basis of insufficient or inadequate clinical evidence required to make scientific conclusions regarding the safety and the effectiveness of the device to support a PMA.[43]

An estimated 200 patients per year in the United States receive the device and since December 2004, nearly 1000 patients have had the device implanted (*The Clarion-Ledger Mississippi News*, 2004).[8,35]

AVAILABLE EVIDENCE ON EFFICACY/EFFECTIVENESS AND SAFETY

The methodology for this review is presented in detail in Appendix A. Eighteen studies were identified that potentially met the inclusion criteria of the review. On closer examination of the full text article, eight of these studies were excluded (Appendix A, Table A.2). Ten studies—one randomized, placebo-controlled, double-blind crossover study[39]; one comparative prospective study[44]; and eight case series[8—11,30,33,40,45-47]met the inclusion criteria of the review. The comparative prospective study and three case series[44-47] reported results from patients who were also presented in a previous publication. This factor potentially overestimates the benefit of the device.

A critical appraisal of the methodological quality of all case series[8,11,30,33,40,45-47] was undertaken from a list of 30 criteria. Details on the method used to assess the methodological quality of the case series and the results of the assessment are presented in Appendix C. Case series are considered to be of the lowest quality based on the hierarchy of evidence. The case series were rated with respect to quality criteria as average (between 50% and 80% of criteria met), with only two studies meeting 22 criteria from the checklist. Because of the paucity of information in the area, information from all case series was extracted and presented. For the same consideration, the studies that included patients who were also reported in other publication are included and the results are presented separately in the report.

Table 2 summarizes the main components and findings of interest relevant to the discussion of the studies to follow. The main findings in Table 2 are graded according to hierarchy of evidence.

Table 2: Summary of main findings of studies on GES for the treatment of GP*

Study*	Follow-up (Range)	No. Patients Etiology Average Duration of GP Symptoms (Range/SEM)	TSS (Frequency and/or Severity)	Vomiting (Frequency and/or Severity)	Nausea (Frequency and/or Severity)	GET Normalized/ Not Changed/ Worsened
Abell et al.[39] Multicentre, randomized, placebo-controlled crossover study Phase I (WAVESS)¶	1 month	N = 33 Diabetic, idiopathic 6.3 years (1 to 28)	Severity NSS	WVF ↓SS (for all patients but NSS for separate etiologies)	N/A	N/A
Cutts et al.[44] Comparative prospective study (patients from two FDA trials - WAVESS; CUESS)	3 years	N = 9 Diabetic, idiopathic 7.2 years + 2.3 N = 9 medication Diabetic, idiopathic 2.8 years + 0.8	Severity ↓SS (for years 1, 2, and 3 in the GES group)	N/A	N/A	N/A

Table 2: Summary of main findings of studies on GES for the treatment of GP* (cont'd)

Study*	Follow-up (Range)	No. Patients Etiology Average Duration of GP Symptoms (Range/SEM)	TSS (Frequency and/or Severity)	Vomiting (Frequency and/or Severity)	Nausea (Frequency and/or Severity)	GET Normalized/ Not Changed/ Worsened
Abell et al.[8] Multicentre prospective case series (GEMS)	1 year	N = 38 Diabetic, idiopathic, postsurgical Phase I: F: 5.1 years (1 to 20) M: 7.7 years (1 to 19) N = 33 (Phase II)	N/A	WVF ↓SS (Phase I and Phase II – at 3, 6, and 12 months)	Frequency ↓SS (Phase I and Phase II – at 3, 6, and 12 months)	N = 15 (at 12 months) 7/6/2; (SS not determined)
McCallum et al.[40] Prospective case series	1 year	N = 16 Postsurgical 5.6 years (1 to 33)	Frequency, severity ↓SS (at 6 and 12 months)	Frequency, severity ↓SS (at 6 and 12 months)	Frequency, severity ↓SS (at 6 and 12 months)	N = 13 (at 12 months) 3/6/4; (SS not determined)
Van der Voort et al.[30] Prospective case series	1 year	N = 17 Diabetic type I > 1 year	N/A	WVF ↓SS (at 6 and 12 months)	Frequency ↓SS (at 6 and 12 months)	N = 17 SS improved (at 6 and 12 months – assessed at 4 hours)
Lin et al.[46] Prospective case series (patients from WAVESS; CUESS)	1 year	N = 37 Diabetic type I, idiopathic, postsurgical 9.4 years (1 to 33)	Severity ↓SS (at 12 months for medication [prokinetics and antiemetics] ON and OFF)	Severity ↓SS (at 12 months for medication [prokinetics and antiemetics] ON and OFF)	N/A	N = 26 at 12 months 8/5/13: NSS
Abell et al.[47] Prospective case series (subgroup from GEMS)	5 years	N = 12 Diabetic, idiopathic Not stated	Not clear if reported for severity and/or frequency	WVF ↓SS (at 1 to 3 years and 5 years)	N/A	N/A
Lin et al.[45] Retrospective case series (WAVESS; CUESS; HDE study)	3 years	N = 55 Diabetic type I, idiopathic, postsurgical 6.2 years (1 to 33)	Frequency, severity ↓SS (at 12 months and 3 years)	Frequency, severity ↓SS (at 12 months and 3 years)	Frequency, severity ↓SS (at 12 months and 3 years)	N/A
Lin et al.[11] Retrospective case series (WAVESS - 3 patients[#])	1 year	N = 48 Diabetic type I 5.9 years (1 to 20)	Frequency, severity ↓SS (at 6 and 12 months)	Frequency, severity ↓SS (at 6 and 12 months)	Frequency, severity ↓SS (at 6 and 12 months)	N = 24 (at 12 months) 5/10/9; (SS not determined)

Table 2: Summary of main findings of studies on GES for the treatment of GP* (cont'd)

Study*	Follow-up (Range)	No. Patients Etiology Average Duration of GP Symptoms (Range/SEM)	TSS (Frequency and/or Severity)	Vomiting (Frequency and/or Severity)	Nausea (Frequency and/or Severity)	GET Normalized/ Not Changed/ Worsened
Mason et al.[33] Retrospective case series	Median 20 months (4 to 37)	N = 29 Diabetic type I, idiopathic Diabetic: median 2 years (1 to 10) Idiopathic: median 2.5 years (1 to 7)	N/A	N/A	N/A	N = 15 (post-GES: 7/2/8 (SS not determined)

*According to hierarchy of evidence

¶The total follow-up of the study was one year, including Phase II open-label study

#Information from the author of the study (Dr. Richard McCallum)

CUESS: Compassionate Use of Electrical Stimulation Study; F: female; FDA: Food and Drug Administration; GEMS: gastric electro-mechanical stimulation; GES: gastric electrical stimulation; GET: gastric emptying; GP: gastroparesis; HDE: Humanitarian Device Exemption; M: male; N: number of patients; N/A: not available; NSS: not statistically significant; SEM: standard error of the mean; SS: statistical significance; TSS: total symptom score; WAVESS: Worldwide Antivomiting Electrical Stimulation Study; WVF: weekly vomiting frequency

Information from studies that did not include patients reported in other publications

One randomized, placebo-controlled, double-blind crossover study[39] and five uncontrolled studies[8,11,30,33,40] (three prospective and two retrospective) published since 2002 evaluated the efficacy/effectiveness and safety of GES for the treatment of patients with GP (See Appendix A: Search and Methodology).

Two studies included patients with different etiologies and presented combined data for all patients.[8,33] Two studies focused only on diabetic patients with GP,[11,30] and one study on patients with postsurgical GP.[40] In one case series study,[11] 3 of 48 patients were also reported in another publication;[39] personal communication Dr. Richard McCallum. Considering that the study present information from an important contingent of diabetic patients and only few patients were referred to in another publication, the study is included in this section of the report. Details of the efficacy/effectiveness and safety results reported in these studies are presented in Appendix B, Table B.1.

Abell et al.[39] published results from the one-year, multicentre Worldwide Antivomiting Electrical Stimulation Study (WAVESS) that included centres in Canada. The study included 33 gastroparetic patients (17 diabetic and 16 idiopathic) and was conducted in two phases, with the aim of investigating the efficacy of GES for the treatment of symptomatic GP that is unresponsive to standard medical therapy. Phase I was designed as a randomized, placebo-controlled, double-blind crossover study and Phase II as an open-label study. Patients were evaluated at baseline and at four follow-up

visits at 1, 2, 6, and 12 months. Results were presented for all patients combined and also separately for both etiologies. In the first phase, after implantation of the GES system, patients were randomized to stimulation either ON or OFF. At the end of the first month, the neurostimulator was programmed to the opposite mode for another month. The primary outcome measure in Phase I was the difference in vomiting frequency with the stimulation OFF compared with ON. Also determined was patients' preference for stimulation ON or OFF. Data were analyzed on an intent-to-treat basis. The results after 1 month from Phase I showed a statistically significant decrease in vomiting frequency and preference for stimulation ON. The results were less compelling when each patient subgroup was examined separately and showed no significant difference in vomiting frequency in both the diabetic and idiopathic subgroup and no significant difference in ON/OFF preference in the diabetic subgroup.

For Phase II, all patients' stimulators were programmed to ON with their knowledge. The primary outcome measures for Phase II were the changes between baseline and 6- and 12-month follow-up visits for weekly vomiting frequency, symptom severity, gastric emptying, and quality of life measured by the SF-36 Health Status Survey questionnaire. Phase II data were analyzed on a treatment-received basis. Only 24 of the 33 patients completed Phase II. Vomiting frequency and total symptom score (TSS) significantly decreased when compared with baseline values for all patients and for both etiologies at 6- and 12-month follow-up ($p<0.05$). A total of 70% of patients with idiopathic GP and 77% of diabetic patients experienced a greater than 50% reduction in weekly vomiting frequency at 12 months compared with baseline. There was no correlation between changes in vomiting frequency and changes in 2- or 4-hour gastric emptying between baseline and 6 months ($r = -0.18$ and $r = -0.22$) and between baseline and 12 months ($r = -0.04$ and $r = 0.10$).

Scores for symptom severity and quality of life significantly improved at 6 and 12 months. The symptom improvement observed was more consistent in the diabetic subgroup. Five patients had their GES explanted or revised during Phase II because of infection or other complications.

The authors' recommendations were to increase the postoperative recovery time to a period of 1 to 3 months before randomization for future studies and also to extend the electrical stimulation in placebo-controlled studies to at least 3 months. They suggested that prolonged postoperative use of pain medication may have interfered with gut motility during Phase I. Although gastric emptying did normalize in approximately 50% of patients who were available at 12 months, improvement varied widely and there was no association between changes in symptoms and gastric emptying. Thus, it seems likely that the effect of GES is due to factors beyond gastric motility or dysrhythmias. Overall, the authors concluded that the high-frequency, low-energy GES significantly decreased vomiting frequency and gastrointestinal symptoms, and improved quality of life in patients with severe GP.

Abell et al.[8] published results from a multicentre, two-phase feasibility study (Gastric Electro-Mechanical Stimulation [GEMS] study) on patients with drug-refractory GP treated with GES. The study included patients from the United States, Canada, and Europe. During Phase I, the effect of temporary GES was evaluated in 38 patients (24 idiopathic, nine diabetic, and five postsurgical) over a period ranging between 2 and 4 weeks. Data were not presented separately for the different etiologies. Patients who experienced a reduction of at least 80% in their symptoms (frequency and intensity of vomiting and nausea) were considered to be responders to treatment and eligible for enrolment in Phase II.

Thirty-three patients qualified for Phase II with an average follow-up of 11 months. Symptom data were provided for 23 patients with more than 12 months of follow-up. Patients voluntarily had the device deactivated for 1 week at 6 months; without blinding, changes in symptoms and gastric emptying were assessed. During Phase I, the median weekly frequency of vomiting episodes dropped from 21 at baseline to 0 and the median weekly number of nausea episodes declined from 21 to 2 during GES. However, gastric emptying improved in only eight patients. Phase II was characterized by a reduction in vomiting frequency by more than 90% on average and a decrease in the median weekly frequency of nausea to one episode per week at 1 year.

The body weight of patients improved at 12 months of follow-up. Fifteen of 23 patients increased their weight by more than 5%, 3 of 23 patients lost more than 5% of their original body weight, and the remaining patients had no change. At 12 months, the number of patients receiving enteral and parenteral support declined, but the changes were not statistically significant. The decrease in the number of patients on prokinetic medication at one year compared with baseline was statistically significant. The number of patients that managed without drugs (prokinetics and antiemetics) almost tripled at one year of follow-up. Of the 18 patients who were able to complete a full week with the stimulator inactivated, eight reported increased symptoms, eight observed no change, and two had a lower symptom score.

Four of the 33 pulse generators initially implanted were removed because of infection within 3 months (two systems) and one each was removed at 8 and 10 months after implantation. The authors were able to obtain long-term information (follow-up longer than 1 year) from 27 patients. During this period, three patients had a total gastrectomy because of increased severity of their original symptoms, three patients had the device removed because of infections or erosion, and two diabetic patients remained symptom free after removal of the pulse generator. The authors reported that the pulse generator was functioning well in the case of 18 patients with a mean follow-up time of 30 months. In several patients, symptoms improved even though GES had no measurable effects on gastric emptying. The authors attempted to explain the symptomatic improvement but could not rule out the possibility of a placebo response.

McCallum et al.[40] examined the response to GES in a population of 16 patients with postsurgical GP. Patients had a variety of surgical procedures, but all involved either a known vagotomy or the potential for accidental injury to the vagus nerve. The parameters evaluated were severity and frequency of symptoms (TSS: vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain), health-related quality of life (physical composite score [PCS] and mental composite score [MCS] summarized from the analysis of the SF-36 Health Status Survey Questionnaire subscales), nutritional status, and gastric emptying. These characteristics were evaluated at baseline (4 weeks before surgery), 6 months, and 12 months following surgery. TSS and frequencies of vomiting and nausea were significantly reduced at 6 months and sustained at 12 months compared with baseline. Both PCS and MCS scores significantly improved at 6 and 12 months, with the majority of improvement seen within the first 6 months. Also, hospitalization decreased significantly during the first year.

Gastric retention at 2 and 4 hours decreased compared with baseline at 6 and 12 months of follow-up, but the values were not statistically significant. Only 3 of 13 patients evaluated for gastric emptying at 12 months experienced a reduction in gastric retention to normal values. The others remained delayed, including four patients whose gastric retention worsened. One patient had the device removed after 12 months because of a local infection. Another patient needed replacement of the implanted GES system at 23 months because one electrode was detached during a physical trauma. The authors concluded that the GES system was efficacious in controlling symptoms and improving quality of life, nutritional support, and the need for hospitalization. The mechanisms by which the upper gastrointestinal symptoms in postsurgical GP patients were improved with GES remain to be elucidated. Because the study was not placebo controlled, the authors could not rule out that the response observed after GES might represent a placebo response. A controlled clinical trial of GES for postsurgical GP patients was recommended.

Van der Voort et al.[30] published results from a study that investigated the effect of GES on gastrointestinal symptoms, gastric emptying, and metabolic control (haemoglobin A1c [HbA1c]) in 17 patients with long-standing insulin-dependent diabetes mellitus who had severe GP. Both nausea and vomiting symptoms significantly decreased at 6 and 12 months of follow-up. Also, improved gastric emptying rates were statistically significant compared with baseline values. The average glycemia control over the preceding 2 to 3 months was determined by measuring HbA1c (a surrogate marker for risk of diabetic complications) at baseline, 6 months, and 12 months of follow-up. The authors reported a significant reduction in HbA1c values that suggested metabolic control in diabetics, but further studies are needed to determine if other aspects of diabetes therapy (such as daily insulin dose and frequency of hypoglycemia) can be positively influenced by GES. No adverse effects were reported during the study's follow-up period.

Lin et al.[11] published results from a retrospective case series that involved 48 diabetic patients with refractory GP who had a GES system implanted surgically and for which at least 12 months of follow-up data were available. The assessment involved the effects of GES on severity and frequency of symptoms (vomiting, nausea, early satiety, bloating, postprandial fullness, epigastric pain), health-related quality of life, nutritional status, gastric emptying, and the degree of glucose control. Both total symptom severity and frequency were significantly reduced at 6 months and sustained at 12 months compared with baseline (12-month results were available on only 28 patients). Of 24 patients who completed the gastric emptying test at 12 months, five normalized their gastric emptying. Hospitalization significantly decreased during the first year. The mean value of HbA1c decreased but remained above the normal range. Removal of the GES device was required in four patients, three of them because of infection at the implant site. Four patients died during the follow-up period and another five patients died at 12 and 63 months postsurgery.

In the authors' opinion, patients with long-term diabetes have high morbidity and mortality rates as a result of cardiovascular and renal complications and are more susceptible to postoperative infections. The study was not placebo controlled but the authors considered that it is unlikely that a placebo effect could explain the sustained clinical improvement in approximately 57% of patients available at one year. They concluded that high-frequency GES in diabetic patients with refractory GP significantly improved upper gastrointestinal symptoms, quality of life, nutritional status, glucose control, and hospitalization rates.

Mason et al.[33] reported results from a retrospective case series that involved 24 type I diabetic and five idiopathic patients with GP who were referred for gastrectomy but agreed to participate in the GES study. The severity and clinical impact of symptoms such as nausea, vomiting, and epigastric pain were assessed using four variables that documented whether the symptoms required prokinetic agents, narcotic analgesia, repeated hospitalizations, or additional procedures. Objective outcome measures included the need for supplemental nutrition postoperatively, changes in body mass index, and gastric empting assessed by a scintigraphic test.

Except for results on the use of supplemental nutrition during the follow-up period, results were combined for patients with diabetes and idiopathic GP. The median follow-up was 20 months (range 4 to 37 months). At each follow-up visit, the neurostimulator was checked, adjusted, and incrementally increased by 1 mA per day if necessary, until the symptoms were relieved. Good and excellent results (no treatment or only one type of treatment [prokinetic agents, narcotic analgesia, repeated hospitalizations, additional procedures]) were reported by 19 patients postintervention. Eight patients had a fair to poor outcome (needed two or three types of treatment). The feeding tube was removed by 6 weeks postintervention in all of the patients and no patient needed supplemental nutrition during the follow-up period. A statistically significant increase in the body mass index was reported at a median follow-up of 20

months but the number of patients included in the calculation was not specified. Gastric emptying was documented by scintigraphy postintervention in only 15 patients (52% of the initial cohort). The results showed a normalized gastric emptying in seven patients; eight patients continued to show abnormal gastric emptying.

During the study period, three patients died from causes considered unrelated to GES treatment and two patients were lost to follow-up. Additional procedures were required in three patients who experienced erosion of the gastric stimulator leads through the gastric mucosa with reoperation and replacement of the leads in the stomach wall at 6 months postoperatively (one patient), removal of the GES device by request owing to pain at the subcutaneous pocket site (one patient), and total gastrectomy for failure to improve with GES (one patient).

In the authors' opinion, there are three categories of patients who should be considered for GES: patients refractory to medications, who have daily nausea and vomiting with an inability to maintain nutrition; patients who continue to have gastric motor dysfunction and arrhythmias causing severe stasis of food and chronic epigastric pain; and patients who have complications related to GP, such as the inability to control glucose levels and problems with line sepsis in those receiving total parenteral nutrition.

Information from studies that included patients reported in other publications

Four studies, one comparative[44] and three case series (two prospective, one retrospective),[45-47] included gastroparetic patients who were participants in other studies (WAVESS[39] and GEMS[8]) or in the Compassionate Use of Electrical Stimulation Study (CUESS). GP in patients in these studies was of diabetic, idiopathic, and postsurgical origin. The results are presented combined for all causes. Details from these studies are presented in Appendix B, Table B.2.

Cutts et al.[44] published results from a 3-year prospective study that compared gastrointestinal symptoms, healthcare resources used, and long-term health benefits for the treatment of patients with GP. Nine patients (one diabetic, eight idiopathic) were treated with GES and nine (one diabetic, eight idiopathic) received standard pharmacological therapy, in a behavioural-based outpatient program. All patients treated with GES were part of two FDA trials. The results were presented combined for all patients in the same treatment group. Patients from the two groups were not comparable for average symptom duration, with 86.7 ± 27.6 months for the GES group versus 33.3 ± 9.28 months for the standard pharmacological therapy group. Patients in both groups did not differ in baseline values for TSS, an investigator-derived independent outcome measure score (IDIOMS), annual costs, and annual hospital days. The TSS were calculated from each patient's self assessment of abdominal bloating/distension, early satiety, abdominal pain, nausea, and vomiting.

The assessment of healthcare resource usage was based on IDIOMS and included three parameters: intensity of service, severity of illness, and number of non-gastrointestinal organ systems involved. Healthcare costs were calculated by considering inpatient and outpatient hospital charges, hospital medications, and inpatient and outpatient nutritional feeding costs for each of three years of follow-up. The costs of the GES device and its implementation were also included. Costs for treatments did not include individual provider charges.

The differences in TSS and IDIOMS scores, annual costs, and annual hospital days between the medication and GES groups were not statistically significant at baseline. Overall, TSS and IDIOMS for the GES group were significantly better than overall TSS and IDIOMS for the medication group. Overall healthcare costs for the GES group declined over time but not for the group treated with drug therapy. Three patients in the medication group died (one in the first and two in the second year), and two of the three deaths were intravenous access related. Limitations of the study, such as small sample size and the potential of skewing of data because of the high mortality rate in the medical controls and lack of population-based control data, were outlined by the authors.

Lin et al.[46] investigated the role of prokinetic and antiemetic medications used in combination with GES in a case series that involved 37 patients (24 diabetes mellitus type I, eight idiopathic, and five postsurgical) who were treated for GP at one centre in the United States. Eight patients were part of WAVESS[39] and 29 patients were from the CUESS. The TSS score for severity, severity of vomiting and nausea, health-related quality of life measured by PCS and MCS scores, and gastric emptying at 4 hours were assessed at baseline (4 weeks before GES therapy) and at 12 months of follow-up.

The degree of symptom reduction in patients OFF medications (especially patients OFF prokinetics) was greater than for patients on medications. Patients OFF antiemetics had a significantly greater mean PCS score than did patients ON antiemetics at 12 months of follow-up ($p<0.05$). GES did not significantly improve gastric emptying. Although patients OFF medications at 12 months had a numerically greater reduction of gastric retention than did patients on medication, these changes were not statistically significant. Three patients required removal of devices because of infection of the pulse generator. The authors emphasized that a limitation of the study is that it is not a placebo-controlled trial. A favourable placebo response during GES could not be ruled out.

Abell et al.[47] published short (3, 6, and 12 months), intermediate (1 to 2 years), and long-term (5 years) results with GES in a subset group of 12 gastroparetic patients, participants in the GEMS study.[8] The assessment was focused mainly on the degree of improvement of nutritional parameters (body weight and body mass index measures and blood test values, including serologic measurement of albumin). TSS, vomiting frequency, and health-related quality of life were also assessed.

Of the 12 patients at baseline, ten were available at intermediate and long-term follow-up. One patient had the device explanted as a result of infection by year 1 and another patient died of an illness unrelated to the GES by year 2. Patients showed a statistically significant improvement in frequency of TSS, weekly vomiting frequency score, patient weight, and body mass index on short and intermediate-term follow-up. There was no statistically significant difference in the body mass index and patient weight on long-term compared with baseline. Also, serum albumin levels were not statistically significant different compared with baseline values, on short-term follow-up. Collection of information on gastric emptying at the intermediate and long term was not the focus of this study. The authors concluded that GES is an optional treatment for patients with drug-refractory GP and nutritional compromise.

Lin et al.[45] reported retrospective results from a case series that involved 55 patients (39 diabetes mellitus type I, nine idiopathic, and seven postsurgical) who were treated with GES at one centre in the United States. The results were reported at baseline, 1 year, and 3 years of GES. This study is an updated report on a longer period of follow-up (beyond 3 years) of another study[48] published by the same group of authors. The outcomes evaluated are TSS, symptom scores for severity and frequency (including scores for vomiting and nausea), nutritional status, weight, hospitalizations, the use of prokinetic and antiemetic medication, HbA1c in diabetics, and adverse events.

Only 37 patients of the 55 were available to provide information at 3 years. During the follow-up period, ten patients died from different complications considered not to be related to GES, and eight patients encountered therapy-related adverse events. Two patients were lost to follow-up. The authors applied multiple statistical analysis, with the aim of decreasing the bias of missed information from a high contingent of patients compared with baseline, such as an intention to treat approach and analysis of data per protocol, and imputed the missing data as the last observation carried forward. The calculations showed a statistically significant improvement of TSS and separate scores for severity and frequency of symptoms, patients' weight, supplementary feeding requirements, and hospitalization rate. The use of prokinetics and antiemetics decreased, and decreased values for HbA1c in diabetic patients were noted, but there were no calculations on the statistically significant difference at one or 3 years of follow-up compared with baseline. The authors could not rule out a possible favourable placebo response during GES therapy and emphasized the role of well-controlled studies to investigate the efficacy of GES therapy and the need to clarify the mechanism of action of GES.

GUIDELINES, POLICIES, AND REPORTS PUBLISHED BY HEALTH TECHNOLOGY ASSESSMENT ORGANIZATIONS

GES is considered an emerging treatment for refractory GP by the American Gastroenterological Association.[3,5] AETNA in the United States issued a policy (reviewed December 2004) that states GES is experimental and investigational for the treatment of refractory GP because the effectiveness for this condition has not yet been established.[12]

The National Institute for Health and Clinical Excellence in the United Kingdom prepared an overview[49] in September 2003 and a consultation document[50] in July 2004, followed by the publication of a guideline on gastroelectrical stimulation for GP[51] (available at http://www.nice.org.uk, accessed June 29, 2005). The guideline specified that current evidence on the safety and efficacy of GES for GP does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research. Clinicians wishing to undertake GES for GP were requested to inform the clinical governance leads in their Trust, ensure that patients understood the uncertainty about the procedure's efficacy and safety, and audit and review clinical outcomes for all patients treated with GES. The procedure is to be performed only in specialized gastroenterology units by specialists with expertise in gastrointestinal motility disorders. The guidance document also specified that current evidence on the efficacy of the procedure relates mainly to relief from the nausea and vomiting that occurs in some patients. There is little evidence that the procedure improves gastric emptying. They recommend that further research studies be undertaken.

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) published a Horizon scanning prioritizing summary in 2005 on GES (Enterra Therapy) for gastroparetic patients.[36] The report emphasized that there is evidence for the safety and effectiveness of the Enterra™ Therapy system, although the analysis showed small sample size studies with an unclear correlation between GES, gastric motility, and symptoms. The safety profile appears to be favourable; however, device infection was present in many of the case series examined. Enterra™ Therapy system has not yet emerged in Australia.

DISCUSSION

The population of interest for this report was a subgroup of patients who suffer from GP and are refractory to drugs available to treat their symptoms of nausea and vomiting.

Gastroparesis (GP) is a disorder manifested by delayed gastric emptying in the absence of mechanical obstruction. Clinically, GP may be associated with severe nausea, vomiting, and malnutrition. There are many causes of GP and delayed gastric emptying. In some cases, delayed gastric emptying may be asymptomatic and incidentally detected. Some digestive and non-digestive disorders may be associated with delay in gastric emptying, mimicking the symptoms of GP.

Diagnosis of GP is made on the basis of symptoms and by documenting delayed gastric emptying. Nuclear scintigraphy is considered the diagnostic gold standard; however, the technique is not standardized, with variations in measurements among different centres. For these reasons, GP patients are difficult to diagnose, treat, and monitor for the effect of the treatment.

Data has yet to be collected to determine the prevalence rate of gastroparetic patients. Because the Humanitarian Device Exemption (HDE) approval by the FDA provided to Medtronic Ltd., the manufacturer of the Enterra™ Therapy system, is limited to rare conditions that affect fewer than 4000 individuals per year, it can be assumed that the prevalence rate in the United States, based on the population base in July 2000 (the year FDA approval was granted), is approximately one in 100,000 persons.

The general principles for the treatment of symptomatic GP presented in a technical review endorsed by the American Gastroenterological Association consists of correction of fluid, electrolyte, and nutritional deficiencies; identification and rectification of the causes if possible; and reduction of the symptoms by administration of prokinetic and antiemetic medications. However, there is no consensus regarding the management of patients with GP who do not respond to drug therapy.[3]

Gastric electrical stimulation (GES) is considered a treatment option for patients with chronic intractable (drug refractory) nausea and vomiting secondary to diabetic and idiopathic GP. Refractory to medical treatment is defined by some researchers to mean that the patient is unresponsive to 2 of 3 classes of prokinetic and antiemetic drugs. The focus of this report is on the efficacy/effectiveness, efficiency, and safety of the Enterra™ Therapy system (Medtronic Inc.), which is a GES system. It consists of a neurostimulator that is implanted subcutaneously in the abdominal wall and provides high-frequency, low-energy stimulation to the muscle wall of the stomach via a pair of electrodes/leads.

Currently, the Enterra™ Therapy system has regulatory approval by Health Canada as a Class 3 device for the treatment of chronic intractable (drug refractory) nausea and vomiting. The device was also approved by the FDA in the United States. The FDA, however, only approved its use at the level of a Humanitarian Device Exemption. HDE approval means that the effectiveness of the Enterra™ Therapy system has not yet been demonstrated. The Gastroparesis and Dysmotilities Association requested the FDA in February 2004 to move the approval status from the level of HDE to Premarket Approval. This request was denied.

The scientific evidence presented in this report was deduced from ten studies that can be separated into two groups: studies that included or did not include patients reported in another publication. There is little comparison of GES with alternative approaches; the only study that presented a comparison of GES with drug therapy (prokinetics and antiemetics) included a small group of patients who were also included in another publication. A rating of each case-series study, based on a quality checklist of 30 criteria, is presented in Appendix C, Table C.1. The methodological quality of the case series in general was average; together with the weak study design and small sample sizes, this puts the evidence from these studies in the insufficient category.

Evidence (efficacy/effectiveness and safety) from studies that did not include patients reported in other publications

Six studies[8,11,30,33,39,40] (Table 2 and Appendix B, Table B.1) included patients whose results were not reported or included with another patient subgroup in another publication. The studies were generally of weak methodological design and average quality. The quality assessment of the case series based on 30 criteria showed ranges of ratings between 22 (maximum) in two studies and 19 (minimum) in two studies. The individual criteria were not weighted (see Appendix C).

Only one study[39] presented findings from a two month, multicentre, crossover blinded study, with results at 1 month of follow-up. The authors of this study recognized the need of extending the period of follow-up in a placebo-controlled randomized study to at least 3 months to obtain a more accurate image of the results of the intervention; they also suggested the need for increasing the postoperative recovery time to between 1 and 3 months before measuring outcomes of efficacy.[30]

The selection criteria for patients' inclusion in these studies were similar: delayed gastric emptying (>60% retention at 2 hours and >10% at 4 hours) based on a standardized scintigraphic test, persistent symptoms for at least 12 months, intolerance or refractoriness to prokinetic and antiemetic drugs, and vomiting frequency of more than seven times weekly. A total of 181 patients with GP were enrolled in the studies;[8,11,30,33,39,40] 134 were females and 45 were males, with ages ranging from 18 to 87 years. One hundred and fifteen patients diagnosed with diabetes mellitus had

GP,[39 8,11,30,33] 45 patients had idiopathic GP,[8,33,39] and 21 were diagnosed with GP following postsurgical interventions.[8,40]

From a total of 181 patients at 12 months of follow-up, data on vomiting frequency were available for 108 patients (59%) and nuclear scintigraphy testing (considered the gold standard diagnostic test for GP) for 104 patients (57%). In one study,[33] patients were followed for a median of 20 months.

Overall, the reported results indicated that although most of the patients had symptomatic improvement, these results were not related to improvement of gastric emptying. GES apparently does not cause stomach muscle contraction and only modestly improves gastric emptying. The results on symptomatic improvement are presented separately by follow-up period and study design.

In the only randomized crossover study[39] that reported results at one month of follow-up (1 of 2 studies on which the FDA based the HDE approval) the outcomes reported are as follows:

- a decrease of weekly vomiting frequency experienced by the diabetic and idiopathic group of patients if the device was either OFF or ON, these levels did not reach statistical significance when investigated separately;
- an improvement of the total symptom score (TSS) for severity for the combined and separate diabetic and idiopathic groups in the ON versus OFF period, although these changes did not reach statistical significance; and
- the preference for stimulation ON when compared with stimulation OFF was statistically significant for the combined group and the idiopathic group but not for the diabetic patients.

The case series reported outcome results mainly at 6 months and 12 months. Only one study reported results at 20 months of follow-up. The symptomatic improvement after implantation of the GES consisted of the following:

- Reduction of vomiting and/or nausea frequency and/or severity. Results are reported in four studies and showed statistically significant improvement compared with baseline at 6 and 12 months of follow-up.[8,11,30,40]
- Improvement of gastrointestinal TSS for severity and frequency. Results are available from two studies[11,40] that reported statistically significant improvement of the TSS for severity and frequency at 6 and 12 months of follow-up.
- Improvement of nutritional status measured by improvement of patient weight after implanting GES. Results are reported in four case series[8,11,33,40] and statistically significant differences were found in three studies[11,33,40] at 6 months and 12 months in two studies[11,40] and 20 months of follow-up in one study.[33]

- Improvement of quality of life measured by mental composite score and physical composite score on the SF-36 Health Status Survey Questionnaire. Statistically significant improvements of these scores at 6 and 12 months of follow-up are reported in two studies.[11,40]
- Reduction of supplementary enteral and parenteral feeding. Forty-nine patients were reported in four studies[8,11,33,40] who received enteral or parenteral feeding before implanting GES and 13 of them continued to receive supplementary feeding at 12 months of follow-up.
- Reduction in reliance on drugs used to alleviate symptoms. Three studies[8,11,30] presented general information about continuation of drug medication (prokinetics and antiemetics) during the follow-up period of 12 months.

Patients with severe nausea and vomiting frequently alter their eating habits in order to minimize symptoms. In two studies,[8,33] the relief of nausea and vomiting attributed to the implantation of gastric stimulator device showed a reduction or discontinuation of total or supplemental nutritional support, weight gain, and a reduction of the prokinetic and antiemetic drugs administration, at 12 months[8] and at a median of 20 months of follow-up,[33] respectively.

Information on gastric emptying at 12 months of follow-up was available only on half of the patients initially enrolled in the studies, sometimes because of loss of follow-up, adverse events resulting in the removal of the device, or information not being provided in the studies. The value of this outcome indicator for measuring the efficacy of GES is also an issue to be further explored.

The authors generally concluded that they could not rule out a possible placebo effect in three of the studies[8,11,40] even if the patients experienced an increase in symptoms when the neurostimulator was inadvertently deactivated in one of the studies.[8] To rule out placebo effect, one needs a well-designed randomized controlled trial.

The use of GES, as well as the use of any other implanted device, is not without risk. Candidates for GES treatment are patients who do not respond to drug therapies, sometimes suffer from malnutrition and depletion of electrolytes, and may also have a depressed immune system. The GES device is a foreign body that may expose this patient population to infections that are difficult to resolve without the removal of the device (see Appendix D, Table D.1). The most common reported adverse event was infection at the pocket site of the impulse generator in approximately 5% to 10% of the cases, and these cases required subsequent device removal.

In five studies[8,11,30,39,40] that presented results at 12 months of follow-up, of 152 patients, 6% had to have their devices explanted and 3% had to have a reintervention to replace or correct the pulse generator or the leads. In the studies included in this analysis, the most commonly reported adverse events related to the implanted device were infection or erosion and removal of the system (nine patients), electrode dislodgement (three

patients), migration of the pulse generator and repositioning (one patient), migration of the pulse generator, skin penetration and infection (one patient), and lead perforation of the stomach (one patient).

Evidence from studies that included patients reported in other publications

Four studies, one a comparative prospective study[44] and three case series,[45-47] included patients with GP who were reported in other publications (see Appendix B, Table B.2). The quality assessment of the case series, based on 30 criteria, showed rating values of 21, 19, and 17, respectively, which means they were rated as average quality.

One study[44] presented a 3-year comparison of symptom scores, annual costs, and annual hospitalization in patients who were treated with GES and patients who continued treatment with medication. The lower total symptom scores and annual costs were found to be statistically significant in the group of patients treated with GES compared with the medication group in the second and third year of treatment. However, the annual hospital days for both groups were not different during the entire follow-up period of the study. Limitations of the study were the inclusion of small groups of patients, nine patients in each group, and loss of follow-up of three patients who died in the medication group.

One study[46] evaluated symptoms in a series of patients treated with GES who were ON or OFF medication (prokinetics and antiemetics) used to alleviate symptoms in gastroparetic patients. Authors reported that patients OFF prokinetic medication had a statistically significant decrease in TSS for severity compared with patients ON prokinetic medication.

In one study,[45] GES maintained the improvement of TSS for severity and frequency, and the symptom scores for severity and frequency, including vomiting and nausea, at 1 and 3 years of follow-up, with a statistically significant improvement in values compared with baseline. Also, an improvement of the nutritional status, with a statistically significant decrease of supplementary feeding beyond 3 years, and an increase of patients' weight at 1 and 3 years, was reported.

Short-, intermediate- (1 to 3 years), and long-term (5 years) results with GES were reported in one study,[47] which was focused mainly on improvement of nutritional parameters. The results showed no statistically significant differences between baseline values of nutritional parameters and values measured after implantation of GES. An improvement in weekly vomiting frequency was statistically significant at 1, 3, and 5 years of follow-up.

General observations

Some general notes of caution follow regarding the validity and reliability of the research evidence results. Medtronic, the manufacturer of the Enterra™ Therapy

system, provided support for all of these studies. In six studies,[8,11,30,39,45,46] specifications are given about patients continuing their drug therapy (prokinetics and antiemetics) in conjunction with the device; they were instructed in some cases to discontinue their drug therapy just prior to the follow-up tests. The patient groups ON and OFF medications during GES therapy were not analyzed separately (with the exception of one study[46]) and this raises the question of whether the effect noted was related to a combination of the two treatments rather than to the GES therapy alone.

More important, there is a discrepancy between the reported results from the Phase I multicentre study (WAVESS, randomized, double-blind crossover study with 1 month stimulation ON and 1 month stimulation OFF) published by Abell et al.[39] and the results presented in the FDA letter of approval[32] and in the Medtronic technical manual[29] (see Appendix F, Table F.1). Specifically, the results on weekly vomiting frequency after one month of follow-up varied. The FDA letter of approval[32] and the technical manual by Medtronic[29] stated that there were no differences in the vomiting frequency whether the stimulation was ON or OFF. In the Abell at al.[39] publication, the results of Phase I showed a statistically significant decrease for vomiting frequency with the device in the ON mode compared with those results with the device in the OFF mode. However, compared to baseline data before the implantation of the device, both periods of either ON or OFF after 1 month showed a decrease in the frequency of vomiting, with a preference by most patients for the ON mode in all reports.

To explain the discrepancy, the author of the study was contacted. He indicated that data from the WAVESS were reanalyzed from a different perspective for diabetic and idiopathic patients, during the same 2-week interval, using the outcome measures: quality of life and patient preference data as a starting point for the analysis (personal communication Dr. Thomas Abell).

There is insufficient information to determine the efficiency of GES. The cost of implanting the Enterra™ Therapy system in the United States is estimated to be US $30,000 and in the United Kingdom, the overall cost, including device and hospitalization, is about £15,000 to £16,000. In Canada, the device itself costs approximately Cdn $10,685. This does not include such costs as the specialist's training, the surgical implantation procedure, and the programming and maintenance of the device.

At least two randomized controlled studies on GES using the Enterra™ Therapy system are ongoing and are expected to be finalized and the results released in 2006 (a randomized multicentre withdrawal study and a randomized study of temporary stimulation [personal communication Dr. Thomas Abell]).

CONCLUSION

Patients with severe GP (not related to mechanical obstructions) of diabetic, postsurgery (gastric resection and vagotomy), or idiopathic causes, whose symptoms cannot be controlled by conventional therapy, are considered to be candidates for GES as a last resort treatment after all conventional treatment regimes have failed. GES is used more often for symptom control than for treatment of the motility disorder. GP is a rare and even life-threatening disorder; in severe and chronic cases, nausea and vomiting may cause weight loss, dehydration, electrolyte disturbances, and poor glycemic control in diabetic patients.

The Enterra™ Therapy system did not restore normal gastric emptying in the majority of the patients included in the studies, but the presented results seemed to indicate an improvement in clinical status and alleviation of symptoms of nausea and vomiting in some cases. The mechanism of action, however, is not well known.

Because of possible risks associated with the implantation of this device, including the risk of infection that would require the removal of the device in 5% to 10% of cases, implantation should be provided by trained professionals and the use of the device should be restricted to those patients who have severe symptoms and are refractory to another less invasive and risky approach such as drug therapy and diet. A continuous follow-up of the patients is necessary to identify any possible adverse events and effects related to condition and treatment, as well as to assess the costs and quality of life experienced by patients. The use of a temporary GES may be considered initially and positive response to this intervention may be predictive of a permanent implanted device (personal communication Dr. Thomas Abell).

The current evidence on the safety and efficacy of GES for GP, based on an average of 12 months of follow-up, is not adequate to support the routine use of this procedure in adults. There seems to be no association between changes in symptoms and gastric emptying in patients with GP treated with high-frequency GES. The research presented is unable to distinguish objectively between symptom improvement and the placebo effect. It is promising that two randomized trials are underway. Once this research is published, this technology should be reviewed again to determine if the cumulative research adds to the knowledge of efficacy/effectiveness.

Current information suggests that the Enterra™ Therapy system has been implanted in 12 patients in Canada (five in Quebec, five in Ontario, and two in British Columbia), some of whom were part of the multicentre trials. However, on the basis of a survey of provincial Health Ministries, the implantation procedure and the device are not covered by public funds. Because this condition is rare, a centralized service provided on a compassionate basis, which is in congruence with the current FDA regulatory status of the device, may be a consideration.

APPENDIX A: SEARCH AND METHODOLOGY

Search

The literature search was conducted by the Alberta Heritage Foundation for Medical Research (AHFMR) Research Librarian (Ms Liz Dennett) between June 1 and June 3, 2005, and was updated between November 9 and November 14, 2005. Major electronic databases used include The Cochrane Library, NHS Centre for Reviews and Dissemination (CRD Databases: NHS EED, HTA, DARE), PubMed, EMBASE, and Web of Science. In addition, relevant library collections, websites of practice guidelines, regulatory agencies, evidence-based resources, and other HTA-related agency resources (AETMIS, CCOHTA, ECRI) were searched. Internet search engines were also used to locate grey literature.

Medical Subject Headings (MeSH) terms relevant to this topic are Electrical Stimulation Therapy, Gastric Emptying, and Gastroparesis.

Keywords used are gastric pacing, gastric pacemaker, stomach, gastric electrical stimulation, and Enterra Therapy.

Table A.1: Databases and search terms used in the search strategy†

Database	Platform	Edition or Date Searched	Search Terms††
Core Databases			
The Cochrane Library	www.thecochranelibrary.com	Issue 2, 2005 Searched Nov 9, 2005	In Abstract OR in Record Title: gastric electrical stimulation OR Enterra OR "gastric pacemaker" OR "gastric pacing"
CRD Databases (DARE, HTA, and NHS EED)	www.york.ac.uk/inst/crd/crddatabases.htm	Searched Nov 9, 2005	Gastric electrical stimulation OR gastric pacemaker OR gastric pacing
EMBASE	Ovid Interface Licensed Resource	Searched Nov 9, 2005	(gastric or stomach).mp. and ((electrical and stimul$).mp. or Electrostimulation/ or pacing.mp. or pacemaker.mp.); Enterra;
Web of Science	ISI Interface Licensed Resource	Searched Nov 9, 2005	TS=((gastric OR stomach) AND (pacing OR pacemaker OR (electric* AND stimul*))) NOT TI=(dog OR dogs OR cat OR cats OR pig OR pigs OR porcine OR rats OR rat OR canine OR canines OR lobster OR lobsters OR mouse OR mice OR murine); TS=Enterra;

Database	Platform	Edition or Date Searched	Search Terms††
Core Databases (cont'd)			
PubMed	www.pubmed.gov	Searched Nov 9, 2005	1. gastric electrical stimulation OR Enterra Therapy OR gastric pacemaker OR gastric pacing OR (electric stimulation therapy AND (stomach OR gastric)) 2. (gastroparesis) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) 3. gastroparesis AND (in process[sb] OR publisher[sb]) 4. #1 OR #2 OR #3 5. #4 Limit to Animals 6. #4 NOT #5 (Searches #4 and #5 limit the search results to human studies without deleting studies that have not been indexed either human or animal)
Library Catalogues			
NEOS Central Alberta Library Consortium	www.library.ualberta.ca/catalogue	Searched Nov 9, 2005	(stomach OR gastric) AND (stimul$ OR pacing OR pacemaker); gastroparesis; Enterra
Guidelines			
AMA Clinical Practice Guidelines	http://www.topalbertadoctors.org/guidelines/guidelinespdf.aspx	Searched Nov 10, 2005	Browsed for relevant guidelines
CMA Infobase	mdm.ca/cpgsnew/cpgs/index.asp	Searched Nov 10, 2005	Gastric electrical stimulation; gastroparesis
National Guideline Clearinghouse	www.ngc.gov	Searched Nov 10, 2005	Gastroparesis
Clinical Trials			
ClinicalTrials.Gov	clinicaltrials.gov/	Searched Nov 10, 2005	Gastric electrical stimulation; gastroparesis
CenterWatch Clinical Trials Listing Service	www.centerwatch.com/	Searched Nov 10, 2005	Gastroparesis
CENTRAL	Cochrane Library (Wiley Licensed Resource)	Searched Nov 10, 2005	Gastric electrical stimulation; gastroparesis

Database	Platform	Edition or Date Searched	Search Terms††
Clinical Trials (cont'd)			
National Research Register	www.update-software.com/national/	Searched Nov 10, 2005	Gastric AND electrical AND stimulation; gastroparesis
Coverage Regulatory Licensing Agencies			
Alberta Health and Wellness	www.health.gov.ab.ca	Searched Nov 10, 2005	Gastric electrical stimulation; gastroparesis
Medical Devices Active Licence Listing	www.mdall.ca/	Searched Nov 14, 2005	Device Name: Enterra
US Food and Drug Administration	www.fda.gov	Searched Nov 10, 2005	Enterra
US Medicare Coverage Database	www.cms.hhs.gov/mcd/search.asp?	Searched Nov 10, 2005	Selected National AND Local Coverage and Searched Entire Document and Exact Phrase: Enterra; Gastric Electrical Stimulation; gastric pacing; gastric pacemaker
Aetna Clinical Policy Bulletins	http://www.aetna.com/cpb/index.html	Searched Nov 10, 2005	Enterra; Gastric Electrical Stimulation
BlueCross BlueShield	http://www.bluecares.com/tec/tecassessments.html	Searched Nov 10, 2005	Enterra; Gastric Electrical Stimulation; gastric pacing; gastric pacemaker
Evidence-Based Medicine Resources			
Aggressive Research Intelligence Facility (ARIF)	www.bham.ac.uk/arif	Searched Nov 10, 2005	Enterra; Gastric Electrical Stimulation; gastric pacing; gastric pacemaker; gastroparesis
ACP Journal Club	Ovid Platform Licensed Resource	Searched Nov 10, 2005	Enterra; Gastric Electrical Stimulation; gastric pacing; gastric pacemaker; gastroparesis
ATTRACT	www.attract.wales.nhs.uk	Searched Nov 10, 2005	Enterra; Gastric Electrical Stimulation; gastric pacing; gastric pacemaker; gastroparesis
Bandolier	http://www.jr2.ox.ac.uk/bandolier/bformHJ.html	Searched Nov 10, 2005	Enterra, Gastric Electrical Stimulation; gastric pacing; gastric pacemaker; gastroparesis
BestBETS	www.bestbets.org	Searched Nov 10, 2005	Enterra; Gastric Electrical Stimulation; gastric pacing; gastric pacemaker; gastroparesis

Database	Platform	Edition or Date Searched	Search Terms[††]
Evidence-Based Medicine Resources (cont'd)			
Clinical Evidence	www.clinicalevidence.com	Searched Nov 10, 2005	Enterra; Gastric Electrical Stimulation; gastric pacing; gastric pacemaker; gastroparesis
TRIP Database	www.tripdatabase.com	Searched Nov 10, 2005	In title and text: Enterra OR "gastric electrical stimulation" OR "gastric pacing" OR "gastric pacemaker" OR gastroparesis
Grey Literature Sources			
NeLH (National electronic Library for Health	www.nelh.nhs.uk	Searched Nov 14, 2005	Enterra; Gastric Electrical Stimulation; gastric pacing; gastric pacemaker; gastroparesis
Google	www.google.com	Searched Nov 14, 2005	"gastric electrical stimulation" gastroparesis -pubmed; "gastric pacemaker" gastroparesis – pubmed; Enterra Therapy -pubmed
Other HTA Resources			
AETMIS	www.aetmis.gouv.qc.ca	Searched Nov 14, 2005	Enterra; Gastric Electrical Stimulation; gastric pacing; gastric pacemaker; gastroparesis
CCOHTA	www.ccohta.ca	Searched Nov 14, 2005	Enterra; Gastric Electrical Stimulation; gastric pacing; gastric pacemaker; gastroparesis
Institute for Clinical and Evaluative Sciences (ICES)	www.ices.on.ca/	Searched Nov 14, 2005	Enterra; gastric; gastroparesis
ECRI	www.ecri.org	Searched Nov 14, 2005	Enterra; Gastric Electrical Stimulation; gastric pacing; gastric pacemaker; gastroparesis
Health Technology Assessment Unit At McGill	www.mcgill.ca/tau	Searched Nov 14, 2005	Browsed list of publications
Medical Advisory Secretariat	http://www.health.gov.on.ca/english/providers/program/mas/archive.html	Searched Nov 14, 2005	Browsed list of publications

[†] Limits: Searches were limited to publication dates 2000-2005; language: English only; studies: human studies only. These limits are applied in databases where such functions are available.

†† "*", "$ ", and "?" are truncation characters that retrieve all possible suffix variations of the root word; e.g. surg* retrieves surgery, surgical, surgeon, etc. Semicolons separate searches that were entered separately.

Methodology

The studies identified by the search strategy were retrieved, reviewed, and assessed to determine the relevance of each study.

Inclusion criteria were as follows:

- Intervention: gastric electrical stimulation (GES).
- Device: Enterra™ Therapy system.
- Indication: gastroparesis (GP).
- Target population: all ages.
- Follow-up: at least one year (*please see exception section*).
- Publication limits: starting with 2000 (*please see exception section*).
- Best level of evidence available.
- Language: English.
- Abstract of the study: available.

Studies were included if the focus was on intervention with the Enterra™ Therapy system and if it clearly described participants and criteria for inclusion in the study, an active comparator (if available), and detailed measurement of the results/outcomes for symptoms and gastric emptying. Where the information was not available or not clearly described, an attempt was made to contact and obtain details from the authors of the study.

Participants

Data were collected, and results presented separately or combined, on patients with documented GP associated with any conditions (etiologies), who had delayed gastric emptying as determined by nuclear scintigraphic measurement and intractable symptoms for at least one year, and who were also refractory to drug therapy (prokinetics and antiemetics). Animal studies were not included.

Intervention

The intervention in the studies was GES involving temporary and/or permanent implantation of a gastric neurostimulator (Enterra™ Therapy system), during a follow-up period of at least one year.

Comparator

Theoretically, possible comparators for GES intervention are the following interventions: administration of prokinetic and antiemetic medication, diet, nutritional support (enteral and/or parenteral), and total gastrectomy. In the absence of comparative studies with conventional interventions, cohort studies, or studies that compared GES with placebo, and case series will be selected.

Outcomes

The publications included must contain information on the following primary outcomes:

- Symptom improvement with follow-up periods of at least one year, measured by frequency and/or severity of nausea and/or vomiting, or weekly vomiting frequency; total symptoms scores of severity and/or frequency; or other symptom score measurements.
- Gastric emptying test with nuclear scintigraphy, used to establish the presence of dysmotility (delayed gastric emptying).

Other secondary outcomes may include quality-of-life measurements, patient weight, and supplementary feeding (enteral, parenteral).

Information for the background section of the report will be obtained from relevant publications in the form of narrative reviews, reports, editorials, and commentary.

Exclusion criteria were as follows:

- Studies with a follow-up period of less than one year.
- Studies older than 2000.
- Language: other than English.
- Unavailable study abstract.
- Conference abstracts.
- In vitro studies.

Exception

One randomized, placebo-controlled, double-blind crossover study was included because it represents the best level of evidence available and was used by the FDA for determining approval status, and, in addition, the patients were followed up for one year through a case-series study. [39]

One study published in 1999 was included that provided information on the prevalence of upper gastrointestinal symptoms in the Canadian population (DIGEST study).[26] Another study[23] published in 1998 was included that presented information on reproducibility and the clinical significance of the scintigraphic gastric emptying test.

Studies recommended by the external reviewers that were not identified by the search strategy (published earlier than 2000 or after November 14, 2005, or needing other search terms for identification) were also considered.

Assessment methods

Quality appraisal of the case series

All case series were critically appraised on the basis of a broad checklist of 30 criteria deduced and adapted by the authors of the review from five reference sources.[52-56] The

references were identified by conducting a limited electronic search of the health technology assessment agency's resources.

The criteria investigate the following areas: study question, study population, comparability of subjects, intervention, outcome measurement, statistical analysis, results, discussion, and funding or sponsorship. A nominal rating scale was used and studies were scored as "yes," "no," "partial," and "unclear/unable to determine." Each criterion in the list has been given the same weight. The case series were categorized on the basis of the number of criteria to which the response was "yes". The authors of the review independently assessed the studies and any disagreements were discussed and resolved together. Prior to the use of the checklist, a discussion took place and questions were clarified. The reliability coefficient (kappa; chance corrected agreement) was measured using the following formula:[57]

$k = p(o) - p(e)/1 - p(e)$

p(o): observed probability of concordance between the two measurements

p(e): expected probability of concordance between the two measurements = $\Sigma a_i b_i$ where a_i ,b_i are the marginal probabilities for the ith category in the c x c contingency table, relating response (i = 4) at the two measurements.

Guidelines for the evaluation of kappa:

$k > 0.75$ denotes excellent reproducibility;

$0.4 \leq k \leq 0.75$ denotes good reproducibility;

$0 \leq k \leq 0.4$ denotes marginal reproducibility.

The quality assessment checklist and the result of the appraisal are available in Appendix C.

Data extraction

Data were extracted using a standardized data extraction form developed a priori by the reviewers, which included the following:

- Study (author, year of publication, country).
- Inclusion criteria.
- Period of follow-up.
- Characteristics of the patients included (number, etiology of GP, gender, mean age, mean duration of gastroparetic symptoms, drug treatment, and supplementary feeding requirement before intervention), and surgical procedure (laparoscopy or laparotomy).
- Characteristics of the Enterra™ Therapy system device (type of neurostimulator, leads used, and parameters [frequency, intensity, pulse width, time for cycle ON/OFF]).

- Outcomes:
  - Efficacy (TSS of severity and/or frequency [measured as sum of frequency/severity of vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain]; frequency and/or severity of vomiting and/or nausea; gastric emptying results measured by scintigraphy at 2 and 4 hours and reported as per cent of reduction or by number of patients who showed normalized, not changed or worsened, gastric emptying; quality of life; patient weight; supplementary feeding required; days of hospitalization).
  - Safety (adverse events related to the device [infection, erosion, stomach wall perforation, reintervention, replacement of the device] and clinical adverse events [morbidity and mortality]).
  - Efficiency (information on costing if available).

Expert review

External and internal reviewers with expertise in health technology assessment methodology evaluated the draft report and provided feedback. In selecting external reviewers, the practice of the AHFMR is to choose clinical and methodology experts who are well recognized and published in the peer-reviewed literature and who can offer a good perspective with respect to the use of GES for the treatment of patients with GP.

In addition, the manufacturer of the Enterra™ Therapy system, Medtronic Canada Ltd., was contacted for technical and costing information.

Table A.2: Summary of studies excluded* and reason for exclusion

Study	Study's Main Characteristics, Reason for Exclusion
Jones et al.[27] 2003	Qualitative systematic review of surgical therapy of gastroparesis. The systematic review did not focus on GES. Included 17 studies from which only two references were on gastric stimulation (one that presented results obtained with the Enterra™ Therapy system sent by the manufacturers to the FDA for HDE approval [available in electronic format] and the study published by Forster et al.[58])
Forster et al.[48] 2003	Case series with a follow-up of 1 year. Included 55 patients initially part of WAVESS and CUESS. An updated study[45] on the same group of patients who were followed for 3 years was included.
Al-Juburi et al.[59] 2005	Case series. Included 36 patients who were treated with GES and the placement of the stimulator electrodes was provided by laparoscopy or laparotomy. There is no clear presentation of the inclusion criteria, and also at least four patients in each group (laparoscopy or laparotomy) did not have delayed gastric emptying at baseline.
Forster et al.[58] 2001	Case series. Included 25 patients from the CUESS and did not report detailed results for the assessment of symptoms and gastric emptying.
Lin et al.[60] 2004	Case series. Included 15 patients from the CUESS and reported results for a follow-up of 3 months.

Table A.2: Summary of studies excluded* and reason for exclusion (cont'd)

Study	Study's Main Characteristics, Reason for Exclusion
Oubre et al.[61] 2005	Case series. Included 6 consecutive patients treated with GES. The duration of follow-up is not clearly specified. Five patients were from the feasibility study by Abell et al.[8]
Ayinala et al.[34] 2005	Study compared the clinical efficacy of temporary GES by orally (endoscopically) or PEG-placed electrodes and results of temporarily and permanent GES. Nine patients were recruited from the GEMS study. Information on technical aspects that resulted from the study were included in the section of the report that presents the GES device.
de Csepel et al.[62] 2005	Case report.

*Studies were excluded because they did not meet the inclusion criteria

CUESS: Compassionate Use of Electrical Stimulation Study; FDA: Food and Drug Administration; GEMS: Gastric electro-mechanical stimulation; GES: gastric electrical stimulation; HDE: Humanitarian Device Exemption; PEG: percutaneous endoscopic gastrostomy, a less invasive procedure that is an alternative to laparotomy; WAVESS: Worldwide Antivomiting Electrical Stimulation Study

APPENDIX B: DATA EXTRACTION TABLES

Table B.1: Evidence on the efficacy/effectiveness and safety

<table>
<tr><th>Study
Inclusion Criteria, Follow-up</th><th>Characteristics of the Intervention
Group and Device</th><th>Results/Authors' Conclusions</th></tr>
<tr>
<td>Abell et al.[39]
2003
Multicentre (11 centres in the United States, Canada, Europe)
Randomized, placebo-controlled, double-blind crossover study (Phase I – 2 months); open-label study (Phase II – 10 months)
WAVESS study
Date of recruitment: not stated
Inclusion criteria:
- vomiting >7 times/week;
- delayed gastric emptying (>60% retention at 2 hours and >10% at 4 hours), based on standardized scintigraphic method for solid meals;
- symptoms consistent with GP for longer than 12 months;
- refractoriness or intolerance to 2 to 3 classes of prokinetic and antiemetic drugs.
Follow-up: 1 year

Competing interest: One author from Medtronic Inc., Minneapolis, MN, USA</td>
<td>Phase I
N = 33 patients GP (n_1 = 17 diabetic GP and n_2 = 16 idiopathic)
Gender: 24 females, 9 males
Mean age: 38.9 years, range 19 to 65 years
Average symptom (GP) duration: 6.3 years, range (1 to 28)
Surgical procedure: laparotomy (USA centres, 27 patients); laparoscopy (Canadian and European centres, six patients)
Intervention: GES (turned ON 1 month and OFF 1 month)
Phase II
N = 33 patients, only N = 24 patients participated in the 12-month follow-up.
Intervention: GES (turned ON)
GES system: implanted neurostimulator Model 7425; Medtronic; two intramuscular electrodes Model 4300; Medtronic, Minneapolis, MN; programmer Model 7432, control software Model 7457
Parameters:
frequency 14 Hz
intensity 5 mA
pulse width 330 µs
cycle ON time 0.1 seconds
cycle OFF time 5.0 seconds

Note: Patients were instructed to continue their current antiemetic or prokinetic therapy during the 12-month study. The number of patients who took drug therapy was not stated.</td>
<td>Efficacy results all patients
<table>
<tr><th>Characteristic,
follow-up, no. patients</th><th>Before GES or GES turned OFF</th><th>GES turned ON</th></tr>
<tr><td colspan="3">WVF (median; interquartile range)</td></tr>
<tr><td>Baseline, before GES, (N = 33)</td><td>17.3 (11.8 – 45.7)</td><td>-</td></tr>
<tr><td>Phase I, 1 month, GES OFF/ON, (N = 33)</td><td>13.5 (5.5-25.4)</td><td>6.8 (3.9 - 16.5)[¶]</td></tr>
<tr><td>Phase II, 6 months, GES ON, (N = 27)</td><td>-</td><td>2.6 (0.6 - 12.0)[¶]</td></tr>
<tr><td>Phase II, 12 months, GES ON, (N = 24)</td><td>-</td><td>4.8 (0.1- 7.6)[¶]</td></tr>
<tr><td colspan="3">TSS* of severity (mean ± SE)</td></tr>
<tr><td>Baseline, before GES, (N = 33)</td><td>16.8 ± 0.9</td><td>-</td></tr>
<tr><td>Phase I, 1 month, GES OFF/ON, (N = 33)</td><td>13.9 ± 1.1</td><td>12.5 ± 1.0</td></tr>
<tr><td>Phase II, 6 months, GES ON, (N = 27)</td><td>-</td><td>11.1 ± 1.3[¶]</td></tr>
<tr><td>Phase II, 12 months, GES ON, (N = 24)</td><td>-</td><td>11.4 ± 1.3[¶]</td></tr>
<tr><td colspan="3">GET (2 h) % retention (median; interquartile range)[§]</td></tr>
<tr><td>Baseline, before GES (N = 33)</td><td>78 (67-84)</td><td></td></tr>
<tr><td>Phase II, 6 months, GES ON, (N = 26)</td><td>-</td><td>65 (53-80)[¶]</td></tr>
<tr><td>Phase II, 12 months, GES ON, (N = 20)</td><td>-</td><td>56 (45-74)[¶]</td></tr>
<tr><td colspan="3">GET (4 h) % retention (median; interquartile range)[§]</td></tr>
<tr><td>Baseline, before GES (N = 33)</td><td>34 (26-57)</td><td></td></tr>
<tr><td>Phase II, 6 months, GES ON, (N = 26)</td><td>-</td><td>27 (14-54)</td></tr>
<tr><td>Phase II, 12 months, GES ON, (N = 20)</td><td>-</td><td>22 (11-37)[¶]</td></tr>
</table>
</td>
</tr>
</table>

Table B.1: Evidence on the efficacy/effectiveness and safety (cont'd)

Study Inclusion Criteria, Follow-up	Characteristics of the Intervention Group and Device	Results/Authors' Conclusions
Abell et al.[39] (cont'd)		Preference for stimulation ON was statistically significant for the combined and idiopathic group ($p < 0.05$). **TSS** significantly improved at 6 and 12 months compared with baseline for the combined and separate etiologies ($p < 0.05$). **Vomiting frequency** decreased 64% for the combined group ($p < 0.01$), 62% for the diabetic group ($p = 0.054$), and 67% for the idiopathic group ($p = 0.057$) when stimulation OFF (Phase I) was compared with the 12 months follow-up of GES ON. **Device-related adverse events** (no. of patients): infection of the neurostimulator pocket and removal of device (2 idiopathic); pain related to lead perforation of the stomach and removal of device (2 idiopathic); pulse generator eroded through the skin and removal of device (1 diabetic); discomfort from migration of the pulse generator and surgical intervention to reposition and reanchor the pulse generator (1 idiopathic). Died due to cardiopulmonary arrest (1); lost to follow-up (3), pregnancy (1). **Symptom severity and quality of life** scores for combined groups improved compared with baseline at 6 and 12 months follow-up: physical functioning, role physical, general health, vitality, social functioning ($p < 0.005$) Mean PCS scores significantly improved for combined and separate groups at 6 months and for diabetic and combined groups at 12 months ($p < 0.025$). Mean MCS scores significantly improved for combined groups at 6 and 12 months ($p < 0.025$). **Supplementary feeding (enteral or parenteral) required** 14 patients at baseline and 7 patients at 12 months. The authors concluded that GES significantly decreased vomiting and GI symptoms, and improved quality of life in patients with severe GP.

*TSS of severity was determined by the sum of the severity ratings of the six symptom subscores (vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain). Symptoms were rated as 0 = absent, 1 = mild (not influencing the usual activities), 2 = moderate (diverting from, but not requiring modifications of, usual activities), 3 = severe (influencing usual activities severely enough to require modifications), and 4 = extremely severe (requiring bed rest).

¶$p < 0.05$ compared with baseline; §GET not assessed in Phase I.

GES: gastric electrical stimulation; GET: gastric emptying; GI: gastrointestinal; GP: gastroparesis; MCS: mental composite score; N, n: number of patients; PCS: physical composite score; SE: standard error; TSS: total symptom score; WAVESS: Worldwide Antivomiting Electrical Stimulation; WVF: weekly vomiting frequency

Table B.1: Evidence on the efficacy/effectiveness and safety (cont'd)

<table>
<tr><th>Study
Inclusion Criteria, Follow-up</th><th>Characteristics of the Intervention Group and Device</th><th>Results/Authors' Conclusions</th></tr>
<tr>
<td>Abell et al.[8]
2002
Multicentre (centres in the United States, Canada, and Europe; number of centres not specified).
Case series (uncontrolled prospective study)
Feasibility study; GEMS study.
Date of recruitment: not stated
Inclusion criteria Phase I:
- documented GP as determined by scintigraphic measurement of solid and/or liquid emptying;
- intractable symptoms for ≥12 months;
- refractoriness to prokinetic and antiemetic drugs;
- experienced significant weight loss prior to entering the study.
Inclusion criteria Phase II:
- reduction of ≥80% of symptoms (frequency and intensity of vomiting and nausea) during Phase I;
- improvement of ≥35% in the solid or liquid gastric emptying (applied only for the USA patients).
Follow-up:
Phase I: 2-4 weeks
Phase II: 11 months (range 2.9-15.6)
Competing interest: not stated</td>
<td>N = 38 patients GP (n_1 = 24 idiopathic n_2 = 9 diabetes mellitus, n_3 = 5 postsurgical)
Gender: 28 females, 10 males
Mean age: female 37.3 years (range 26 to 49); male 34.9 years (range 18 to 47)
Mean symptom (GP) duration: female 5.1 years (range 1 to 20); male 7.7 years (range 1 to 19)
Phase I – temporary intervention
GES for 2 to 4 weeks
System: external pulse generator Medtronic Model 7424; temporary percutaneous electrodes Medtronic Model 6500; programmer Medtronic Model 7432, control software Model 7454
Parameters:
frequency 12 stimuli/min
intensity 5 mA
pulse width 330 µs
Phase II – permanent intervention
N = 33 patients permanent GES at the beginning of Phase II.
N = 18 patients GES OFF 1 full week after 6 months.
Surgical procedure: laparotomy (19 patients); laparoscopy (14 patients)
System: implanted neurostimulator (Medtronic model no. 7424); 2 intramuscular electrodes (Medtronic model no. 4300).
Parameters:
same as in Phase I.</td>
<td>Efficacy results all patients:
<table>
<tr><th>Characteristic, follow-up</th><th>No GES</th><th>GES OFF</th><th>GES ON</th></tr>
<tr><td colspan="4">WVF* score (median)</td></tr>
<tr><td>Baseline, before GES, (N = 38)</td><td>21</td><td>-</td><td>-</td></tr>
<tr><td>Phase I (2 to 4 weeks) temporary GES (N = 38)</td><td></td><td></td><td>0[§]</td></tr>
<tr><td>Phase II, at 3 months GES ON (N = 25)</td><td></td><td></td><td>0.25[¶]</td></tr>
<tr><td>Phase II, at 6 months GES ON/OFF (N_{ON} = 22; N_{OFF} = 19)</td><td></td><td>1[¶]</td><td>0[¶]</td></tr>
<tr><td>Phase II, at 12 months GES ON (N = 23)</td><td></td><td></td><td>1[¶]</td></tr>
<tr><td colspan="4">Nausea frequency (median)</td></tr>
<tr><td>Baseline, before GES, (N = 33)</td><td>21</td><td>-</td><td>-</td></tr>
<tr><td>Phase I (2 to 4 weeks) temporary GES (N = 34)</td><td></td><td></td><td>2[§]</td></tr>
<tr><td>Phase II, at 3 months GES ON (N = 25)</td><td></td><td></td><td>1[§]</td></tr>
<tr><td>Phase II, at 6 months GES ON/OFF (N_{ON} = 19; N_{OFF} = 17)</td><td></td><td>7[§]</td><td>0[§]</td></tr>
<tr><td>Phase II, at 12 months GES ON (N = 19)</td><td></td><td></td><td>1[§]</td></tr>
<tr><td colspan="4">GET (no. patients[abc])</td></tr>
<tr><td>Phase I (2 to 4 weeks) temporary GES (N = 34)</td><td></td><td></td><td>8/17/9</td></tr>
<tr><td>Phase II, at 3 months GES ON (N = 21)</td><td></td><td></td><td>9/11/1</td></tr>
<tr><td>Phase II, at 6 months GES ON/OFF (N = 22)</td><td></td><td></td><td>11/8/3</td></tr>
<tr><td>Phase II, at 12 months GES ON (N = 15)</td><td></td><td></td><td>7/6/2</td></tr>
<tr><td colspan="4">Patient weight (kg) (median)</td></tr>
<tr><td>Baseline, before GES, (N = 38)</td><td>59</td><td>-</td><td>-</td></tr>
<tr><td>Phase II, at 12 months GES ON (N = 23) [#]</td><td></td><td></td><td>64</td></tr>
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Table B.1: Evidence on the efficacy/effectiveness and safety (cont'd)

Study Inclusion Criteria, Follow-up	Characteristics of the Intervention Group and Device	Results/Authors' Conclusions
Abell et al.[8] (cont'd)	**Note**: Drugs administrated before GES: prokinetics (20 patients), antiemetics (13 patients). A total of 14 patients failed to respond to both drug therapies.	**Supplementary feeding (enteral or parenteral) required**: 19 patients at baseline (14 patients enteral and 5 patients parenteral); 5 patients at 12 months (3 patients enteral and 2 patients parenteral). **Therapy-related adverse effects** (no. of patients): inadvertent deactivation of the pulse generator Model 7424 (10), for these patients, manufacturers replaced the pulse generator with a new Model 7425 stimulator; infection and removal of the system (4). Disease-related adverse effects (no. of patients): pain (6), obstruction (3), hepatitis (2), infection (2), electrode dislodgement (2), stimulation of the abdominal rectus (1), insomnia (1), transient ischemic attack (1), lost weight (2), total gastrectomy (2), rib fracture (1), kidney failure (2), J tube replacement or correction (3), and diarrhea (3). At >12 months follow-up (information available from n = 27 patients): total gastrectomy (3), infection or erosion and removal of the system (3). Three patients died: lung cancer (1), heart failure (1), necrosis of transplanted pancreas (1). Two patients were symptom free after removal of the pulse generator. The number of patients who managed without either type of drug (prokinetic, antiemetic) increased from 5 to 14 at 12 months. **Follow-up**: 5 patients refused or were unable to return for follow-up. The authors concluded that GES has an antiemetic effect in patients with symptomatic GP.

*Five patients could not eat during the entire study period, did not vomit, and were excluded from vomiting data.

[§]$p < 0.002$; [¶]$p < 0.0005$

GET: [a]improved, [b]no change, [c]worsened

[#]The average weight gain for 23 patients was 8.4% ($p = 0.007$), at 12 months.

GEMS: Gastric Electro-Mechanical Stimulation; GES: gastric electrical stimulation; GET: gastric emptying; GP: gastroparesis; N, n: number of patients; WVF: weekly vomiting frequency

Table B.1: Evidence on the efficacy/effectiveness and safety (cont'd)

Study Inclusion Criteria, Follow-up	Characteristics of the Intervention Group and Device	Results/Authors' Conclusions
McCallum et al.[40] 2005 USA **Case series (uncontrolled prospective study), one centre** **Date of recruitment**: between 2000 and 2003 **Inclusion criteria**: - documented diagnosis of GP for >1 year; - refractoriness to antiemetics and prokinetics; - ≥7 vomiting episodes per week; or chronic daily nausea (for patients with fundoplication who cannot vomit); - delayed gastric emptying (gastric retention >60% at 2 hours and >10% at 4 hours) documented by scintigraphy. **Follow-up**: at 6 and 12 months after implantation **Competing interest**: The authors acknowledged the contribution from a representative Medtronic and Medtronic Gastroenterology Group.	***N*** = 16 postsurgical GP patients ***Gender***: 15 females, one male ***Mean age***: 46 years (range 21to 66) ***Mean symptom (GP) duration***: 5.6 years range (1 to 33) ***Surgical procedure***: laparotomy (16 patients) ***Intervention***: GES Description of the GES system not stated **Note**: Before GES: six patients required feeding tube (J-tube) and two patients total parenteral nutrition.	Efficacy results **Characteristic, follow-up, no. of patients** / **Results** **TSS* of frequency (0 to 24), (mean ± SE), N = 16** Baseline, before GES: 19.2 ± 0.7 6 months GES: 7.9 ± 1.3[¶] 12 months GES: 9.8 ± 1.5[¶] **Vomiting (frequency score[§]), (mean ± SE), N = 16** Baseline, before GES: 2.1 ± 0.5 6 months GES: 0.6 ± 0.3[¶] 12 months GES: 1.2 ± 0.3[¶] **Nausea (frequency score[§]), (mean ± SE), N = 16** Baseline, before GES: 3.9 ± 0.1 6 months GES: 1.8 ± 0.3[¶] 12 months GES: 1.8 ± 0.3[¶] **GET (no. patients[abc]), N = 13** 12 months GES: 3/6/4 **Patient weight (kg) (average), (mean ± SE), N = 16** Baseline, before GES: 60.8 ± 4.7 6 months GES: 64.2 ± 4.5[¶] 12 months GES: 64.5 ± 4.3[¶]

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Table B.1: Evidence on the efficacy/effectiveness and safety (cont'd)

Study Inclusion Criteria, Follow-up	Characteristics of the Intervention Group and Device	Results/Authors' Conclusions
McCallum et al.[40] (cont'd)		**Quality of life**: PCS and MCS improved at 6 and 12 months ($p < 0.05$) **Hospitalization**: decreased from 31 ± 13 days, range 0 to 200 (the year before GES therapy) to 6 ± 2 days, range 0 to 29 ($p < 0.05$). **Supplementary feeding required**: three patients at 12 months follow-up. **Adverse effects (no. of patients)**: infection and removal device (1), electrodes detached and replaced because of trauma (1). The authors concluded that GES significantly improved upper GI symptoms, quality of life, nutritional status, and hospitalization requirements of patients with postsurgical GP.

*****TSS is the sum of frequency of vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain. The frequency was graded by each patient as 0 = absent, 1 = rare [once/week], 2 = occasional [2 to 3 times/week], 3 = frequent [4 to 6 times/week], and 4 = extremely frequent [equal or more than 7 times/week]). The sum of the frequency ratings of the 6 symptom subscores comprised the overall total symptom score. TSS of severity at 6 and 12 months are also available and values are statistically significant (lower) compared with baseline.

[¶]$p < 0.05$ compared with baseline; [§]frequency of symptoms was graded as 0: absent, 1: rare (1/w), 2: occasional (2 to 3/w), 3: frequent (4 to 6/w), 4: extremely frequent (≥7/w)

GET: [a]normalized, [b]no change, [c]worsened.

GES: gastric electrical stimulation; GET: gastric emptying; GP: gastroparesis; MCS: mental composite score; N: number of patients; PCS: physical composite score; SE: standard error; TSS: total symptom score; w: week

Table B.1: Evidence on the efficacy/effectiveness and safety (cont'd)

<table>
<tr><th>Study
Inclusion Criteria, Follow-up</th><th>Characteristics of the Intervention Group and Device</th><th>Results/Authors' Conclusions</th></tr>
<tr>
<td>Van der Voort et al.[30]
2005
Germany
Case series (uncontrolled prospective study), one centre
Date of recruitment: not stated
Inclusion criteria:
- symptoms consistent with GP for >1 year;
- refractoriness or intolerance to 2 of 3 classes of antiemetics and prokinetics;
- ≥7 vomiting episodes per week;
- delayed gastric emptying (gastric retention >60% at 2 hours and >10% at 4 hours) documented by scintigraphy.
Follow-up: at baseline (4 weeks before surgery), at 6 and 12 months after implantation

Competing interest: Study sponsored by Medtronic Europe, Tolochenaz, Switzerland.</td>
<td>N = 17 patients with diabetes mellitus type I, insulin-dependent for at least 10 years
Gender: 12 females, five males
Age: range 25 - 73 years
Mean symptom (GP) duration: >1 year
Surgical procedure: laparotomy (17 patients, same surgeon)
Intervention: GES
GES system:
Stimulator (Itrel 3, Model 7425, Medtronic, Kerkrade, the Nederlands); two unipolar intramuscular electrodes (Model 4300)
Parameters:
frequency 14 Hz
intensity 5 mA
pulse width 330 µs
cycle ON time 0.1 seconds
cycle OFF time 5.0 seconds

Note:
Patients were allowed to continue current antiemetic or prokinetic therapy during the study but were asked to discontinue prokinetic medications 3 days before follow-up tests.</td>
<td>Efficacy results
<table>
<tr><th>Characteristic, follow-up, no. of patients</th><th>Results</th></tr>
<tr><td colspan="2">WVF[§] (mean, range), N = 17</td></tr>
<tr><td>Baseline, before GES</td><td>26 (19 – 41)</td></tr>
<tr><td>6 months GES</td><td>3 (0 – 10)[¶]</td></tr>
<tr><td>12 months GES</td><td>4 (0 – 13)[¶]</td></tr>
<tr><td colspan="2">Nausea[§] (frequency score) (weekly mean, range), N = 17</td></tr>
<tr><td>Baseline, before GES</td><td>34 (21 -49)</td></tr>
<tr><td>6 months GES</td><td>8 (1 – 18)[¶]</td></tr>
<tr><td>12 months GES</td><td>12 (2 – 20)[¶]</td></tr>
<tr><td colspan="2">GET % (2 h) (mean ± SEM), N = 17</td></tr>
<tr><td>Baseline, before GES</td><td>83 ± 3</td></tr>
<tr><td>6 months GES</td><td>35 ± 10[¶]</td></tr>
<tr><td>12 months GES</td><td>25 ± 5[¶]</td></tr>
<tr><td colspan="2">GET % (4 h) (mean ± SEM), N = 17</td></tr>
<tr><td>Baseline, before GES</td><td>38 ± 5</td></tr>
<tr><td>6 months GES</td><td>14 ± 5[‡]</td></tr>
<tr><td>12 months GES</td><td>17 ± 2[‡]</td></tr>
</table>
HbA1c baseline values ≥7.5%; values were significantly reduced at 6 and 12 months compared with baseline ($p < 0.05$). HbA1c levels fell below 6.05% in 5 patients at 6 months and in 4 patients at 12 months; only in 4 subjects was HbA1c above 7% at both times. (In a healthy population, limits were between 3.4% and 4.7%.)
No adverse events were reported during the study follow-up.
The authors concluded that patients with diabetes mellitus and GP experienced improvement of subjective and objective parameters of gastric emptying.</td>
</tr>
</table>

[¶]$p < 0.01$, [‡]$p < 0.05$ compared with baseline; [§]frequencies reported by patients.

GES: gastric electrical stimulation; GET: gastric emptying; GP: gastroparesis; HbA1c: hemoglobin A1c; N: number of patients; SEM: standard error of the mean; WVF: weekly vomiting frequency

Table B.1: Evidence on the efficacy/effectiveness and safety (cont'd)

<table>
<tr><th>Study
Inclusion Criteria, Follow-up</th><th>Characteristics of the Intervention Group and Device</th><th>Results/Authors' Conclusions</th></tr>
<tr>
<td>Lin et al.[11]
2004
USA
Retrospective case series (uncontrolled study), one centre
Date of recruitment: between April 1998 and June 2002, same centre
Inclusion criteria:
- documented diagnosis of GP for >1 year;
- refractoriness to antiemetics and prokinetics;
- ≥7 vomiting episodes per week;
- delayed gastric emptying (gastric retention >60% at 2 hours and >10% at 4 hours) documented by scintigraphy.
Follow-up: at 6 and 12 months after implantation

Competing interest: One author is the recipient of grant/research support from Medtronic Inc.</td>
<td>N = 48 diabetic insulin-dependent patients, duration of diabetes averaged 18.9 years (range 1 to 39), n = 45 Caucasian
Gender: 33 females, 15 males
Mean age: 38 years (range 21to 65)
Mean symptom (GP) duration: 5.9 years range (1 to 20)
Surgical procedure: laparotomy (48 patients)
Intervention: GES
GES system: implantable neurostimulator (Medtronic Model 7425G); intramuscular leads (Medtronic Model 4301); external programmer (Medtronic Model 7432).
Parameters:
frequency 14 Hz
intensity 5 mA
pulse width 330 µs
cycle ON time 0.1 seconds
cycle OFF time 5.0 seconds
Note:
Before GES: 13 patients required enteral nutrition through a variety of feeding tubes and 9 patients total parenteral nutrition.
Patients were required to stop the administration of prokinetics at least 3 days before measuring gastric emptying by scintigraphy.</td>
<td>Efficacy results
<table>
<tr><th>Characteristic, follow-up, no. of patients</th><th>Results</th></tr>
<tr><td colspan="2">TSS* of frequency (0 to 24) (mean ± SE)</td></tr>
<tr><td>Baseline, before GES, N = 48</td><td>18.5 ± 0.6</td></tr>
<tr><td>6 months GES, N = 37</td><td>8.9 ± 1.0¶</td></tr>
<tr><td>12 months GES, N = 28</td><td>8.9 ± 1.4¶</td></tr>
<tr><td colspan="2">Vomiting (frequency score§) (mean ± SE)</td></tr>
<tr><td>Baseline, before GES, N = 48</td><td>3.4 ± 0.1</td></tr>
<tr><td>6 months GES, N = 37</td><td>1.5 ± 0.2¶</td></tr>
<tr><td>12 months GES, N = 28</td><td>1.4 ± 0.3¶</td></tr>
<tr><td colspan="2">Nausea (frequency score§) (mean ± SE)</td></tr>
<tr><td>Baseline, before GES, N = 48</td><td>3.6 ± 0.1</td></tr>
<tr><td>6 months GES, N = 37</td><td>1.9 ± 0.2¶</td></tr>
<tr><td>12 months GES, N = 28</td><td>1.9 ± 0.3¶</td></tr>
<tr><td colspan="2">GET (no. patients[abc]) (mean ± SE)</td></tr>
<tr><td>12 months GES, N = 24</td><td>5/10/9</td></tr>
<tr><td colspan="2">Patient weight (kg) (average) (mean ± SE)</td></tr>
<tr><td>Baseline, before GES, N: not stated</td><td>64.3 ± 1.8</td></tr>
<tr><td>6 months GES, N: not stated</td><td>66.5 ± 2.1¶</td></tr>
<tr><td>12 months GES, N: not stated</td><td>67.3 ± 2.4¶</td></tr>
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Table B.1: Evidence on the efficacy/effectiveness and safety (cont'd)

Study Inclusion Criteria, Follow-up	Characteristics of the Intervention Group and Device	Results/Authors' Conclusions
Lin et al.[11] (cont'd)		**Quality of life**: PCS and MCS improved at 6 and 12 months ($p < 0.05$) **Hospitalization**: decreased from 75 ± 11 days, range 0 to 252 (the year before GES therapy) to 23 ± 4 days, range 0 to 75 ($p < 0.05$); 9 patients had no hospital admission. **Supplementary feeding required**: 5 patients at 12 months follow-up. **HbA1c mean** levels decreased from 9.4% (baseline) to 8.7% (6 months) and 8.4% (12 months) (normal range 3.5 to 6.0%). **Therapy-related adverse events** (no. of patients): Removal device (4): infection at the pulse generator site at 3 and 10 months postsurgery (2), pulse generator pushed against the skin in a thin patient, skin penetration and infection (1), volvulus about the wires that required surgery to resect part of the small bowel (1). Other adverse events: 2 patients died before 6 months follow-up (pulmonary embolus, stop hemodialysis); 2 patients died after 9 months of GES (myocardial infarction, aspiration pneumonia); 5 patients died at 12 to 63 months by causes unrelated to GES therapy. Lost to follow-up: 12 patients. The authors concluded that GES improved upper GI symptoms, quality of life, nutritional status, and hospitalization of patients with insulin-dependent diabetes and GP and was associated with an acceptable low level of complications.

*TSS is the frequency for vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain. The frequency of each symptom was graded as 0 = absent, 1 = rare [once/week], 2 = occasional [2 to 3 times/week], 3 = frequent [4 to 6 times/week], and 4 = extremely frequent [more than 7 times/week]). The sum of the frequency ratings of the 6 symptom subscores comprised the overall total symptom score. TSS of severity at 6 and 12 months are also available and values are statistically significant (lower) compared with baseline.

¶$p < 0.05$ compared with baseline; §frequency of symptoms was graded as 0: absent, 1: rare (1/w), 2: occasional (2 to 3/w), 3: frequent (4 to 6/w), 4: extremely frequent (≥7/w)

GET: [a]normalized, [b]no change, [c]worsened.

GES: gastric electrical stimulation; GET: gastric emptying; GP: gastroparesis; MCS: mental composite score; N, n: number of patients; PCS: physical composite score; SE: standard error; TSS: total symptom score; w: week

Table B.1: Evidence on the efficacy/effectiveness and safety (cont'd)

Study Inclusion Criteria, Follow-up	Characteristics of the Intervention Group and Device	Results/Authors' Conclusions
Mason et al.[33] 2005 **Retrospective case series (uncontrolled study), tertiary care university hospital and university-affiliated community hospital** **Date of recruitment**: December 2001 through October 2004. **Inclusion criteria**: Patients with a median follow-up of 20 months - delayed gastric emptying (>60% retention at 2 hours, and >10% at 4 hours) as documented by radionuclide studies; - duration of vomiting >12 months; - ≥7 vomiting episodes per week; - refractoriness or intolerance to prokinetic and antiemetic drugs; **Follow-up**: median 20 months (range 4 to 37 months). Weekly for the first 2 weeks, at 6 months, and then every 6 months. **Competing interest**: Two authors are consultants for Medtronic Inc., and one author received honoraria for presentations on GES. **Note:** The main author was contacted to obtain detailed information on the number of patients and periods of follow-up for some calculations. The author did not respond.	***N*** = 29 patients GP (n_1 = 24 insulin-dependent diabetes mellitus [duration of diabetes mellitus median 16 years, range {1 to 20 years}], n_2 = 5 idiopathic); N = 27 patients followed for a median of 20 months ***Gender***: 22 females (19 diabetes mellitus); seven males (5 diabetes) ***Median age***: diabetes 39 years (range 22 to 60); idiopathic 34 years (range 20 to 87) ***Median symptom (GP) duration***: diabetes: 24 months (range 12 to 240); idiopathic: 30 months (range 12 to 84) ***Surgical procedure***: laparotomy (five patients); laparoscopy (24 patients) ***Intervention***: GES GES system: Implanted neurostimulator (Medtronic model no. 7425G); 2 intramuscular electrodes (Medtronic model no. 4301). Parameters: frequency 14 Hz intensity* median 7.75 mA (range 4.30 to 10.00 mA) 5 mA pulse width 330 µs cycle ON time 0.1 seconds cycle OFF time 5.0 seconds *The stimulating current was incrementally increased by 1 mA/day until the symptoms were relieved.	**Efficacy results** (N = 27): Treatment necessary to cope with symptoms: (a) prokinetic agents, (b) narcotic analgesia, (c) repeat hospitalizations, and (d) additional procedures, measured postoperatively: - Good to excellent outcome: 19 of 27 patients: if no treatment or only one type of treatment was necessary to cope with symptoms. - Fair to poor outcome: 8 of 27 patients: if two or three types of treatment were necessary to cope with symptoms. Supplementary feeding: 19 of the 29 patients were dependent on nutritional support preoperatively. No patient needed supplementary feeding during a median follow-up period of 20 months. Body mass index (median ± SD): preoperative 22.9 ± 7.5; median follow-up of 20 months 25.1 ± 7.45 (p = 0.006). (No. of patients included in the calculation not stated.) Gastric emptying postoperatively (N = 15 patients): normalized (7), unchanged (2), poor results (6). **Postoperative morbidity** (no. of patients): aspiration pneumonia (1), atrial fibrillation (1), subcutaneous abscess around a feeding jejunostomy tube site and removal of the feeding tube (1), postoperative hypoglycemia (1). No wound infections or complications related to the subcutaneous pocket were reported. **Postoperative mortality** (no. of patients): complications due to renal failure (2), myocardial infarction (1); **Lost to follow-up** (2) **Device related adverse events** (no. of patients): erosion of the gastric stimulator leads through the gastric mucosa at 6 months postoperatively, reoperation, and replacement of the leads (1); request for removal of the GES device owing to pain at the subcutaneous pocket site (1); and total gastrectomy for failure to improve with GES (1). The **authors' conclusion** was that GES improved symptoms, returned patients to normal oral nutritional intake, increased body mass index, improved gastric emptying rates, and represent an alternative to gastrectomy in patients with end-stage gastric disease.

GES: gastric electrical stimulation; GP: gastroparesis; N, n: number of patients

Table B.2: Evidence on the efficacy/effectiveness and safety, including patients reported in other publications

<table>
<tr><th>Study
Inclusion Criteria, Follow-up</th><th>Characteristics Intervention/Control Groups</th><th>Results/Authors' Conclusions</th></tr>
<tr>
<td>Cutts et al.[44]
2005
USA
Patients in the GES group were part of two FDA trials for GES
Comparative prospective study, outpatient program
Date of recruitment: not stated
Inclusion criteria:
- documented chronic nausea and vomiting or nausea frequency ≥7 times/week;
- documented abnormalities in solid and/or liquid gastric emptying at baseline using a standardized nuclear medicine meal;
- symptoms for ≥1 year, evidence of weight loss and/or needed nutritional support;
- patients refractory to at least two classes of prokinetic and antiemetic drugs
Follow-up: 3 years
Competing interest: One author from Medtronic Inc., Minneapolis, MN, USA</td>
<td>Medication (control group)
N = 9 patients (n_1 = 1 diabetic GP, n_2 = 8 idiopathic) enrolled in an outpatient program
Gender: females
Mean age: 40 years
Average symptom (GP) duration: 33.3 ± 9.28 months
Treatment: antiemetic, prokinetic, other medications

GES (intervention group)
N = 9 patients (one with diabetic GP and 8 idiopathic)
Gender: 6 females, 3 males
Mean age: 39.4 years
Average symptom duration: 86.7 ± 27.6 months
Surgical procedure: not stated
GES system: information about device and its parameters not stated</td>
<td>Efficacy results all patients
<table>
<tr><th>Characteristic follow-up</th><th>Medication (mean ± SEM)</th><th>GES (mean ± SEM)</th><th>SS (p value)</th></tr>
<tr><td colspan="4">TSS* of severity</td></tr>
<tr><td>Baseline</td><td>39.3 ± 2.8</td><td>37.9 ± 2.73</td><td>NS</td></tr>
<tr><td>Year 1</td><td>31.7 ± 3.1</td><td>24.1 ± 4.8</td><td>p < 0.05</td></tr>
<tr><td>Year 2</td><td>36.9 ± 0.33</td><td>21.3 ± 5.1</td><td>p < 0.05</td></tr>
<tr><td>Year 3</td><td>34.8 ± 3.45</td><td>23.4 ± 5.4</td><td>p < 0.05</td></tr>
<tr><td colspan="4">IDIOMS[¶]</td></tr>
<tr><td>Baseline</td><td>11.0 ± 0.71</td><td>12.6 ± 1.6</td><td>NS</td></tr>
<tr><td>Year 1</td><td>11.9 ± 0.73</td><td>8.3 ± 1.4</td><td>p < 0.05</td></tr>
<tr><td>Year 2</td><td>13.3 ± 0.62</td><td>7.0 ± 1.13</td><td>p < 0.05</td></tr>
<tr><td>Year 3</td><td>13.8 ± 0.45</td><td>6.4 ± 1.03</td><td>p < 0.05</td></tr>
<tr><td colspan="4">Annual costs (US $000's)</td></tr>
<tr><td>Baseline</td><td>80.2 ± 26.7</td><td>83.7 ± 27.9</td><td>NS</td></tr>
<tr><td>Year 1</td><td>85.7 ± 28.6</td><td>79.2 ± 26.4</td><td>NS</td></tr>
<tr><td>Year 2</td><td>71.9 ± 24.0</td><td>23.7 ± 7.9</td><td>p < 0.05</td></tr>
<tr><td>Year 3</td><td>63.4 ± 22.4</td><td>22.1 ± 7.8</td><td>p < 0.05</td></tr>
<tr><td colspan="4">Annual hospital days</td></tr>
<tr><td>Baseline</td><td>26.8 ± 8.4</td><td>24.8 ± 13.7</td><td>NS</td></tr>
<tr><td>Year 1</td><td>13.3 ± 5.8</td><td>14.1 ± 9.0</td><td>NS</td></tr>
<tr><td>Year 2</td><td>11.6 ± 5.4</td><td>3.2 ± 1.5</td><td>NS</td></tr>
<tr><td>Year 3</td><td>6.4 ± 5.5</td><td>2.8 ± 1.8</td><td>NS</td></tr>
</table>
Adverse effects 3 patients in the medication group died
The cumulative costs were US $133,991 for the GES group and US $222,470 for the medication group by the end of the third year.
Authors concluded that GES was more effective in improving long-term GI symptoms and costs and decreasing use of healthcare resources than intensive medication therapy.</td>
</tr>
</table>

*TSS of severity is self assessment of abdominal bloating/distension, early satiety, abdominal pain, nausea, and vomiting. The rating scale for each symptom ranges from 1 to 10, with 10 being the most severe; the TSS range is 0 to 50.

[¶]IDIOMS includes three parameters associated with healthcare resource use: intensity of service, severity of illness, and number of non-GI organ systems involved. The rating scale for each parameter ranges from 0 to 10; the IDIOMS range is 0 to 30.

FDA: Food and Drug Administration; GES: gastric electrical stimulation; GI: gastrointestinal; GP: gastroparesis; IDIOMS: investigator-derived independent outcome measure score; N, n: number of patients; NS: not significant; SS: statistical significance; TSS: total symptom score

Table B.2: Evidence on the efficacy/effectiveness and safety, including patients reported in other publications (cont'd)

<table>
<tr><th>Study
Inclusion Criteria, Follow-up</th><th>Characteristics of the Intervention Group and Device</th><th>Results/Authors' Conclusions</th></tr>
<tr>
<td>Lin et al.[46]
2005
USA
Case series (uncontrolled retrospective study), one centre
Date of recruitment: between April 1998 and June 2001
N_1 = 8 patients WAVESS study
N_2 = 29 patients compassionate use (CUESS)
Patients underwent implantation of GES system from April 1998 to June 2001
Inclusion criteria:
- documented diagnosis of GP for >1 year;
- refractoriness or intolerance to 2 of 3 classes of antiemetics and prokinetics;
- >7 vomiting episodes per week;
- delayed gastric emptying (gastric retention >60% at 2 hours and >10% at 4 hours) documented by scintigraphy
Follow-up: at 12 months after implantation
Competing interest: Study sponsored in part by Medtronic Inc.</td>
<td>N = 37 patients (n_1 = 24 diabetes mellitus type I, n_2 = 8 idiopathic, n_3 = 5 postsurgery). The average duration of diabetes was 19 years (range 1 to 39 years)
Gender: 29 females, eight males
Mean age: 41 years (range 21 to 66)
Mean symptom (GP) duration: 9.4 years range (1 to 33)
Intervention: GES
Surgical procedure: laparotomy (37 patients)
GES system:
Implantable pulse generator (Medtronic Model 7425G); intramuscular leads (Medtronic Model 4300); external programmer (Medtronic Model 7432).
Parameters:
frequency 14 Hz
intensity 5 mA
pulse width 330 µs
cycle ON time 0.1 seconds
cycle OFF time 5.0 seconds
Note:
Before GES: 20 patients were receiving enteral or parenteral nutritional support.
Patients were required to stop the administration of prokinetics 3 days before measuring gastric emptying by scintigraphy.</td>
<td>Efficacy results
<table>
<tr><th rowspan="2">Characteristic, follow-up (no. patients)</th><th colspan="2">Results</th></tr>
<tr><th>Medication ON (no. patients)</th><th>Medication OFF (no. patients)</th></tr>
<tr><td colspan="3">TSS* of severity (mean ± SE)</td></tr>
<tr><td>Baseline# prokinetics (27)</td><td>18.1 ± 0.9 (19)</td><td>17.0 ± 0.8 (8)</td></tr>
<tr><td>12 months GES, prokinetics (27)</td><td>7.4 ± 1.3 (19)§</td><td>2.6 ± 1.1 (8)§¶</td></tr>
<tr><td>Baseline# antiemetics (26)</td><td>19.1 ± 0.7 (17)</td><td>17.7 ± 1.3 (9)</td></tr>
<tr><td>12 months GES, antiemetics (26)</td><td>9.9 ± 1.8 (17)§</td><td>5.0 ± 2.1 (9)§</td></tr>
<tr><td colspan="3">Vomiting (severity score) (mean ± SE)</td></tr>
<tr><td>Baseline# prokinetics (27)</td><td>3.0 ± 0.4 (19)</td><td>3.1 ± 0.4 (8)</td></tr>
<tr><td>12 months GES, prokinetics (27)</td><td>0.9 ± 0.2 (19)§</td><td>0.6 ± 1.1 (8)§</td></tr>
<tr><td>Baseline# antiemetics (26)</td><td>3.3 ± 0.3 (17)</td><td>3.3 ± 0.4 (9)</td></tr>
<tr><td>12 months GES, antiemetics (26)</td><td>1.4 ± 0.3 (17)§</td><td>1.1 ± 0.5 (9)§</td></tr>
<tr><td colspan="3">GET† % (mean ± SE)</td></tr>
<tr><td>Baseline# prokinetics (27)</td><td>46.4 ± 8.0 (19)</td><td>64.8 ± 12.0 (8)</td></tr>
<tr><td>12 months GES, prokinetics (27)</td><td>40.6 ± 8.1 (19)</td><td>50.7 ± 18.0 (8)</td></tr>
<tr><td>Baseline# antiemetics (26)</td><td>51.9 ± 7.6 (17)</td><td>66.5 ± 10.0 (9)</td></tr>
<tr><td>12 months GES, antiemetics (26)</td><td>49.6 ± 9.8 (17)</td><td>36.3 ± 11.9 (9)</td></tr>
</table>
Quality of life: PCS and MCS improved at 12 months in both groups ON and OFF medications ($p < 0.05$). Patients OFF antiemetics had a significantly greater mean PCS score than did patients ON antiemetics at 1 year of GES (41.2 ± 4.3 versus 30.6 ± 2.2, $p < 0.05$).</td>
</tr>
</table>

Continued on next page

Table B.2: Evidence on the efficacy/effectiveness and safety, including patients reported in other publications (cont'd)

Study Inclusion Criteria, Follow-up	Characteristics of the Intervention Group and Device	Results/Authors' Conclusions
Lin et al.[46] (cont'd)		**Hospitalization**: decreased from 50 ± 10 days, range 0 to 220 (the year before GES therapy) to 14 ± 3 days, range 0 to 69 ($p < 0.05$); nine patients had no hospital admission. The reasons for hospitalization after GES therapy were glucose control in diabetics, some recurrence of nausea and vomiting, feeding tube complications, and concern about infection or injury at the pulse generator site. **Supplementary enteral tube feeding**: seven patients at 12 months follow-up ($p < 0.05$). **Medication use (no. of patients)**: At least one prokinetic before GES (27); none at 12 months (8) Antiemetics before GES (26); at 12 months (17) Both medications before GES (20); at 12 months (9) **Therapy-related adverse events (no. of patients)**: removal of device because of infection of the pulse generator (3). The authors concluded that GES significantly reduced the use of prokinetic/antiemetic medications and the need for hospitalization in GP patients, whose clinical and quality of life outcomes also significantly improved.

*TSS is the sum of severity of vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain. The severity was graded by patients as 0 = absent, 1 = mild (not influencing usual activities), 2 = moderate (diverting from, but not urging modifications of, usual activities), 3 = severe (influencing usual activities, severe enough to urge modifications), and 4 = extremely severe (requiring bed rest). The sum of the frequency ratings of the 6 symptom subscores comprised the overall total symptom score.

[#]Baseline was defined as the 4-week period before GES; [§]$p < 0.05$ compared with baseline; [¶]$p < 0.05$ compared with patients on prokinetics at 1 year of GES; [†]eight patients had normalized GET and 13 patients worsened at 12 months.

GES: gastric electrical stimulation; GET: gastric emptying; GP: gastroparesis; MCS: mental composite score; N, n: number of patients; PCS: physical composite score; SE: standard error; TSS: total symptom score

Table B.2: Evidence on the efficacy/effectiveness and safety, including patients reported in other publications (cont'd)

<table>
<tr><th>Study
Inclusion Criteria, Follow-up</th><th>Characteristics of the Intervention
Group and Device</th><th>Results/Authors' Conclusions</th></tr>
<tr>
<td>Abell et al.[47]
2003 USA
Case series (uncontrolled prospective study)
Date of recruitment: not stated
N = 12 patients GEMS study[8]
Inclusion criteria: not stated Inclusion criteria in GEMS study[8]:
Phase I (temporary):
- documented GP as determined by scintigraphic measurement of solid and/or liquid emptying;
- intractable symptoms for ≥12 months;
- refractoriness to prokinetic and antiemetic drugs;
- experienced significant weight loss prior to entering the study.
Phase II (permanent):
- reduction of ≥80% of symptoms (frequency and intensity of vomiting and nausea) during Phase I;
- improvement of ≥35% in solid or liquid gastric emptying (applied only to the USA patients).
Follow-up: at baseline, and at 3, 6, and 12 months, 1 to 2 years, 5 years after implantation
Competing interest: Study sponsored in part by Medtronic Inc.</td>
<td>N = 12 patients (n_1 = 3 diabetes mellitus, n_2 = 9 idiopathic)
Gender: 8 females, four males
Mean age: 35.7 years, (range 19 to 48)
Average symptom (GP) duration: not stated
Intervention: GES
Surgical procedure: Laparotomy (permanent intervention)

Phase I – temporary intervention
GES for 2 to 4 weeks
System: external pulse generator; temporary percutaneous electrodes Medtronic Model 6500 or FSE model 1000;
Phase II – permanent intervention
GES System: pulse generator ITREL 3 (Medtronic model 7425) or ITREL-II (Medtronic model 7424); 2 intramuscular electrodes (Medtronic model 4300).
Parameters:
frequency 14 Hz
intensity 5 mA
pulse width 330 µs
cycle ON time 0.1 seconds
cycle OFF time 5.0 seconds
Note:
Treatment with prokinetics before and/or after GES not stated.</td>
<td>Efficacy results
<table>
<tr><th>Characteristic, follow-up, no. of patients</th><th>Results</th></tr>
<tr><td colspan="2">TSS* (mean ± SEM); (median)</td></tr>
<tr><td>Baseline, before GES, N = 12; (mean ± SEM); (median)</td><td>35.6 ± 1.9; (37.1)</td></tr>
<tr><td>3 months GES, N = 12; (mean ± SEM);</td><td>16.3 ± 4.3¶</td></tr>
<tr><td>6 months GES, N = 12; (means ± SEM);</td><td>12.3 ± 3.3¶</td></tr>
<tr><td>12 months GES, N = 12; (means ± SEM);</td><td>16.6 ± 5.4¶</td></tr>
<tr><td>1 to 3 years GES, N = 10; (median)</td><td>15.75†</td></tr>
<tr><td>5 years GES, N = 10; (median)</td><td>20.3†</td></tr>
<tr><td colspan="2">WVF** score (mean ± SEM)</td></tr>
<tr><td>Baseline, before GES, N = 12</td><td>3.9 ± 0.1</td></tr>
<tr><td>1 to 3 years GES, N = 10</td><td>1.4 ± 0.6§</td></tr>
<tr><td>5 years GES, N = 10</td><td>1.7 ± 0.5§</td></tr>
<tr><td colspan="2">Patient weight (kg) (mean ± SEM)</td></tr>
<tr><td>Baseline, before GES, N = 12</td><td>69.9 ± 3.6</td></tr>
<tr><td>1 to 3 years GES, N = 10</td><td>72.7 ± 6.4‖</td></tr>
<tr><td>5 years GES, N = 10</td><td>71.4 ± 5.9‖</td></tr>
<tr><td colspan="2">BMI (mean ± SEM)</td></tr>
<tr><td>Baseline, before GES, N = 12</td><td>24.1 ± 1</td></tr>
<tr><td>1 to 3 years GES, N = 10</td><td>25.6 ± 2‖</td></tr>
<tr><td>5 years GES, N = 10</td><td>24.6 ± 2‖</td></tr>
</table>
Nutrition quality of life[#] at 5 years: +2.1 (mean) with +2 (median)
Overall quality of life[#] at 5 years: +2.1 (mean), +3 median
GET: no information provided</td>
</tr>
</table>

Continued on next page

Table B.2: Evidence on the efficacy/effectiveness and safety, including patients reported in other publications (cont'd)

Study Inclusion Criteria, Follow-up	Characteristics of the Intervention Group and Device	Results/Authors' Conclusions
Abell et al.[47] (cont'd)		**Type of nutrition by follow-up** (no. of patients): *Baseline*: oral nutrition only (8), tube feeding gastrostomy or jejunostomy (2), oral with parenteral hyperalimentation (2). *1 to 2 years*: oral nutrition only (8), tube feeding gastrostomy or jejunostomy (1), oral with parenteral hyperalimentation (1). *5 years*: oral nutrition only (9), nutrition orally or tube feeding (1). **Therapy-related adverse events** (no. of patients): device explanted because of infection by first year (1). One patient died of an illness unrelated to the GES by year 2. Authors' conclusion is that GES improves nutritional status in gastroparetic patients. GES should be considered as possible treatment option for patients with drug-refractory GP and nutritional compromise.

*TSS was calculated on a scale of 0 to 10; 0 = none, 10 = worst for each symptom: nausea, vomiting, abdominal pain, bloating or distension, and anorexia or early satiety. Maximum TSS was 50.

**WVF episodes/week: 0 = absent, 1 = rare (1/week), 2 = occasional (2 to 3/week), 3 = frequent (4 to 6/week), extremely frequent (= 7/week).

[¶]$p < 0.01$ compared with baseline; [†]$p < 0.005$ compared with baseline; [§]$p < 0.05$ compared with baseline; [‖]$p = 0.8$ compared with baseline.

[#]Nutrition and overall quality of life: scored -3 to +3 (worst to best) compared with baseline.

BMI: body mass index; GEMS: Gastric Electro-Mechanical Stimulation; GES: gastric electrical stimulation; GET: gastric emptying; GP: gastroparesis; N, n; number of patients; SEM: standard error of the mean; TSS: total symptom score; WVF: weekly vomiting frequency

Table B.2: Evidence on the efficacy/effectiveness and safety, including patients reported in other publications (cont'd)

<table>
<tr><th>Study
Inclusion Criteria, Follow-up</th><th>Characteristics of the Intervention Group and Device</th><th>Results/Authors' Conclusions</th></tr>
<tr>
<td>Lin et al.[45]
2006 USA
Case series (uncontrolled prospective study reported results retrospectively), one centre: University of Kansas Medical Center
Date of recruitment: between April 1998 and October 2001
Inclusion criteria:
- vomiting >7 times/week;
- delayed gastric emptying (>60% retention at 2 hours and >10% at 4 hours), based on standardized scintigraphic method for solid meals;
- symptoms consistent with GP for longer than 12 months;
- refractoriness or intolerance to 2 to 3 classes of prokinetic and antiemetic drugs.
Follow-up: at baseline (4-week period before surgical placement of GES), at 12 months, and 3 years after implantation
Competing interest: Study sponsored in part by Medtronic Inc., Minneapolis, MN.</td>
<td>N = 55 patients (n_1 = 39 diabetes mellitus type I for a mean period of 18.4 years (range 1 to 39), n_2 = 7 idiopathic, n_3 = 9 postsurgical)
Only N = 37 patients (23 diabetic, 9 idiopathic, five postsurgical) were available for follow-up beyond 3 years after GES therapy and had the device activated for a mean of 45 months (range 36 to 79)
Gender: 42 females (27 diabetic, nine idiopathic, six postsurgical), 13 males (12 diabetic, one postsurgical)
Mean age: 41 years (range 21 to 66)
Mean symptom (GP) duration: 6.2 years, (range 1 to 33)
Intervention: GES
Surgical procedure: Not stated
GES system: (Medtronic Inc.) not stated

Note:
Before GES: 20 patients required enteral nutrition through feeding tube and eight patients required total parenteral nutrition.
Patients were instructed to continue all medications they were previously taking before implantation. Prokinetics and antiemetics were maintained at the same dose for the first 3 to 6 months.</td>
<td>Efficacy results
<table>
<tr><th rowspan="2">Characteristic, follow-up, no. of patients</th><th colspan="2">Results</th></tr>
<tr><th>Per protocol</th><th>ITT** LOCF[#]</th></tr>
<tr><td colspan="3">TSS* of frequency (0 to 28) (median, interquartile range)</td></tr>
<tr><td>Baseline, before GES, N = 55</td><td>23 (19-25)</td><td>23 (19-25)</td></tr>
<tr><td>1-year, GES, N = 42</td><td>9 (5-17)[¶]</td><td>12 (6-21)[¶]</td></tr>
<tr><td>3-year, GES, N = 37</td><td>7 (1-14)[¶]</td><td>9 (2-16)[¶]</td></tr>
<tr><td colspan="3">Vomiting* (frequency score) (median, interquartile range)</td></tr>
<tr><td>Baseline, before GES, N = 55</td><td>3 (2-4)</td><td>3 (2-4)</td></tr>
<tr><td>1-year, GES, N = 42</td><td>1 (0-2)[¶]</td><td>1 (0-3)[¶]</td></tr>
<tr><td>3-year, GES, N = 37</td><td>0 (0-1)[¶]</td><td>1 (0-3)[¶]</td></tr>
<tr><td colspan="3">Nausea* (frequency score) (median, interquartile range)</td></tr>
<tr><td>Baseline, before GES, N = 55</td><td>4 (3-4)</td><td>4 (3-4)</td></tr>
<tr><td>1-year, GES, N = 42</td><td>2 (1-2)[¶]</td><td>2 (1-4)[¶]</td></tr>
<tr><td>3-year, GES, N = 37</td><td>1 (0-3)[¶]</td><td>1 (0-4)[¶]</td></tr>
<tr><td colspan="3">Patient weight (kg) (median, interquartile range)</td></tr>
<tr><td>Baseline, before GES, N = 55</td><td>63 (53-71)</td><td>63 (53-71)</td></tr>
<tr><td>1-year, GES, N = 42</td><td>64 (58-69)[§]</td><td>65 (53-70)[§]</td></tr>
<tr><td>3-year, GES, N = 37</td><td>68 (56-77)[§]</td><td>68 (54-77)[§]</td></tr>
</table>
Hospitalization: decreased from a median of 31 days (range 0 to 252) the year before GES therapy to 14 days (range 0 to 69; $p < 0.05$; N = 35) beyond 3 years after GES therapy.</td>
</tr>
</table>

Continued on next page

Table B.2: Evidence on the efficacy/effectiveness and safety, including patients reported in other publications (cont'd)

Study Inclusion Criteria, Follow-up	Characteristics of the Intervention Group and Device	Results/Authors' Conclusions
Lin et al.[45] (cont'd) **Note:** This study is an updated publication by the same group of authors (Forster et al. [48]). Patients included in the study were reported in other publications: WAVESS - one idiopathic and three diabetic patients [39], 39 diabetic patients[11] (personal communication Dr. Richard McCallum). In the study by Forster et al,[48] it is specified that N_1 = 9 patients WAVESS study N_2 = 32 patients compassionate use (CUESS) N_3 = 14 patients under HDE protocol		**Supplementary feeding required**: of the 37 patients with follow-up data beyond 3 years: enteral feeding:15 patients; intermittent enteral tube supplements: 5 patients ($p < 0.05$), total parenteral nutrition: 0 patients. **Medication use**: of the 35 patients with follow-up data beyond 3 years, 14 were off prokinetics after 3 years of GES, and 19 were still on antiemetics. **HbA1c** (mean) levels decreased from 9.5% (at baseline) to 8.4% at 1 year and 7.9% at 3 years (normal range 3.5 to 6.0%). At 3 years data were available from 15 patients. **Therapy-related adverse events** (no. patients): device removed because of infection at 3, 10, 12, and 16 months (4 patients): infection at the pulse generator pocket site (2), skin penetration and infection (1), small bowel volvulus around the wires (1). Removal of GES system and total gastrectomy because of persistency of symptoms of vomiting (2), injury involving fractured sternum and ribs (1). Ten patients died beyond 3 years (9 diabetic, 1 idiopathic): pulmonary embolus postoperatively (1), aspiration pneumonia (1), myocardial infarction (2), cardiomyopathy (1), coronary artery disease (1), renal failure (1), complication of diabetes (1), sepsis and renal failure (1), suicide (1). Lost to follow-up: two patients. The authors concluded that GES improves total symptom scores and symptom scores for severity and frequency, glycemic control, and nutritional parameters, and it decreases hospitalization in patients with GP from different etiologies during a follow-up beyond 3 years. The mechanism of action of GES remains to be elucidated and a favourable placebo response during GES therapy could not be ruled out.

*Values are also available for severity scores and are statistically significant (lower) compared with baseline. The gastrointestinal TSS was calculated using a 5-point categorical scale (0 to 4) as the sum of the frequency and severity ratings of seven symptoms: vomiting, nausea, early satiety, bloating, postprandial fullness, epigastric pain, and epigastric burning.

**All patients receiving treatment are included in the final analysis of data, regardless of whether they completed the intervention. ITT per protocol analysis addresses only patients who complete study therapy in the final data analysis.

[#]The LOCF procedure replaces a missing value by the most recent previous value.

[¶]$p < 0.0001$ compared with baseline; [§]$p < 0.05$ compared with baseline.

CUESS: Compassionate Use of Electrical Stimulation Study; GES: gastric electrical stimulation; GP: gastroparesis; HbA1c: hemoglobin A1c; HDE: Humanitarian Device Exemption; ITT: intention to treatLOCF: last observation carried forward; N, n: number of patients; TSS: total symptom score; WAVESS: Worldwide Antivomiting Electrical Stimulation Study

APPENDIX C: QUALITY ASSESSMENT CHECKLIST FOR CASE SERIES*

This checklist includes 30 criteria and the case series were ranked on the basis of all criteria (Table C.1.).

Study question

1. Is the hypothesis/aim/objective of the study stated in the abstract, introduction, or methods section?

Study population

2. Are the characteristics of the patients included in the study clearly described? (number, gender, age, etiology).
3. Was the case series collected in more than one centre?
   (If the study is multicentre, the question should be answered "yes".)

Comparability of subjects

4. Are the eligibility criteria explicit and appropriate?
   (Inclusion and exclusion criteria should be stated. If there were no exclusion criteria discussed, the question should be answered "partial".)
5. Were data collected prospectively?
6. Were patients recruited consecutively?
7. Did patients enter the study at a similar point in the disease?
   (If there is a high range of duration [higher than 5 years] for a gastroparetic condition or for etiology [diabetes mellitus, postsurgery, idiopathic] of the disease, the question should be answered "no." If there is no information about the duration of condition, the question should be answered "unclear/unable to determine".)
8. Were the subjects recruited during the same period of time?
   (The period of time [year(s), ±month(s)] when the patients were recruited/included in the study should be specified. If the information is not available, the question should be answered "unclear/unable to determine".)

Intervention

9. Description of the intervention
   (description of the Enterra™ Therapy system).
10. In addition to intervention, did the patients receive any cointervention?
    (If patients received medication [prokinetics and antiemetics] or supplementary feeding [enteral or parenteral] after GES, the question should be answered "yes".)

11. Was there loss to follow-up reported?
(The information should include the number of patients who were lost to follow-up and a description of the reason. If there were no patients lost to follow-up, the question should be answered "yes". If the information is not available, the question should be answered "unclear/unable to determine." Subjects lost to follow-up contribute to the analysis until their follow-up ends.)

Outcome measurement

12. Are outcomes (primary [measurement of gastric emptying and/or symptoms' improvement] and secondary [quality of life, supplementary feeding, patient weight, etc.) clearly defined in the introduction or methodology section?
13. Were the outcomes assessed blind/independent to intervention status?
14. Did the authors use accurate (standard, valid, reliable) objective methods to measure the outcomes?
(If the authors used a standardized method to measure gastric emptying and that method is described in the methodology section of the publication, the question should be answered "yes." If the study did not focus on measuring gastric emptying, but symptoms' improvement, the question should be answered "yes". If description of the measurement method is not available in the methodology section but the outcome results are available, the question should be answered "unclear/unable to determine".)
15. Did the authors use standardized subjective measures to assess the outcomes?
(The measurement tools may consist of self administered questionnaires, standardized forms, or patient symptoms interview forms. If description of the measurement tools is not available in the methodology section but the outcome results are available, the question should be answered "unclear/unable to determine".)
16. Was there assessment of outcome before and after intervention?
17. Was the length of follow-up clearly described/reported?

Statistical analysis

18. Were the statistical tests used to assess the primary outcomes appropriate?
19. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the primary outcome measurements except where the probability value is less than 0.001?
20. Does the study provide estimates of the random variability in the data for the primary outcomes?
(e.g. standard error, standard deviation, confidence intervals)

21. Was there a discussion/assessment of possible confounders?
(If there was an actual paragraph available in the discussion or conclusion section that presents the possible confounders [continuation of administration of drugs after GES, supplementary feeding after GES, duration of condition and symptoms, comorbidities, etc.], the question should be answered "yes".)

22. Was the analysis of outcomes based on the number of patients available at the time when the follow-up measures were taken?
(If the authors calculated outcomes on all of the patients who should have been present at the time of follow-up)

Results

23. Are the main findings of the study clearly described?
(If the author used words such as "often," "frequently," or "some" when describing the findings or if the results are available in graphics that are difficult to extract data from, the question should be answered "no".)

24. Are outcomes of the study stratified?
(e.g. based on follow-up periods, etiologies, cointervention. The question should be answered "yes" if the authors present separate results for separate etiologies and also separate follow-ups, or separate follow-ups and cointerventions. If the study involves patients with gastroparesis that results from a single cause (etiology) and the results are stratified on the basis of the follow-up periods, the question should be answered "yes." If the study presents results of a combination of etiologies and different follow-ups, the question should be answered "no".)

25. Do the study's findings respond to research objectives/question(s)?
(If the authors did not respond to research objective(s), the question should be answered "no." If only part of the objectives were responded to, the question should be answered "partial".)

26. Are adverse events that may be a consequence of the intervention reported?

27. Are results based on data dredging?
(Any analyses that had not been planned at the outset of the study should be clearly indicated. If the results or discussion session includes outcomes not planned in the methodology section, the question should be answered "yes." If a number of patients were initially part of another study, the question should be answered "unable to determine".)

Discussion/Conclusion

28. Are the conclusions supported by results?
(If the authors provide results that were not included in the research question(s), the question should be answered "no".)

29. Are the limitations of the study taken into consideration?
(If there was a paragraph available in the discussion or conclusion section that discussed the limitations of the study, the question should be answered "yes". Also, if in the discussion or conclusion section of the publication the authors presented the need for further studies or measurements/assessments that may add more information and knowledge, the question should be answered "yes".)

Funding or sponsorship

30. Is there a competing interest statement about the type and source of support received for the study or about the relationship of the author(s) or other contributors with the manufacturer of the device (GES)?
(If the information is not available, the answer should be "unclear/unable to determine".)

* Criteria included in the checklist were adapted from the following sources:

1. NICE.[52] *Preoperative tests, the use of routine preoperative tests for elective surgery; evidence, methods, guidelines.* June 2003. Available from: http://www.nice.org.uk/pdf/PreopTests_Apps.pdf , p. 87-88.
2. AHRQ.[53] *Systems to rate the strength of scientific evidence, table 9: domains and elements for observational studies.* Evidence reports and summaries. AHRQ Evidence Reports: Numbers 1-60, 47. Available from: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.table.71573.
3. Downs H, Black N.[54] The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomized studies of health care interventions. *Journal of Epidemiology and Community Health* 1998;52:377-84.
4. Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.[55] Do the findings of case series studies vary significantly according to methodological characteristics? *Health Technology Assessment* 2005;9(2):176.
5. Elwood M, editor.[56] *Critical appraisal of epidemiological studies and clinical trials*. 2nd edition. New York: Oxford University Press; 1998.

Table C.1: Critical appraisal of case series

Criterion		Study							
		Abell et al.[8]	McCallum et al.[40]	Van der Voort et al.[30]	Lin et al.[11]	Mason et al.[33]	Lin et al.[45]	Lin et al.[46]	Abell et al.[47]
Study question									
1	Hypothesis/aim/objective of the study clearly described	✓	✓	✓	✓	✓	✓	✓	✓
Study population									
2	Description of the study population	✓	✓	✓	✓	✓	✓	✓	✓
3	Case series collected in more than one centre	✓	X	X	X	✓	X	X	?
Comparability of subjects									
4	Eligibility criteria (inclusion and exclusion criteria)	✓	✓	✓	✓	P	✓	✓	P
5	Data collected prospectively	✓	✓	✓	X	X	✓	✓	✓
6	Patients recruited consecutively	?	?	?	?	?	?	?	?
7	Entered study at similar point in disease	X	X	?	?	?	X	?	?
8	Subjects recruited during the same period of time	?	✓	?	✓	✓	✓	✓	?
Intervention									
9	Description of the intervention	✓	X	✓	✓	✓	X	✓	✓
10	Administered a cointervention	✓	✓	✓	✓	✓	✓	✓	✓
11	Description of loss to follow-up	✓	✓	✓	✓	✓	✓	X	✓

Continued on next page

Table C.1: Critical appraisal of case series (cont'd)

Criterion		Study							
		Abell et al.[8]	McCallum et al.[40]	Van der Voort et al.[30]	Lin et al.[11]	Mason et al.[33]	Lin et al.[45]	Lin et al.[46]	Abell et al.[47]
Outcome measurement									
12	Primary/secondary outcomes clearly defined	✓	✓	✓	✓	✓	✓	✓	✓
13	Outcomes assessed blind/independent to intervention	X	?	?	?	?	?	?	?
14	Objective assessment of the outcomes	✓	✓	✓	✓	✓	✓	✓	✓
15	Subjective assessment of the outcomes	?	✓	✓	✓	✓	✓	✓	✓
16	Assessment of outcome before and after intervention	✓	✓	✓	✓	✓	✓	✓	✓
17	Report of length of follow-up	✓	✓	✓	✓	✓	✓	✓	✓
Statistical analysis									
18	Statistical tests appropriate	✓	✓	✓	✓	✓	✓	✓	✓
19	Probability values	✓	X	X	X	✓	✓	X	X
20	Provision of estimates of the random variability in the data of the main outcomes	X	✓	✓	✓	✓	✓	✓	✓
21	Description of possible confounders	X	X	X	X	X	X	✓	X
22	Analysis based on number of patients available at the time when the follow-up measures were taken	✓	✓	✓	✓	X	X	✓	X
Results									
23	Main findings of the study clearly described	✓	✓	X	✓	X	✓	P	✓
24	Outcomes stratified	X	✓	✓	✓	P	X	P	X
25	Findings relate to the research question	✓	✓	✓	✓	✓	✓	?	✓
26	Adverse events reported	✓	✓	✓	✓	✓	✓	✓	✓
27	Results based on data dredging	X	X	X	X	X	?	?	?

Continued on next page

Table C.1: Critical appraisal of case series (cont'd)

Criterion		Study							
		Abell et al.[8]	McCallum et al.[40]	Van der Voort et al.[30]	Lin et al.[11]	Mason et al.[33]	Lin et al.[45]	Lin et al.[46]	Abell et al.[47]
Discussion/Conclusion									
28	Conclusions supported by results	P	✓	✓	✓	X	✓	X	P
29	Limitations taken into consideration	✓	✓	✓	✓	✓	✓	✓	X
Funding or sponsorship									
30	Declaration of possible competing interest	?	✓	✓	✓	✓	✓	✓	✓
Total*									
	YES = ✓	19	22	21	22	19	21	19	17
	NO = X	6	6	5	5	6	6	4	5
	PARTIAL = P	1	-	-	-	2	0	2	2
	UNCLEAR/UNABLE TO DETERMINE = ?	4	2	4	3	3	3	5	6
	Quality rating¶	A	A	A	A	A	A	A	A
	Rank#	3	1	2	1	3	2	3	4

*Total rating is determined from all 30 criteria. Each criterion in the checklist has been given the same weight. The cut-off value for inclusion in the case series was arbitrary established at >50% of the criteria met.

¶The case series were rated with respect to quality criteria as follows:

Good (G): at least 80% of criteria met; average (A): between 50% and 80% of criteria met; poor (P): ≤ 50% of criteria met.

#Rank is established from the number of criteria that were answered with a "yes."

The observed probability of concordance between the two measurements (calculated for 7 studies) p(o) = 0.780
The expected probability of concordance between the two measurements (calculated for 7 studies) p(e) = 0.464
The reliability coefficient (kappa) (calculated for 7 studies) k = 0.58 (0.4 ≤ k ≤ 0.75 = good reproducibility)

APPENDIX D: ADVERSE EVENTS REPORTED IN TWO MULTICENTRE CLINICAL STUDIES

Table D.1: Summary of adverse events reported through September 30, 1999* [29]

Event	Number of Events	Number of Patients (%)
Device- or implant-related[a]		
Lead impedance out of range	7	6 (12)
Device infections[b]	2	2 (4)
Device erosion[c]	1	1 (2)
Device migration[d]	2	1 (2)
Stomach-wall perforation[e]	1	1 (2)
Disease-related		
Upper gastrointestinal symptoms	81	23 (45)
Extra-abdominal pain	33	14 (27)
Feeding tube complications	23	14 (27)
Lower gastrointestinal symptoms	17	9 (20)
Dehydration	15	8 (16)
Bone and joint related	11	8 (16)
Acute diabetic complications	9	6 (12)
Dysphagia	5	1 (2)
Cardiovascular/renal related	2	2 (4)
Other therapy complications		
Feeding tube or intravenous complications	23	14 (27)
Miscellaneous		
Urinary tract infections	4	4 (8)
Stress incontinence	2	2 (4)
Fever	6	4 (8)
Other infections: sinus, pink eye, herpes zoster	3	3 (6)

*Data collected from two clinical studies[§] (N = 51) conducted in the United States, Canada, and European countries.[32]

[§]Worldwide Antivomiting Electrical Stimulation Study (WAVESS): double-blind, randomized, crossover study, n = 33 patients; and Compassionate Use of Electrical Stimulation Study (CUESS): open-label, non-randomized study, n = 18 patients

[a]Three types of device-related adverse events (device infection [n = 3], stomach wall perforation [n = 1], and migration of the pulse generator [n = 1]) required surgical intervention

[b]The device system was removed in both patients; a new system was implanted in one patient
[c]The device system was removed in one patient; a new system was implanted
[d]The device system was twice surgically revised, but not removed, in the same patient
[e]The device system was removed and not reimplanted or replaced with a new system

APPENDIX E: COVERAGE STATUS ACROSS CANADA

Table E.1: Coverage of the Enterra™ Therapy by provincial plans*

Province	Is Enterra™ Therapy provided anywhere in your province/territory (hospital, surgical clinic)?	If it is provided, is it publicly funded?	Is there a code in your schedule of medical benefits for reimbursement of physician services that could or does include the surgical implantation of a GES device like Enterra™ Therapy?	Does your ministry, in any way, provide public funding to cover the purchase of the Enterra Therapy device?	Have hospitals/ regional health authorities been directed to provide this treatment or is this decision left to the discretion of the hospital/RHA?
AB	No	No	No	No	No
BC	No response	No response	No	No response	No response
MB	No	No response	No response	No response	No response
NB	No	No	No	No	No
NL	No response	No response	No response	No response	No response
NS	No	No	No	No	No response
NT	No response	No response	No response	No response	No response
NU	No	No	No	No response	No response
ON	No response	No response	No	No response	No response
PE	No	No	No response	No response	No response
QC	No	No	No	No	No
SK	No	No	No	No	No
YT	No	No response	No response	No response	No response

*Results from a survey conducted in the fall of 2005

AB: Alberta; BC: British Columbia; GES: gastric electrical stimulation; MB: Manitoba; NB: New Brunswick; NL: Newfoundland and Labrador; NS: Nova Scotia; NT: Northwest Territories; NU: Nunavut; ON: Ontario; PE: Prince Edward Island; QC: Quebec; RHA: Regional Health Authority; SK: Saskatchewan; YT: Yukon

APPENDIX F: WAVESS PHASE I RESULTS[§]

Table F.1: WAVESS Phase I, mean and median results—vomiting episodes per week[#]

Vomiting Episodes Per Week	Baseline	ON	OFF	Difference OFF-ON	% Difference
FDA*, Medtronic*					
Mean (N ± SD)	47.6 ± 52.6	23.0 ± 35.5	29.0 ± 38.2	6.0 ± 22.4	21
Median (N)	26.3	12.0	14.0	2.0	14.3
Abell et al**					
Median (N, interquartile range)	17.3 (11.8–45.7)	6.8 (3.9–16.5)	13.5 (5.5–25.4)	NA	NA

[§]Adapted from Jones[14]

[#]All subjects (N = 33)

*Values presented in the Food and Drug Administration letter of approval, March 31, 2000,[32] and *Medtronic Enterra Therapy Technical Manual*[29]

**Values published by Abell et al.[39]

FDA: Food and Drug Administration; N: number of patients; NA: not available; SD: standard deviation; WAVESS: Worldwide Antivomiting Electrical Stimulation Study

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