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Gastric Electrical Stimulation

An Evidence-Based Analysis

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The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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Abbreviations

AHFMR	Alberta Heritage Foundation for Medical Research
BMI	Body mass index
CI	Confidence interval
CUESS	Compassionate Use of Electrical Stimulation Study
EWL	Excess weight loss
FDA	Food and Drug Administration
GEMS	Gastric Electro-Mechanical Stimulation
GES	Gastric electrical stimulation
GP	Gastroparesis
HDE	Humanitarian device exemption
HOMA	Homeostatic Model Assessment Insulin Resistance Index
HQOL	Health related quality of life
HTA	Health technology assessment
HTPA	Health technology policy assessment
Hz	Hertz
ITT	Intent to treat
LOSS	Laparoscopic Obesity Stimulation Survey
MCS	Mental composite score
NA	Not applicable
NICE	National Institute for Clinical Excellence
OR	Odds ratio
OGGT	Oral glucose tolerance test
QoL	Quality of life
RR	Relative risk
SBU	Swedish Council of Technology Assessment in Healthcare
SD	Standard deviation
SEM	Standard error of the mean
SHAPE	Screened Health Assessment and Pacer Evaluation
Tc99	Technetium99
TSS	Total symptom score
WAVESS	Worldwide Antivomiting Electrical Stimulation Study

Glossary

Antiemetic drug: A drug that prevents or alleviates nausea and vomiting

Body mass index: Body weight expressed in kilograms (kg) divided by height expressed in square metres (m^2).

Dumping Syndrome: A group of symptoms that occur when food or liquid enters the small intestine too rapidly. These symptoms include cramps, nausea, diarrhea and dizziness.

Dyspepsia: Impairment of digestion, usually applied to epigastric discomfort following meals.

Enteral: A method of nutrient delivery where fluid is given directly into the gastrointestinal tract.

Excess weight loss: Percentage of excess weight los = (weight loss/excess weight) x 100 (where excess weight = total preoperative weight – ideal weight).

Fundoplication: The upper curve of the stomach (the fundus) is wrapped around the esophagus and sewn into place so that the lower portion of the esophagus passes through a small tunnel of stomach muscle. This surgery strengthens the valve between the esophagus and stomach which stops acid from backing up into the esophagus as easily.

Gastric electrical stimulation: Electrical stimulation delivered to the stomach via an implanted system that consists of a neurostimulator and 2 leads.

Gastroparesis: A disorder characterized by symptoms of and evidence for gastric retention in the absence of mechanical obstruction.

Hertz: The System International unit of frequency. One hertz (Hz) is defined as the reciprocal second.

Idiopathic: Characterizing a disease arising primarily, and not in consequence of some other disease or injury.

Jejunostomy: Surgical formation of an opening through the abdominal wall into the jejunum, usually for enteral hyperalimentation.

Morbid obesity: Body mass index of at least 40 kg/m^2 or at least 35 kg/m^2 with comorbid conditions.

Obesity: Body mass index greater than 30 kg/m^2.

Prokinetic drug: A drug that increases the number and strength of GI muscle contractions.

Pylorus: The opening from the stomach to the intestine.

Technetium-99: An isotope of technetium which is used in many medical radioactive isotope tests because of its short half-life (6.01 hours), the energy of the gamma radiation it emits, and its ability to bind chemically to many biologically active molecules.

Vagus nerve: A nerve that enervates the gastrointestinal tract, heart and larynx.

Executive Summary

Objective

The objective of this analysis was to assess the effectiveness, safety and cost-effectiveness of gastric electrical stimulation (GES) for the treatment of chronic, symptomatic refractory gastroparesis and morbid obesity.

Background

Gastroparesis - Epidemiology

Gastroparesis (GP) broadly refers to impaired gastric emptying in the absence of obstruction. Clinically, this can range from the incidental detection of delayed gastric emptying in an asymptomatic person to patients with severe nausea, vomiting and malnutrition. Symptoms of GP are nonspecific and may mimic structural disorders such as ulcer disease, partial gastric or small bowel obstruction, gastric cancer, and pancreaticobiliary disorders.

Gastroparesis may occur in association with diabetes, gastric surgery (consequence of peptic ulcer surgery and vagotomy) or for unknown reasons (idiopathic gastroparesis). Symptoms include early satiety, nausea, vomiting, abdominal pain and weight loss. The majority of patients with GP are women.

The relationship between upper gastrointestinal symptoms and the rate of gastric emptying is considered to be weak. Some patients with markedly delayed gastric emptying are asymptomatic and sometimes, severe symptoms may remit spontaneously.

Idiopathic GP may represent the most common form of GP. In one tertiary referral retrospective series, the etiologies in 146 GP patients were 36% idiopathic, 29% diabetic, 13% postgastric surgery, 7.5% Parkinson's disease, 4.8% collagen vascular disorders, 4.1% intestinal pseudoobstruction and 6% miscellaneous causes.

The true prevalence of digestive symptoms in patients with diabetes and the relationship of these symptoms to delayed gastric emptying are unknown. Delayed gastric emptying is present in 27% to 58% of patients with type 1 diabetes and 30% with type 2 diabetes. However, highly variable rates of gastric emptying have been reported in type 1 and 2 diabetes, suggesting that development of GP in patients with diabetes is neither universal nor inevitable. In a review of studies examining gastric emptying in patients with diabetes compared to control patients, investigators noted that in many cases the magnitude of the delay in gastric emptying is modest.

GP may occur as a complication of a number of different surgical procedures. For example, vagal nerve injury may occur in 4% to 40% of patients who undergo laparoscopic fundoplication[1] for gastroesophageal reflux disease.

The prevalence of severe, refractory GP is scantily reported in the literature. Using data from a past study,

[1] The upper curve of the stomach (the fundus) is wrapped around the esophagus and sewn into place so that the lower portion of the esophagus passes through a small tunnel of stomach muscle. This surgery strengthens the valve between the esophagus and stomach which stops acid from backing up into the esophagus as easily.

it has been estimated that the prevalence of severe, symptomatic and refractory GP in the United States population is 0.017%. Assuming an Ontario population of 13 million, this would correspond to approximately 2,000 people in Ontario having severe, symptomatic, refractory GP.

The incidence of severe refractory GP estimated by the United States Food and Drug Administration (FDA) is approximately 4,000 per year in the United States. This corresponds to about 150 patients in Ontario. Using expert opinion and FDA data, the incidence of severe refractory GP in Ontario is estimated to be about 20 to 150 per year.

Treatment for Gastroparesis

To date, there have been no long-term studies confirming the beneficial effects of maintaining euglycemia on GP symptoms. However, it has been suggested that consistent findings of physiologic studies in healthy volunteers and diabetes patients provides an argument to strive for near-normal blood glucose levels in affected diabetes patients.

Dietary measures (e.g., low fibre, low fat food), prokinetic drugs (e.g., domperidone, metoclopramide and erythromycin) and antiemetic or antinausea drugs (e.g, phenothiazines, diphenhydramine) are generally effective for symptomatic relief in the majority of patients with GP.

For patients with chronic, symptomatic GP who are refractory to drug treatment, surgical options may include jejunostomy tube for feeding, gastrotomy tube for stomach decompression and pyloroplasty for gastric emptying.

Few small studies examined the use of botulinum toxin injections into the pyloric sphincter. However, the contribution of excessive pyloric contraction to GP has been insufficiently defined and there have been no controlled studies of this therapy.

Treatment with GES is reversible and may be a less invasive option compared to stomach surgery for the treatment of patients with chronic, drug-refractory nausea and vomiting secondary to GP. In theory, GES represents an intermediate step between treatment directed at the underlying pathophysiology, and the treatment of symptoms. It is based on studies of gastric electrical patterns in GP that have identified the presence of a variety of gastric arrhythmias. Similar to a cardiac pacemaker, it was hypothesized that GES could override the abnormal rhythms, stimulate gastric emptying and eliminate symptoms.

Morbid Obesity Epidemiology

Obesity is defined as a body mass index (BMI) of at last 30 kg/m^2. Morbid obesity is defined as a BMI of at least 40 kg/m^2 or at least 35 kg/m^2 with comorbid conditions. Comorbid conditions associated with obesity include diabetes, hypertension, dyslipidemias, obstructive sleep apnea, weight-related arthropathies, and stress urinary incontinence.

In the United States, the age-adjusted prevalence of extreme obesity (BMI $\geq$ 40 kg/m^2) for adults aged 20 years and older has increased significantly in the population, from 2.9% (1988–1994) to 4.7% (1999–2000). An expert estimated that about 160,000 to 180,000 people are morbidly obese in Ontario.

Treatment for Morbid Obesity

Diet, exercise, and behavioural therapy are used to help people lose weight.

Bariatric surgery for morbid obesity is considered an intervention of last resort for patients who have attempted first-line forms of medical management.

Gastric stimulation has been investigated for the treatment of morbid obesity; the intention being to reduce appetite and induce early satiety possibly due to inhibitory effects on gastric motility and effects on the central nervous system (CNS) and hormones related to satiety and/or appetite.

Possible advantages to GES for the treatment of morbid obesity include reversibility of the procedure, less invasiveness than some bariatric procedures, e.g., gastric bypass, and less side effects (e.g., dumping syndrome).

The Device

Electrical stimulation is delivered via an implanted system that consists of a neurostimulator and 2 leads. The surgical procedure can be performed via either an open or laparoscopic approach. An external programmer used by the physician can deliver instructions to the GES, i.e., adjust the rate and amplitude of stimulation (Figure 1). GES may be turned off by the physician at any time or may be removed. The battery life is approximately 4-5 years

For treatment of GP, the GES leads are secured in the muscle of the lower stomach, 10 cm proximal to the pylorus (the opening from the stomach to the intestine), 1 cm apart and connected to an implantable battery-powered neurostimulator which is placed in a small pocket in the abdominal wall

For treatment of morbid obesity, GES leads are implanted along the lesser curvature of the stomach where the vagal nerve branches spread, approximately 8 cm proximal to the pylorus. However, the implant positioning of the leads has been variably reported in the literature.

Regulatory Status

The Enterra Therapy System and the Transcend II Implantable Gastric Stimulation System (Medtronic Inc.) are both licensed as class 3 devices by Health Canada (license numbers 60264 and 66948 respectively). The Health Canada indications for use are:

Enterra Therapy System

- "For use in the treatment of chronic intractable (drug-refractory) nausea and vomiting."

Transcend II Implantable Gastric Stimulation System

- "For use in weight reduction for obese adults with a body mass index greater than 35."

The GES device that is licensed by Health Canada for treatment of GP, produces high-frequency GES. Most clinical studies examining GES for GP have used high-frequency (4 times the intrinsic slow wave frequency, i.e., 12 cycles per minute), low energy, short duration pulses. This type of stimulation does not alter gastric muscular contraction and has no effect on slow wave dysrhythmias. The mechanism of action is unclear but it is hypothesized that high-frequency GES may act on sensory fibers directed to the CNS.

The GES device licensed by Health Canada for treatment of morbid obesity produces low-frequency GES, which is close to or just above the normal/native gastric slow wave cycle (approximately 3 cycles/min.). This pacing uses low-frequency, high-energy, long-duration pulses to induce propagated

slow waves that replace the spontaneous ones. Low-frequency pacing does not invoke muscular contractions.

Most studies examining the use of GES for the treatment of morbid obesity use low-frequency GES. Under normal circumstances, the gastric slow wave propagates distally and determines the frequency and propagation direction of gastric peristalsis. Low-frequency GES aims to produce abnormal gastric slow waves that can induce gastric dysrhythmia, disrupt regular propagation of slow waves, cause hypomotility of the stomach, delay gastric emptying, reduce food intake, prolong satiety, and produce weight loss.

In the United States, the Enterra Therapy System is a Humanitarian Use Device (HUD), meaning it is a medical device designated by the FDA for use in the treatment of medical conditions that affect fewer than 4,000 individuals per year.[2] The Enterra Therapy System is indicated for "the treatment of chronic, drug- refractory nausea and vomiting secondary to GP of diabetes or idiopathic etiology" (not postsurgical etiologies).

GES for morbid obesity has not been approved by the FDA and is for investigational use only in the United States.

Review Strategy

The Medical Advisory Secretariat systematically reviewed the literature to assess the effectiveness, safety, and cost-effectiveness of GES to treat patients who have: a) chronic refractory symptomatic GP; or b) morbid obesity.

The Medical Advisory Secretariat used its standard search strategy to retrieve international health technology assessments and English-language journal articles from selected databases.

The GRADE approach was used to systematically and explicitly make judgments about the quality of evidence and strength of recommendations.

[2] The regulation provides for the submission of a humanitarian device exemption (HDE) application, which is similar in both form and content to a premarket approval application (PMA), but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations showing that the device is effective for its intended purpose. The application must however contain sufficient information for the FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of injury or illness from its use.
A HUD may only be used after IRB approval has been obtained for the use of the device for the FDA approved indication.

Findings

As stated by the GRADE Working Group, the following definitions were used in grading the quality of the evidence in Tables 1 and 2.

High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Table 1: GRADE Quality of Studies – Gastroparesis

Outcome	Design	Quality	Consistency	Directness	Overall Quality
Reduced vomiting & nausea (1° end point)	RCT (Abell et al. 2003) Case Series	Low *Why?* *1. Confounders related to diabetes.* *2. Possible Type 2 error for subgroup analyses.* *3. Subjective self-reported end point.* *4. Posthoc change in primary end point analysis.* *5. No sample size justification.* *6. Concomitant prokinetic/antiemetic therapy.* Same as above.	Some uncertainty. *Why?* *1. Only 1 RCT (with different results for FDA and publication).*	Some uncertainty. *Why?* *1. GES originally hypothesized to correct gastric rhythms, stimulate gastric emptying and therefore eliminate symptoms.* *2. Now hypothesized to directly act on neurons to the CNS to control symptoms.* *3. Weak correlation between symptoms and gastric emptying.* 4. *Unclear whether gastric emptying is still considered an end point to investigate.*	Low
Improved gastric emptying (2° end point)	Open label portion of Abell et al. 2003 & Case series	Low *Why?* *Same limitations as above.* *Not a 1° end point.* *No intent-to-treat analysis.*	Wide variation in improvement. Same uncertainties as above.	Same uncertainties as above.	Low/Very Low

Table 2: GRADE Quality of Studies – Morbid Obesity

Outcome	Design	Quality	Consistency	Directness	Overall Quality
Weight Loss	RCT "O-01 Trial" According to Shikora (2004), considered "update of ongoing clinical trials". Case series	Low *Why?* *1. No sample size calculation.* *2. Small sample size.* *3. No ITT analysis.* *4. Lack of detail regarding dropouts.* *5. Possible Type 2 error.* *6. Sparse details about randomization/blinding.* *7. Full, final results not published.* Same as above.	Some uncertainty. *Why?* *1. Only 1 RCT (technically grey literature).*	Generally direct (%EWL).	Very Low
Resolution of Comorbidities	Case series	Same as above	? Scanty data	? Scanty data	Very Low

Economic Analysis

No formal economic analysis was identified in the literature search.

The Alberta Heritage Foundation for Medical Research reported that the cost of implanting a GES in the United States for the treatment of GP is estimated to be $30,000 US. In Canada, the device costs approximately $10,700 Cdn; this does not include costs associated with the physician's training, the implantation procedure, or device programming and maintenance.

Ontario Context

There is no Schedule of Benefits code for GES.

There is no Canadian Classification of Health Interventions Index (CCI) procedure code for GES.

Since the ICD-10 diagnosis code for gastroparesis falls under K31.8 "Other specified diseases of the stomach and duodenum", it is impossible to determine how many patients in Ontario had discharge abstracts because of gastroparesis.

In 2005, there were less than 5 out-of-country requests for GES (for either consultation only or for surgery).

Gastroparesis

The prevalence of severe, refractory GP is variably reported in the literature.

The Alberta Heritage Foundation for Medical Research estimated that the prevalence of severe, symptomatic and medically refractory GP in the United States population was 0.017%. Assuming a total Ontario population of 13 million, this would correspond to a budget impact of approximately $23.6 M

Cdn ($10,700 Cdn x 2,210 patients) for the device cost alone.

The incidence of severe refractory GP estimated by the FDA is approximately 4,000 per year in the United States. This corresponds to about 150 patients in Ontario. Using expert opinion and FDA data, the incidence of severe refractory GP in Ontario is estimated to be about 20 to 150 per year. This corresponds to a budget impact of approximately $107,000 Cdn to $1.6M Cdn per year for the device cost alone.

Morbid Obesity

An expert in the field estimated that there are 160,000 to 180,000 people in Ontario who are morbidly obese. This would correspond to a budget impact of approximately $1.7B Cdn to $1.9B Cdn for the device cost alone (assuming 100% uptake). However, the true uptake of GES for morbid obesity is unknown in relation to other types of bariatric surgery (which are more effective).

Conclusion

As per the GRADE Working Group, overall recommendations consider 4 main factors.

- The tradeoffs, taking into account the estimated size of the effect for the main outcome, the confidence limits around those estimates and the relative value placed on the outcome.
- The quality of the evidence.
- Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects such as proximity to a hospital or availability of necessary expertise.
- Uncertainty about the baseline risk for the population of interest.

The GRADE Working Group also recommends that incremental costs of healthcare alternatives should be considered explicitly alongside the expected health benefits and harms. Recommendations rely on judgments about the value of the incremental health benefits in relation to the incremental costs. The last column in Table 3 shows the overall trade-off between benefits and harms and incorporates any risk/uncertainty.

For GP, the overall GRADE and strength of the recommendation is "weak" – the quality of the evidence is "low" (uncertainties due to methodological limitations in the study design in terms of study quality, consistency and directness), and the corresponding risk/uncertainty is increased due to a budget impact of approximately $107,000 Cdn to $1.6M Cdn for the device cost alone, while the cost-effectiveness of GES is unknown and difficult to estimate considering that there are no high-quality studies of effectiveness. Further evidence of effectiveness should be available in the future since there is a RCT underway that is examining the use of GES in patients with severe refractory GP associated with diabetes and idiopathic etiologies (ClinicalTrials.gov identifier NCT00157755).

For morbid obesity, the overall GRADE and strength of the recommendation is "weak" – the quality of the evidence is "low" (uncertainties due to methodological limitations in the study design in terms of study quality and consistency), and the corresponding risk/uncertainty is increased due to a budget impact of approximately $1.7B Cdn to $1.9B Cdn for the device cost alone (assuming 100% uptake) while the cost-effectiveness of GES is unknown and difficult to estimate considering that there are no high quality studies of effectiveness. However, the true uptake of GES for morbid obesity is unknown in relation to other types of bariatric surgery (which are more effective).

Table 3: Overall GRADE and Strength of Recommendation (Including Uncertainty)

	Quality	Estimated Prevalence in Ontario	Cost-Effective-ness	Cost in Ontario	Risks/Burden	Benefits	Overall Grade & Strength of Recommendation
Severe, chronic refractory GP	Low	Incidence ~ 20 to 150	?	Cdn $107,000 to $1.6M	Removal rate ~ 5-10% of cases due to infection, stomach perforation, device migration/erosion. Cost effectiveness unknown. Ongoing/lifetime monitoring of patient. Battery change ~ 5 years. Post hoc change in end point analysis. Another RCT is underway.	Uncertain short/long- term benefits (reduced frequency of vomiting/nausea; improved gastric emptying; quality of life).	Weak
Morbid obesity	Very Low	~ 160,000 to 180,000	?	Uptake not determined in relation to other types of bariatric surgery (which are more effective).	Adverse effects – stomach perforation and lead dislodgment – difficult to determine rate given mid-study changes in surgical technique. Cost effectiveness and uptake unknown. Ongoing/lifetime monitoring of patient. Battery change ~ < 5 years?	Uncertain short/long-term benefits (EWL and improvement / resolution of comorbidities).	Weak

Objective

The objective of this analysis was to assess the effectiveness, safety and cost-effectiveness of GES for the treatment of chronic, symptomatic refractory gastroparesis and morbid obesity.

Background

Gastroparesis

Epidemiology

Gastroparesis (GP) broadly refers to impaired gastric emptying in the absence of obstruction. (1) Clinically, this can range from the incidental detection of delayed gastric emptying in an asymptomatic person, to patients with severe nausea, vomiting and malnutrition. Symptoms of GP are nonspecific and may mimic structural disorders such as ulcer disease, partial gastric or small bowel obstruction, gastric cancer, and pancreaticobiliary disorders.

Gastroparesis may occur in association with diabetes, gastric surgery (consequence of peptic ulcer surgery and vagotomy) or for unknown reasons (idiopathic gastroparesis). (1) Symptoms include early satiety, nausea, vomiting, abdominal pain and weight loss. The majority of patients with GP are women. (2) Women exhibit slower emptying rates than men, especially during the latter half of the menstrual cycle. (3)

Idiopathic Gastroparesis

Idiopathic GP may represent the most common form of GP. (3;4) In one tertiary referral retrospective series, the etiologies in 146 GP patients were 36% idiopathic, 29% diabetic, 13% postgastric surgery, 7.5% Parkinson's disease, 4.8% collagen vascular disorders, 4.1% intestinal pseudoobstruction and 6% miscellaneous causes. (2) The associated clinical states of the idiopathic group were: patients presenting after an acute viral gastroenteritis-like illness (23%); gastroesophageal reflux disease and nonulcer dyspepsia (19%); an abdominal-pain-dominated subset (48%); patients who were thought to be depressed or who had received antidepressants in the recent past or were being currently given antidepressants (23%); and a subgroup whose symptoms started immediately after a cholecystectomy (8%). (2)

Gastroparesis Associated With Diabetes

The true prevalence of digestive symptoms in patients with diabetes and the relationship of these symptoms to delayed gastric emptying are unknown. Delayed gastric emptying is present in 27% to 58% of patients with type 1 diabetes and 30% with type 2 diabetes. (5) However, highly variable rates of gastric emptying, including acceleration of transit, have been reported in type 1 and 2 diabetes, suggesting that development of GP in patients with diabetes is neither universal nor inevitable. (3;6;7) Kong and Horowitz (8) reviewed studies examining gastric emptying in patients with diabetes compared to control patients and noted that in many cases, the magnitude of the delay in gastric emptying is modest and suggested that a distinction should be made between the term 'gastroparesis' and 'delayed gastric emptying' with a diagnosis of GP restricted to patients in whom gastric emptying is grossly delayed.

Postsurgical Gastroparesis

GP may occur as a complication of a number of different surgical procedures. Vagal nerve injury may occur in 4% to 40% of patients who undergo laparoscopic fundoplication[3] for gastroesophageal reflux disease.

Some cases of GP have been reported after heart and lung transplantation; this is mostly likely due to vagal nerve injury. (3)

Refractory Gastroparesis

The prevalence of severe, refractory GP is scantily reported in the literature. Tougas et al. (9) examined the prevalence of upper gastrointestinal (GI) symptoms among a sample of 1,036 Canadians. One hundred and fifty-three of the participants surveyed reported having substantial GI symptoms for greater than 3 months. Eighty-four of the 153 participants reported dysmotility-like symptoms (e.g., early satiety, nausea, vomiting, or postprandial [after a meal] fullness) as predominant symptoms. Forty-nine of the 84 participants were diagnosed by a physician; diagnoses consisted of peptic ulcer, reflux disease, gallstones, and hiatus hernia. Thirty-seven of the 153 participants were prescribed drugs for their chronic symptoms. A major limitation to the paper by Tougas et al. was reliance on patient self-reported symptoms, rather than physician diagnoses. (10) "Gastroparesis" was neither reported nor discussed in the paper by Tougas et al.

Using data from Abell and Minocha (11), the Alberta Heritage Foundation for Medical Research (AHFMR) estimated that the prevalence of severe, symptomatic and refractory GP in the United States population was 0.017%. (10) Assuming an Ontario population of 13 million (12), this would correspond to approximately 2,210 people in Ontario having severe, symptomatic, refractory GP.

The incidence of severe refractory GP estimated by the United States Food and Drug Administration (FDA) is approximately 4,000 per year in the United States. This corresponds to about 150 patients in Ontario (3.8% of 4,000). Using expert opinion and FDA data, the incidence of severe refractory GP in Ontario is estimated to be about 20 to 150 cases per year.

Relationship Between Symptoms and Delayed Gastric Emptying

In the past it was generally assumed that upper gastrointestinal symptoms are a direct result of a delay in gastric emptying, but this concept is now generally recognized to be overly simplistic. (13;14) In most studies of delayed gastric emptying, symptoms were not evaluated using validated measures and total symptom scores rather than severity of individual symptoms were quantified. The relationship between upper gastrointestinal symptoms and the rate of gastric emptying is considered to be weak. (8;13;14) Some patients with markedly delayed gastric emptying are asymptomatic and sometimes, severe symptoms may remit spontaneously. (5;8;15)

Effects of Blood Glucose Concentration on Gastric Emptying

Acute changes in the blood glucose concentration (both hyper-and hypoglycemia) have a substantial and reversible effect on gastric motility in both healthy subjects and patients with diabetes. (8;16) Marked hyperglycemia slows gastric emptying in uncomplicated Type 1 and Type 2 diabetes patients and in

[3] The upper curve of the stomach (the fundus) is wrapped around the esophagus and sewn into place so that the lower portion of the esophagus passes through a small tunnel of stomach muscle. This surgery strengthens the valve between the esophagus and stomach which stops acid from backing up into the esophagus as easily.

diabetes patients with autonomic neuropathy. (17;18) It is not known whether the response to hyperglycemia is dependent on the rate of gastric emptying during euglycemia (normal blood glucose concentration), previous long-term glycemic control or autonomic nerve function. (8)

Changes in the blood glucose concentration within the normal postprandial range can also influence gastric emptying and motility. Emptying of solids and liquids is slower at blood glucose of 8 mmol/l than 4 mmol/l in healthy subjects, and patients with type 1 diabetes. In patients with type 1 diabetes (as well as autonomic neuropathy), gastric emptying is accelerated during hypoglycemia. The effect of hypoglycemia on gastric emptying in patients with severe GP has not been studied. (8)

There is some evidence that the blood glucose concentration may also affect perception of gastrointestinal sensations (e.g., satiety) in patients with type 1 and 2 diabetes. (8;16) The mechanism by which hyperglycemia affects gut perception/symptoms is unknown. (8)

Effects of Gastric Emptying on Blood Glucose Concentration

Gastric emptying is a determinant of postprandial glycemia and accounts for approximately 35% of the variance in peak postprandial glucose levels after oral glucose in both healthy subjects and in patients with type 2 diabetes. (8;16) In patients with type 1 diabetes and GP, it has been shown that less insulin is initially required to maintain euglycemia after a meal compared to patients having type 1 diabetes with normal gastric emptying. (8)

It is unknown if treatment with prokinetic (to increase gastric motility) drugs improves glycemic control in patients with type 1 diabetes. (8)

In the past, delayed gastric emptying was considered to confer a poor prognosis for patients with diabetes; however, its high prevalence (~ 30% to 50% in patients with diabetes) and recent studies suggest that this may be incorrect. (19) Jones et al. (20)
showed that neither the rate of emptying nor symptoms changed markedly in 20 patients with diabetes over a mean follow-up period of 12 years.

Diagnosis

GP is diagnosed by demonstrating delayed gastric emptying in a symptomatic patient after exclusion of other potential etiologies of symptoms and obstruction with endoscopy and radiological imaging. (4) Patients with GP may present with nausea, vomiting, early satiety, bloating, discomfort or pain and belching. Rapid gastric emptying, dumping or gastric dysaccomodation may also result in similar symptoms that would not respond to a prokinetic agent; therefore it has been suggested to measure gastric emptying rather than assume symptoms reflect delayed gastric emptying. (4)

Measuring Gastric Emptying

Gastric emptying scintigraphy of a solid-phase meal is considered the gold standard for the diagnosis of GP because this test quantifies the emptying of a physiologic caloric meal. (3) Measurement of gastric emptying in patients with diabetes should be done during euglycemia. (8) Rayner and Horowitz (21) point out that many studies have either not controlled or not reported the blood glucose concentration in diabetes patients with GP.

In the past literature on gastric emptying, there was generally a lack of standardization of scintigraphic techniques, with variation between different centres, particularly in relation to the volume and composition of the test meal, timing of imaging and the calculation of gastric emptying rates (e.g.,

percentage of the meal remaining at 2 hours or half-emptying time). (8;21-23) This made comparisons between studies difficult and required each lab to have access to an appropriate control range. (8;22)

Many centres in the past obtained frequent scans over a period of 90 minutes and used a computer-generated curve to predict gastric emptying rates (e.g., half-time). (24) If the emptying rate has not reached 50%, the extrapolated value for the half-time may be unreliable.
Camilleri et al. (24) state that the current preferred strategy is to use actual data at 2 and 4 hours postprandially? since it has high predictive value for identifying dumping and stasis respectively. (24) *The Society of Nuclear Medicine Procedure Guideline for Gastric Emptying and Motility* states that images should be obtained for up to 4 hours, since retention of greater than 10% of the meal in the stomach at 4 hours is considered abnormal. (25-27)

A commercially prepared meal of technetium- (^{99m}Tc) labeled egg whites with standard imaging at 0, 1, 2 and 4 hours postprandially, has been proposed to facilitate standardization between different centres. (23)

Camilleri et al. (24) reported that scintigraphic gastric emptying measurements have coefficients of variation of almost 15% (below 10% is considered good). In terms of clinical interpretation of a single test, only unequivocal results are clinically important. (24)

Treatment for Chronic, Symptomatic Gastroparesis

To date, there have been no long-term studies confirming the beneficial effects of maintaining euglycemia in GP symptoms. However, it has been suggested that consistent findings of physiologic studies in healthy volunteers and diabetes patients provide an argument to strive for near-normal blood glucose levels in affected diabetes patients. (3;8)

Dietary measures (e.g., low fibre, low fat food), prokinetic drugs (e.g., domperidone, metoclopramide, erythromycin, tegaserod, and itopride [still in clinical trials]) and antiemetic or antinausea drugs (e.g., phenothiazines, diphenhydramine, dimenhydrinate, ondansetron, desipramine, nortriptyline, amitriptyline, scopolamine, hyoscyamine, and aprepitant [not listed in the Health Canada Drug Product Database but approved by the FDA on July 11 2006]) are generally effective for symptomatic relief in the majority of patients with GP. (28;29) Talley (15) conducted a meta-analysis of trials examining the use of prokinetics in patients with diabetes and GP, and suggested that prokinetics are associated with better improvement in symptoms than in measured gastric emptying.
For patients with chronic, symptomatic GP who are refractory to drug treatment, surgical options may include jejunostomy tube for feeding, gastrotomy tube for stomach decompression and pyloroplasty for gastric emptying. (29;30)

Few small studies (N=10 and N=3) have examined the use of botulinum toxin injections into the pyloric sphincter. (31;32) However, the contribution of excessive pyloric contraction to GP has been insufficiently defined and there have been no controlled studies of this therapy. (21)

Treatment with GES is reversible and may be a less invasive option compared to stomach surgery for the treatment of patients with chronic, drug-refractory nausea and vomiting secondary to GP.

In theory, GES represents an intermediate step between treatment directed at the underlying pathophysiology and the treatment of symptoms. (14) It is based on studies of gastric electrical patterns in GP that have identified the presence of a variety of gastric arrhythmias. Similar to a cardiac pacemaker, it was hypothesized that GES could override the abnormal rhythms, stimulate gastric emptying and eliminate symptoms. (14).

Morbid Obesity

Obesity is defined as a body mass index (BMI) of at last 30 kg/m^2. Morbid obesity is defined as a BMI of at least 40 kg/m^2 or at least 35 kg/m^2 with comorbid conditions. Comorbid conditions associated with obesity include diabetes, hypertension, dyslipidemias, obstructive sleep apnea, weight-related arthropathies, and stress urinary incontinence.

In the United States, the age-adjusted prevalence of extreme obesity (BMI $\geq$ 40 kg/m^2) for adults aged 20 years and older has increased significantly in the population, from 2.9% (1988–1994) to 4.7% (1999–2000). An expert estimated that about 160,000 to 180,000 people are morbidly obese in Ontario (Personal communication, May 2006_)

Treatment For Morbid Obesity

Diet, exercise, and behavioural therapy are used to help people lose weight. Drugs may be used if behavioural interventions fail. However, estimates of efficacy may be confounded by high rates of noncompliance, in part owing to the side-effects of the drugs.

Bariatric surgery for morbid obesity is considered an intervention of last resort for patients who have attempted first-line forms of medical management, such as diet, increased physical activity, behavioural modification, and drugs.

Gastric stimulation has been investigated for the treatment of morbid obesity; the intention being to reduce appetite and induce early satiety, possibly due to inhibitory effects on gastric motility and effects on the central nervous system (CNS) and hormones related to satiety and/or appetite. In animal studies, Chen (33) showed that chronic gastric stimulation impairs the intrinsic gastric myoelectrical activity in the fed state. This is associated with impaired digestion and emptying of the stomach, which may lead to early satiety and reduced food intake. (34;35) GES may also induce gastric distention in the fasting state, which results in activation of stretch receptors causing satiety. It has also been hypothesized that, depending on the stimulation parameters, GES may affect postprandial contractions, leading to reduced food intake. (35;36)

Possible advantages to GES for the treatment of morbid obesity include reversibility of the procedure; less invasiveness than some bariatric procedures e.g., gastric bypass, and fewer side-effects (e.g., dumping syndrome).

Gastric Electrical Stimulation - Treatment Procedure

Patterns of Electrical Stimulation

In general, 3 patterns of electrical stimulation have been studied in the literature.

1. "Low frequency GES" (in the sub Hertz range[4]) – Close to or just above the normal/native gastric slow wave cycle (approximately 3 cycles/min.). This pacing is called *gastric electrical pacing* and uses low-frequency, high-energy, long-duration pulses to induce propagated slow waves that replace the spontaneous ones. (1) This pacing does not release acetylcholine (which in turn does not invoke

[4] One hertz is defined as the reciprocal second. The Hertz (symbol Hz) is the System International unit of frequency.

muscular contractions) because previous administration of atropine[5] does not block the appearance of induced slow waves.

Most studies examining the use of GES for the treatment of morbid obesity use frequencies near this range. (37;38) Under normal circumstances, the gastric slow wave propagates distally and determines the frequency and propagation direction of gastric peristalsis. "Low frequency GES" aims to produce abnormal gastric slow waves that can induce gastric dysrhythmia, disrupt regular propagation of slow waves, cause hypomotility of the stomach, delay gastric emptying, reduce food intake, prolong satiety, and produce weight loss. (37) The positioning and number of electrodes/leads attached to the stomach varies in many studies (e.g., proximal versus distal section of the stomach, 1 or mutiple leads). (39)

Seven studies (40-46) were identified in the literature that examined the use of "low frequency GES" for the treatment of GP. The studies showed that GES propagated slow waves but did not produce muscular contractions. Gastric emptying was shown to be enhanced in 1 published case series (46) which assessed the effect of GES (using 4 electrodes per patient) over a 1 to 3 month period in 9 patients. The case series was not placebo-controlled, not blinded and all 9 patients continued taking cisapride (a prokinetic drug) during the study; metoclopramide was also used by 4 patients. (46) Cisapride was withdrawn from the market by the FDA and Health Canada due to a high rate of potentially fatal cardiac arrhythmias associated with its use.

2. "High frequency GES" (still sub-Hertz range but higher than "low-frequency") – Most clinical studies examining GES for GP have used high-frequency (4 times the intrinsic slow wave frequency, i.e., 12 cycles per minute), low-energy, short-duration pulses. This type of stimulation does not alter gastric muscular contraction (is unaffected by atropine), and has no effect on slow wave dysrhythmias. (1) The mechanism of action is unclear but it is hypothesized that "high-frequency GES" may act on sensory fibers directed to the CNS. (47)

3. "Very high frequency GES" (higher than 5-10 Hertz) – Induces a release of acetylcholine which in turn stimulates muscle cell contraction because previous administration of atropine prevents contraction. (48) This pacing is called *neural gastric electrical stimulation*. (49) An electrical frequency of 1000 times the frequency of the slow wave has been reported in dog studies. (47;49) To date, studies examining "very high frequency GES" have involved animals and have used sequential activation via a series of electrodes around the distal stomach. (48)

No large studies of examining the effect of "very high frequency GES" on patients with chronic, symptomatic refractory GP have been published; the potential for symptomatic benefit is unclear.

In animal studies, there has been investigation into neural gastric electrical stimulation using retrograde peristalsis to delay gastric emptying as a potential treatment for morbid obesity. (50)

The Device

Electrical stimulation is delivered via an implanted system that consists of a neurostimulator and 2 leads. The surgical procedure can be performed via either an open or laparoscopic approach. An external programmer used by the physician can deliver instructions to the GES, i.e., adjust the rate and amplitude of stimulation. GES may be turned off by the physician at any time, or may be removed. The battery life is approximately 4-5 years.

[5] Atropine is a competitive antagonist of the muscarinic acetylcholine receptors. Generally, atropine lowers the "rest and digest" activity of all muscles and glands regulated by the parasympathetic nervous system.

Gastric Electrical Stimulation for Chronic Symptomatic Gastroparesis

For treatment of GP, the GES leads are secured in the muscle of the lower stomach, 10 cm proximal to the pylorus (the opening from the stomach to the intestine), 1 cm apart and connected to an implantable battery-powered neurostimulator, which is placed in a small pocket in the abdominal wall.

Gastric Electrical Stimulation for Morbid Obesity

For treatment of morbid obesity, GES leads are implanted along the lesser curvature of the stomach where the vagal nerve branches spread, approximately 8 cm proximal to the pylorus. (51) However, the implant positioning of the leads has been variably reported in the literature.

Regulatory Status

Canada

The Enterra Therapy System and the Transcend II Implantable Gastric Stimulation System (Medtronic Inc.) are both licensed as class 3 devices by Health Canada (license numbers 60264 and 66948 respectively). The Health Canada indications for use are:

Enterra Therapy System

- "For use in the treatment of chronic intractable (drug-refractory) nausea and vomiting."

Transcend II Implantable Gastric Stimulation System

- "For use in weight reduction for obese adults with a body mass index greater than 35."

United States

In the United States, the Enterra Therapy System is a Humanitarian Use Device (HUD), meaning it is a medical device designated by the FDA for use in the treatment of medical conditions that affect fewer than 4,000 individuals per year.[6] The Enterra Therapy System is indicated for "the treatment of chronic, drug refractory nausea and vomiting secondary to GP of diabetes or idiopathic etiology." (not postsurgical etiologies)

A petition by the Gastroparesis and Dysmotilities Association (52), which represents patients in Canada and the United States, was sent to the FDA in February 2004 to request the transfer of the Enterra Therapy System from a HDE approval status to a premarket approval (PMA).[7] The request was denied by the FDA in November 2004 because "…after a preliminary review of the information…the agency does not believe that your summary of the clinical literature is sufficient or adequately complete to make scientific conclusions regarding the safety and effectiveness of the device in support of PMA approval."[8]

GES for morbid obesity has not been approved by the FDA and is for investigational use only in the United States. (53)

Literature Review on Effectiveness

Objective

- To assess the effectiveness, safety and cost-effectiveness of GES for the treatment of chronic, symptomatic refractory GP.
- To assess the effectiveness, safety and cost-effectiveness of GES for the treatment of morbid obesity.

Methodology

Inclusion criteria:

- English language articles (January 2000 – March 2006).
- Journal articles that report primary data on the effectiveness or cost-effectiveness of GES treatment obtained in a clinical setting, or analysis of primary data maintained in registries or databases.
- Study design and methods must be clearly described.

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[6] The regulation provides for the submission of a humanitarian device exemption (HDE) application, which is similar in both form and content to a premarket approval application (PMA), but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations showing that the device is effective for its intended purpose. The application must however contain sufficient information for the FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of injury or illness from its use.
A HUD may only be used after IRB approval has been obtained for the use of the device for the FDA approved indication.

[7] http://www.fda.gov/ohrms/dockets/dailys/04/feb04/022604/04p-0091-cp00001-vol1.pdf

[8] http://www.fda.gov/ohrms/dockets/dailys/04/nov04/110504/04p-0091-pdn00001-vol1.pdf

- Systematic reviews, randomized controlled trials (RCTs), non-randomized controlled trials and/or cohort studies that have 10 or more patients, cost-effectiveness studies.

Exclusion criteria

- Studies that are duplicate publications (superseded by another publication by the same investigator group, with the same objective and data).
- Studies with less than 10 patients.
- Non-English articles.
- Nonsystematic reviews, letters and editorials.
- Animal and in vitro studies.
- Case reports.
- Studies that do not examine the outcomes of interest.

Literature Search

Details of the search strategy are outlined in Appendix 1.

- Cochrane Library
- International Agency for Health Technology Assessment (INAHTA) database
- EMBASE
- OVID MEDLINE
- MEDLINE In-Process & Other Non-Indexed Citations
- Reference section from reviews and extracted articles

Outcomes of Interest

Gastroparesis

- Symptomatic relief – decreased nausea, vomiting and abdominal pain
- Adverse effects
- Nutritional improvement
- Increased gastric emptying
- Quality of life
- Economics data

Morbid Obesity

- Weight loss
- Resolution/improvement of obesity-related comorbidities
- Quality of life
- Economics analysis data

Strength of Recommendation

The GRADE approach (54)was used to systematically and explicitly make judgments about the quality of evidence and strength of recommendations. GRADE provides a framework for structured reflection and can help to ensure that appropriate judgments are made. GRADE takes into account study design, study quality, consistence and directness in judging the quality of evidence for each outcome. The balance between benefits and harms, quality of evidence, applicability and the certainty of the baseline risks are all considered in judgments about the strength of recommendations.

Results of Literature Search

The Cochrane and INAHTA databases yielded 4 health technology assessments on GES. A search of Medline and Embase since the last assessment was conducted, which yielded119 citations, of which 15 met the inclusion criteria. The quality of the studies for GES treatment of: 1) GP and 2) morbid obesity is presented below (Table 1).

Table 1. Quality of Evidence

Study Design	Level of Evidence	Number of Eligible Studies: Gastroparesis	Number of Eligible Studies: Morbid Obesity
Large randomized controlled trial, systematic reviews of RCTs	1		
Large randomized controlled trial unpublished but reported to an international scientific meeting	1(g)		
Small randomized controlled trial	2	1	
Small randomized controlled trial unpublished but reported to an international scientific meeting	2(g)		1
Nonrandomized study with contemporaneous controls	3a	1	
Nonrandomized study with historical controls	3b		
Nonrandomized study presented at international conference	3(g)		
Surveillance (database or register)	4a		
Case series (multi-site)	4b	2	3
Case series (single site)	4c	4	
Retrospective review, modeling	4d	3	
Case series presented at international conference	4(g)		

g=grey literature

Gastric Electrical Stimulation for Gastroparesis: Study with the Highest Level of Evidence

The following is a detailed analysis of the study with the highest level of evidence identified by the literature search (Level 2 evidence).

Abell et al. (55) studied 33 patients (17 diabetes and 16 idiopathic) with GP that were unresponsive to standard medical therapy. The 12-month study was conducted in 2 phases. Phase 1 was a 2-month, randomized, placebo-controlled, double-blind crossover study, and Phase 2 was a 10-month open-label study. Patients were evaluated at baseline and at 4 follow-up visits at 1, 2, 6, and 12 months. This is the same study that was presented to the FDA for HDE approval in 1999 (Appendix 2).

Inclusion criteria consisted of:
More than 7 episodes of vomiting per week.
Delayed gastric emptying (>60% retention at 2 hours and >10% at 4 hours on the basis of a standardized

scintigraphic method for solid meals).
Symptoms consistent with GP for longer than 12 months.
Refractoriness or intolerance to 2 of 3 classes of prokinetic drugs and 2 of 3 classes of antiemetics.

Exclusion criteria consisted of:
Documented intestinal pseudo obstruction.
Prior gastric surgery.
Vagotomy.
Organ transplantation.
Seizures.
Primary swallowing disorders.
Chemical dependency.
Pregnancy.
Psychogenic vomiting.
Medical unstable or at high surgical risk.

Phase 1

Patients were randomized to stimulation either ON or OFF, and after the first month, the GES was programmed to the opposite mode for another month. The primary outcome measure was the difference in vomiting frequency with the stimulation OFF compared with ON. To monitor vomiting frequency, patients recorded daily vomiting episodes in either 2-week (idiopathic) or 4-week (diabetes) diaries before baseline and at each follow-up visit (because "diabetes symptoms fluctuate more"); the authors did not provide any evidence to support this statement. The secondary end point was the patients' preference for stimulation ON or OFF; at the end of the second month, while still blinded, patients were asked for their preference (month 1 or month 2) as a global measure of quality of life in Phase 1.

Phase 2

All the patients' GES were programmed to ON. The subjective severity of upper GI tract symptoms (vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain) at baseline and each follow-up visit (1, 2, 6, and 12 months) was assessed by using a 5-point symptom interview questionnaire in which symptoms were rated by the study coordinator. The sum of the severity ratings of the 6 symptoms was used as an overall total symptom score (TSS). For Phase 2, the primary outcome measures were the changes between baseline and the 6- and 12-month follow-up visits for weekly vomiting frequency, symptom severity, gastric emptying, and health-related quality of life (HQOL).

Gastric emptying was not an end point that was assessed during the randomized Phase 1 study. Gastric emptying was quantified after a solid meal at baseline and at the 6- and 12-month follow-up visits by using a standardized scintigraphy method and a low-fat test meal. According to the authors, this method was developed specifically for this study to standardize the measurement of solid food emptying over 4 hours. Patients were asked to discontinue prokinetic medication 2 to 3 days before the test.

HQOL was assessed at baseline, and at the 1-, 2-, 6- and 12-month follow-up visits by using the SF-36 Health Status Survey questionnaire. Two summary scores, the Physical Composite Score (PCS) and the Mental Composite Score (MCS), in addition to 8 subscores, were derived from the SF-36.

Patients were instructed to continue their current antiemetic or prokinetic therapy during the 12-month study.

A sample size calculation was not reported by the authors. Abell et al. (55) stated that

"The initial study plan provided for an enrollment of 40 diabetes and 40 idiopathic patients. Because of slow recruitment, the sponsor stopped the study after enrollment of 33 patients in total. These 33 patients were randomized to Phase 1, continued to Phase 2 and form the basis of this report."

Patient Enrollment

Sixty-three patients were screened for the study. Of these,
- 5 vomited before completing the gastric emptying test
- 20 did not meet the gastric emptying requirements
- 1 had a history of seizures
- 3 were unstable or at high surgical risk
- 1 did not meet the etiology requirement.

Phase 1 data were analyzed on an intent-to-treat (ITT) basis. The 33 patients continued into Phase 2 and between the 2nd and 6th month, 1 patient dropped out because of lead perforation of the stomach, 2 were lost to follow-up and 1 was too ill to complete the 6 month follow-up visit. Of the 29 patients eligible for the 6- month follow-up, diary data were unavailable for 2 and gastric emptying data were incomplete for 3 (1 patient refused and 2 patients vomited after the test meal).

Five of the 29 patients did not complete the 12-month follow-up: 1 was pregnant, 2 had infection at the implant site, 1 died of cardiopulmonary arrest, and 1 was lost to follow-up. Therefore, 24 patients were eligible for the 12-month follow-up. Of the 24 patients, 2 and 4 hour gastric emptying data were not reported for 5 patients (1 had illness unrelated to GP or GES; 1 refused the test, 2 completed their tests more than 2 months later than scheduled, and 1 had unavailable 4 hour gastric emptying data (due to vomiting during the test).

Phase 2 data were analyzed on a treatment-received basis.

Results

Baseline

The median weekly vomiting frequency at baseline was 17.3 (11.8-45.7) episodes per week. Most patients received antiemetic (n=25) or prokinetic (n=28) therapy, and 14 required some form of enteral or parenteral feeding.

Phase 1

The results after 1 month from Phase 1 showed a statistically significant decrease in vomiting frequency and preference for stimulation ON (Table 2). When patient subgroups were examined separately, there were no significant differences in vomiting frequency in both the diabetes and idiopathic subgroups, and no significant difference in ON or OFF preference in the diabetes subgroup. The study was not designed to show a difference between ON and OFF within the patient subgroups

Table 2: Results of Phase 1.

Outcome†	All patients (N=33)		Diabetes patients (n=17)		Idiopathic patients (n=16)	
	OFF	ON	OFF	ON	OFF	ON
Weekly vomiting frequency Median (interquartile range)	13.5 (5.5-25.4)	6.8 (3.9-16.5)*	12.8 (5.5-24.2)	6.0 (3.0-14.8)	13.8 (5.4-27.8)	12.8 (4.0-20.3)
Total symptom score Mean (standard error)	13.9 ± 1.1	12.5 ± 1.0	13.2 ± 1.7	11.3 ± 1.5	14.8 ± 1.3	13.8 ± 1.4
Patient preference†	7	21*	4	10	3	11*

* $P<0.05$.
† Patient preference is the number of patients who preferred ON or OFF before the blind was broken in Phase 1; 3 diabetes and 2 idiopathic patients expressed no preference.

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For the combined group, there were no statistically significant differences for the symptom severity scores, TSS, 5 of the 8 SF-36 subscores, and the 2 composite summary scores (PCS and MCS) (despite a 50% reduction in weekly vomiting frequency). Specific statistics were not reported by the authors.

Gastric emptying was not reported as an end point for the randomized, sham-controlled Phase 1 trial.

Phase 2 (Open label, not sham-controlled)

Vomiting frequency at the 6- (n=27) and 12- (n=24) month follow-up visits significantly decreased when compared with baseline ($P<0.05$). TSS significantly improved ($P<0.05$) at 6 and 12 months compared with baseline for the combined group and for both etiologies.

Mean PCS and MCS scores were significantly improved for the combined group at 6 (n= 29) and 12 (n=24) months compared to baseline values ($P<0.025$).

Baseline 2-hour gastric retention of an isotope-labeled meal was 78% for the combined group and this decreased significantly ($P<0.05$) to 65% at 6 months and 56% at 12 months. Baseline 4-hour gastric retention of an isotope-labeled meal was 34% for the combined group and this decreased significantly ($P<0.05$) to 22% at 12 months (Table 3).

Table 3: Phase 2 Results* - Gastric Emptying Time (GET).

	Baseline			All Patients		Diabetes		Idiopathic	
GET	All N=33	Diabetes n=17	Idiopathic n=16	6 mos n=26	12 mos n=20	6 mos n=11	12 mos n=9	6 mos n=15	12 mos n=11
2 hour	78 (67 to 84)	80 (69 to 88)	77 (64 to 79)	65 (53 to 80)†	56 (45 to 74)†	67 (50 to 79)	46 (29 to 61)	62 (54 to 80)	59 (52 to 77)
4 hour	34 (26 to 57)	46 (28 to 68)	28 (25 to 38)	27 (14 to 54)	22 (11 to 37)†	44 (21 to 67)	16 (1 to 30)†	20 (11 to 46)	23 (17 to 49)

*GET (% retention) is reported as median and interquartile range.
† $P<0.05$

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There was no reported correlation between baseline vomiting frequency and gastric emptying at 2 or 4 hours (r=0.03 and r=0.02, respectively). There was no reported 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) or between baseline and 12 months (r=-0.04 and r=0.10) (no *P* values reported).

Five patients had the GES explanted or revised due to infection or other complications.

Overall, there is low quality Level 2 evidence of the short-term effectiveness of GES for the reduction of weekly vomiting episodes compared to placebo for patients with severe refractory GP due to diabetes or idiopathic causes.

Limitations to the study were:

- The results reported by Abell et al. (55) are different from the results reported by Abell et al. to the FDA (Table 4 and Appendix 2). AHFMR contacted Abell, who stated that data from the study were "reanalyzed from a different perspective for diabetes and idiopathic patients, during the same 2-week interval using the outcome measures of quality of life and patient preference data as a starting point for the analysis". (10) Quality of life and patient preference are subjective qualitative data, compared to objective data such as gastric emptying.

Table 4: Comparison of data from Worldwide Antivomiting Electrical Stimulation Study: FDA Submission Compared to Published Article*

WAVESS Data	Vomiting Episodes per Week (diaries) (N=33)	Baseline	ON	OFF
Submitted to FDA (1999)	Median	26.3	12.0 *	14.0 *
	Mean (SD)	47.6 (52.6)	23.0 (35.5) *	29.0 (38.2) *
Published in Journal (2003)	Median (interquartile range)	17.3 (11.8-45.7)	6.8 (3.9-16.5) * †	13.5 (5.5-25.4)
	Mean (SD)	NR	NR	NR

*NR refers to not reported; SD, standard deviation, WAVESS, Worldwide Antivomiting Electrical Stimulation Study.

Interquartile range not reported for FDA data
* *P*<0.05 versus baseline
† *P*<0.05 for "ON" versus "OFF"

- Jones (56) submitted a letter to the journal that accepted the study by Abell et al. (55) requesting clarification to what appeared to be a change in a primary study end point. Abell et al. (56) provided the following explanation.

Food and Drug Administration Report in 1999

Vomiting frequency, derived from the patient diary records, was calculated differently for idiopathic and diabetes patients. For idiopathic patients, vomiting frequency was the total number of vomiting episodes recorded divided by the number of weeks in the diary period (2 weeks), yielding a "normal average" vomiting frequency. For diabetes patients, weekly vomiting frequency was defined differently as the number of episodes in a 7-day window within the 4-week diary period, in which the number of episodes was the maximum for that diary period. The diabetes diary period was 4 weeks because Abell et al. felt that vomiting symptoms fluctuate more in diabetes patients than idiopathic patients (no evidence for this reported) "and therefore the worst week of the diary period was most representative of the patients overall symptoms."

Published Journal Article in 2003

For consistency, the authors analyzed vomiting frequency for both etiologies in the same way. Therefore, for diabetes patients, the "normal average" was calculated over the 4-week diary period. The analysis for idiopathic vomiting frequency was unchanged, i.e. the "normal average" over a 2-week period. The change in vomiting frequency for the diabetes patients did not affect the statistical significance of ON versus OFF or the baseline versus 6- or 12- month follow-up for the diabetes patient subgroup. However, it did affect the statistical significance of ON versus OFF for the combined patient group.

- Confounders related to diabetes (unknown status of glycemic index, renal insufficiency and antidiabetes drugs in the diabetes patients).
- The published journal article by Abell et al. reported a post hoc change in the primary end point analysis.
- It is unclear why the idiopathic group did not have their vomiting frequency calculated over a 4-week period similar to the diabetes patients.
- No evidence is provided that demonstrates that vomiting symptoms fluctuate more in diabetes patients than idiopathic patients.
- Possible placebo effect.
- Possible type 2 error.
- The interval between implantation and device programming was very short. The authors stated that there was "prolonged postoperative use of pain medication that may have interfered with gut motility during phase 1". Gastric emptying time (GET) was not measured during phase 1.
- The authors commented that the duration of phase 1 may not have been sufficiently long enough for improvements in symptoms for GI function for all patients. A longer interval of 1-3 months was suggested.
- Subjective primary end point.
- Concurrent prokinetic and antiemetic therapy in some patients. It is unclear why (and how many) patients continued on drug therapy if all patients were treatment-resistant upon entry to the study.
- No sample size calculation or justification.

Studies of lesser quality than Abell et al. (less than Level 2 evidence) were also identified in the literature search (detailed analyses of the case series is in Appendix 3).

Overall limitations to the case series included:

- Small sample sizes; no sample size calculation/justification.
- Not placebo-controlled
- Subjective nausea, vomiting and TSS severity scores that were self-reported by the patient.
- Concurrent prokinetic/antiemetic therapy.
- Large number of patients lost to follow-up.
- Numerous inter-and intra-subanalyses and statistical comparisons that the study was never designed to test.
- Patient overlap with Worldwide Antivomiting Electrical Stimulation Study (WAVESS); reanalysis of data from selected patients included in previous studies.
- Unclear what baseline values were used to calculate some follow-up results.
- In the GEMS study, the OFF 6-month results suggest a placebo response.
- It is unclear why some patients continued on drug therapy if they had treatment-resistant GP.
- Unclear reporting of data.

Gastric Electrical Stimulation for Gastroparesis: International Health Technology Assessments

Alberta Heritage Foundation for Medical Research , January 2006

The AHFMR systematically reviewed the literature on GES for the treatment of GP from 2000 to November 2005. (10) The following is a commentary from the AHFMR report. (10)

The literature search found:

1. 1 two-month multicentre, crossover, blinded, randomized placebo-controlled study
2. 1 comparative prospective study that compared GES with medication
3. 8 case series

Appendix 4 summarizes the studies included in the AHFMR report.

Four of the 10 studies (the comparative prospective study and 3 case series) reported results from patients who were previously presented in past publications. This potentially overestimates the benefit of the device. AHFMR stated that the studies were generally of weak methodologic design. Results on long-term follow-up were not available from all patients initially included in the studies.

The AHFMR made the following conclusions.

- GES is used more often for symptom control rather than treatment of the motility disorder.
- Based on an average of 12 months of follow-up on the safety and efficacy of GES for patients with idiopathic GP, GP associated with diabetes or GP due to gastric surgery, the current evidence is <u>not</u> adequate to support the routine use of this procedure. There appears 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 would, however, be considered a last resort treatment after all conventional treatments had failed to control symptoms of nausea and vomiting." (10) "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." (10)
- Since possible risks associated with the implantation of the device, including the risk of infection that would require the removal of the GES in 5-10% of cases, implantation should be provided by trained professionals, and use of GES should be restricted to patients who have severe symptoms and are refractory to another less invasive approach such as drugs and diet.
- A continuous follow-up of the patients is necessary to identify adverse events and effects, assess costs, and study quality of life.
- After further research is conducted, this technology should be reviewed again to determine if the cumulative research adds to the knowledge of efficacy/effectiveness.

The AHFMR noted the following limitations to the studies in their HTA. (10)

1. The manufacturer of the GES device for GP supported all of the studies.
2. Six studies reported concomitant drug therapy. It is difficult to determine if any changes were attributable to GES alone.
3. The results reported by Abell et al. (55) are different from the results reported by Abell et al. to the FDA.

AHFMR stated that GES for the treatment of GP has been implanted in 12 patients in Canada (5 in Quebec, 5 in Ontario, and 2 in British Columbia), some of whom were part of the multicentre trials. (10)

National Institute for Clinical Excellence: Interventional Procedures Programme, September 2003

National Institute for Clinical Excellence (NICE) conducted a systematic review that consisted of a rapid overview of the literature and specialist opinion. (30) The following is a commentary of the evidence as assessed by NICE.

Efficacy

The evidence on efficacy is based on the results for a small number of patients in primarily uncontrolled studies. These studies suggested that the frequency of vomiting was improved during stimulation and fewer patients required nutritional support following the procedure. Improvement in symptoms was not always correlated with improved gastric emptying.

Limitations to the studies were:

- Self-reported measures of symptom relief.
- Lack of a comparative group in the majority of the studies.
- The Specialist Advisors expressed uncertainties regarding whether the procedure benefits patients solely by altering symptoms rather than accelerating gastric emptying.

Safety

Data collected on patients from 2 multicentre trials reported that 27% (14/51) of patients experienced pain and 22% (11/51) of patients experienced device- or implant-related adverse events including infection (n=2), device erosion (n=1), device migration (n=1) and stomach wall perforation (n=1). The complications required removal of the device in 8% (4/51) of patients.

The Specialist Advisors did not have any particular safety concerns relating to GES.

The manufacturer of the device stated that patients may not be treated with any type of diathermy because the energy can be transferred through the implanted system, causing tissue damage and can potentially result in severe injury or death.

Comments

- Gastric emptying was not considered a primary outcome despite delayed gastric emptying being a requirement for participation in the studies.
- Only a percentage of patients were considered evaluable for the end point of gastric emptying. It is unclear whether this has now been dismissed as an end point to study in these patients. What is the most appropriate primary end point for GES for the treatment of gastroparesis?
- Many patients continued to receive medication, despite undergoing GES. It is difficult to distinguish how GES by itself affected patient outcomes.
- It is unclear to what extent the same patients were included in multiple reports.
- Heterogenous groups of patients. It is unknown whether the underlying cause of GP influences efficacy outcomes (diabetes versus idiopathic versus postsurgical patients).
- Heterogenous procedure parameters. It is unclear what impact this may have on efficacy considering that the mechanism of action is unknown.

- The majority of outcomes (symptom scores) were based on self-reports (diary entries on the frequency of vomiting) or obtained at follow-up visits by the investigators.
- Many of the studies did not use validated measures to assess outcomes.
- There was 1 study that attempted to blind patients to stimulation. It is possible that patients experienced a placebo response with this procedure.
- The studies report on a small number of patients and although 12-month data is reported, it is not available for all patients assessed in these studies.
- In general the reports were not well written.
- There are discrepancies in the WAVESS study results presented to the FDA and subsequent publication/reanalysis of the results.
- A United Kingdom registry exists that is currently maintained by the manufacturer. It is anticipated that the data will be transferred to a European registry to collect and analyze data. (57)

Jones and Maganti: Systematic Review of Surgical Therapy for Gastroparesis, October 2003

Jones and Maganti (1) systematically reviewed the literature between 1966 to 2001, to identify all English-language literature regarding surgical interventions in GP (gastric pacing/stimulation, gastrostomy, jejunostomy, gastrectomy and surgical drainage procedures in patients with diabetes, idiopathic or postsurgical GP). Inclusion criteria consisted of human patients and surgical series or trials.

Seventeen articles met the inclusion criteria. These included studies reporting on gastrostomy (n=2), jejunostomy (n=3), gastric stimulation (n=2), and gastrectomy for postsurgical (n=6), diabetes (n=3), and idiopathic (n=1) GP. According to Jones and Maganti, all the studies were unblinded, uncontrolled case series or retrospective reviews. Methodologic differences between the studies did not allow the authors to do a pooled analysis.

For GES, Jones and Maganti concluded that the device improves symptoms of nausea and vomiting, but therapeutic gain beyond placebo has not been demonstrated.

Gastric Electrical Stimulation for Gastroparesis Trials Underway or Unpublished

In January 2006, AHFMR reported that at least 2 RCTs on GES are ongoing and expected to be finalized and the results released in 2006. (10) These trials consist of "a randomized multicentre withdrawal study and a randomized study of temporary stimulation." (10)

The ClinicalTrials.org website listed the following trial related to GES for the treatment of refractory GP.

Enterra Therapy Clinical Study (Gastric Stimulation for Gastroparesis)

The study design is reported to be randomized, double blind, active control, crossover assignment. (58)

The purpose of the study (which started in June 2002) is to evaluate the safety and effectiveness of gastric stimulation in the reduction of nausea and vomiting in patients with GP using an approved Humanitarian Device. (58) Eighty to 100 patients from up to 10 centres in the United States will be followed for 12 months and then once a year after that until the study closes. (58) The study duration was not reported.

The primary outcome is the reduction in frequency of weekly vomiting episodes. (58)

GES for Morbid Obesity: Study with the Highest Level of Evidence

The following is a detailed analysis of the study with the highest level of evidence identified by the

literature search (Level 2 evidence).

Shikora (59) reviewed the O-01 Trial of GES for the treatment of morbid obesity from the United States (a tabular summary of the O-01 Trial is in Appendix 5). To date, full results from the trial have not been published. (60)

O-01 Trial

This was a multicentre (10 sites), randomized double-blinded placebo-controlled trial (N=103). Inclusion criteria consisted of morbidly obese patients. Exclusion criteria consisted of patients with prior gastrointestinal or bariatric surgery or GI diseases.

Midway through the study it was found that a number of the leads were completely or partially dislodged from the stomach wall (17 of the first 41 patients). These patients underwent a repeat operation in order to secure all leads in place with sutures, metal clips or both.

One month after insertion, patients were randomized to either the treatment group (ON) or the control group (OFF). The primary end point was the percentage change in weight from baseline after 6 months of stimulation. After the 6-month period, patients in the control group had the devices activated and all 103 patients were followed for the remainder of the investigation. Throughout the study, no dietary or behavioural advice or counseling were provided to the patients.

The patient population consisted of 87 women (85%) and 16 men (15%). The mean age was 40 years (range 23-54), mean baseline weight was 129 kg (range 84.5-183) and mean BMI 46 kg/m2 (range 38-56 kg/m2). There were no major complications or mortalities and most patients were discharged from hospital on the day after surgery.

There was no statistically significant difference in weight loss between the study and control groups at the end of the 6-month randomization period. The excess weight loss (EWL) was 1.3% for the ON group and 2.4% for the OFF group. At 12 months postimplantation, the EWL was 2.5%. In general, the EWL that occurred with GES is less than that obtained with other bariatric procedures (up to 80% EWL).

At 29 months, 34 of the 103 patients remained in the trial; the overall mean EWL was 20%.

Gastric luminal penetrations and lead dislodgements occurred with a high frequency early in the trial but decreased later as the technique became more familiar to the surgeons. Penetration of the stomach wall occurred during lead implantation in 20 patients.

Lead dislodgement (n=20; 12 complete and 8 partial) was a problem during the first half of the study. With change in the surgical technique, 3 additional leads in the next 62 patients were discovered to be dislodged.

Limitations to the O-01 Trial were:
- Large dropout rate.
- Lead placement was initially inadequate.
- Many patients confessed to overeating to see if they could determine whether they were in the ON or OFF group.
- No sample size calculation or justification reported in the paper. Small sample size could have produced a type 2 error.

Studies with a lower level of evidence than the O-01 Trial are summarized in Appendix 5 and 6. Overall

comments about these studies include:

- Small sample size; no sample size calculation/justification. Small sample size could have produced a type 2 error.
- GES produced less weight loss than other bariatric surgery procedures (20% versus up to 80%).
- Variable programming of the GES device during the trials.
- Lack of details regarding resolution/improvement of comorbidities.
- Numerous subanalyses.
- Unclear details about patient dropouts.

GES for Morbid Obesity: International Health Technology Assessments

Swedish Council of Technology Assessment in Healthcare, March 2004

The Swedish Council of Technology Assessment in Healthcare (SBU) reviewed GES for the treatment of morbid obesity, however only a summary of the report is available in English. (61) SBU noted that gastric pacing has been marketed in some countries for patients with a BMI of 30 kg/m^2 or more (not necessarily patients who are considered morbidly obese).

At the time the SBU report was written, no RCTs had been conducted. The literature search of GES for the treatment of morbid obesity consisted of a few small uncontrolled studies. The most frequent adverse effect in the studies was electrode dislodgement from the stomach wall. Another adverse effect noted in the studies was perforation of the gastric mucosa. This was reported in 3 studies at rates of 10%, 15% and 32%. No deaths were reported in connection with GES.

Preliminary results from a Swedish study of 10 patients indicated that weight loss after 6 months was the same regardless of whether or not the pulse generator had been activated.

No economic assessments of GES for the treatment of morbid obesity were identified in the literature.

The batteries for the device were estimated to have a lifespan of 2 to 4 years.

Overall, SBU made the following conclusions.

1. There is insufficient scientific evidence on the short-term patient benefit of gastric pacing.
2. There is no scientific evidence on the long-term patient benefit of gastric pacing.
3. No scientific evidence is available on the cost-effectiveness of the treatment.

Gastric Electrical Stimulation for Morbid Obesity Trials Underway or Unpublished

The ClinicalTrials.org website listed the following trial related to the treatment of morbid obesity with GES.

Screened Health Assessment and Pacer Evaluation (SHAPE)

The purpose of this double-blind, multicentre RCT was to evaluate the efficacy and safety of a GES system in 150 patients with a BMI between 35 and 55 kg/m2. (62) The primary outcome was the %EWL from baseline after 12 months from randomization.

On December 8 2005, the manufacturer announced that the preliminary results of SHAPE did not meet the efficacy end point of a difference in mean EWL at one year. (63) The trial was initiated in May 2004.

The manufacturer believes that SHAPE was "affected by factors including variances in trial execution and unplanned treatment changes." (63)

Appetite Suppression Induced by Stimulation Trial (ASSIST)

ASSIST is a feasibility trial designed to assess the safety and efficacy of GES for the treatment of obesity in patients with type 2 diabetes. (64) The trial is taking place in a small number of select centres in the United States; the first implant occurred June 7, 2005. The investigators are determining "if type 2 diabetes patients with concomitant obesity who receive GES have a minimum mean EWL greater than a control group." (64)

GRADE Quality of the Evidence

The quality of the trials was examined according to the GRADE Working Group criteria (54) (Tables 5 and 6).

Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.

Consistency refers to the similarity of estimates of effect across studies. If there is important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect and the significance of the differences guide the decision about whether important inconsistency exists.

Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions were used in grading the quality of the evidence.

High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Table 5: GRADE Quality of Studies – Gastroparesis

Outcome	Design	Quality	Consistency	Directness	Overall Quality
Reduced vomiting & nausea (1° endpoint)	RCT (Abell et al. 2003) Case Series	Low *Why?* *1. Confounders related to diabetes.* *2. Possible Type 2 error for subgroup analyses.* *3. Subjective self-reported endpoint.* *4. Posthoc change in primary endpoint analysis.* *5. No sample size justification.* *6. Concomitant prokinetic/antiemetic therapy.* Same as above.	Some uncertainty. *Why?* *2. Only 1 RCT (with different results for FDA and publication).*	Some uncertainty. *Why?* *1. GES originally hypothesized to correct gastric rhythms, stimulate gastric emptying and therefore eliminate symptoms.* *2. Now hypothesized to directly act on neurons to the CNS to control symptoms.* *3. Weak correlation between symptoms and gastric emptying.* 4. *Unclear whether gastric emptying is still considered an endpoint to investigate.*	Low
Improved gastric emptying (2° end point)	Open label portion of Abell et al. 2003 & Case series	Low *Why?* *Same limitations as above.* *Not a 1° end point.* *No intent-to-treat analysis.*	Wide variation in improvement. Same uncertainties as above.	Same uncertainties as above.	Low/Very Low

Table 6: GRADE Quality of Studies – Morbid Obesity

Outcome	Design	Quality	Consistency	Directness	Overall Quality
Weight Loss	RCT "O-01 Trial" According to Shikora (2004), considered "update of ongoing clinical trials". Case series	Low *Why?* *1. No sample size calculation.* *2. Small sample size.* *3. No ITT analysis.* *4. Lack of detail regarding dropouts.* *5. Possible Type 2 error.* *6. Sparse details about randomization/blinding.* *7. Full, final results not published.* Same as above.	Some uncertainty. *Why?* *1. Only 1 RCT (technically grey literature).*	Generally direct (%EWL).	Very Low
Resolution of Comorbidities	Case series	Same as above	? Scanty data	? Scanty data	Very Low

Economic Analysis

Literature Review

No formal economic analysis was identified in the literature search.

Cutts et al. (65) prospectively studied the effect of GES on 18 patients (n=9 for GES and n=9 for drug therapy [MED]) with refractory GP. The 9 patients (1 diabetes GP and 1 idiopathic GP) who received GES were already reported in the WAVESS and Compassionate Use Study ("…as part of 2 FDA trials for GES"). (65) The outcomes for the study were symptoms, resource utility and costs. All patients were refractory to a least 2 classes of available prokinetic and antiemetic drugs. No sample size calculation or justification was provided by the authors.

The 9 patients receiving MED (1 diabetes GP and 1 idiopathic GP) were treated with antiemetic, prokinetic and other medications. All nine of the MED patients had been offered GES but had either declined it or did not have medical coverage to pay for the device.

The average symptom duration for the GES patients was 86.7$\pm$27.6 months while MED patients had an average symptom duration of 33.3$\pm$9.28 months.

TSS was the sum of each patient's self-assessment of abdominal bloating/distention, early satiety, abdominal pain, nausea, and vomiting.

Patients' health care resource usage, the authors calculated an investigator-derived independent outcome measure score (IDIOMS), previously known as a diagnostic and predictive score (ADAPS). IDIOMS is a global health related QoL measure.

Patients' health care cost was calculated by totaling all hospital charges for hospitalization, medication, nutrition, and outpatient services (including hospital surgical expenses and the cost of the GES device and surgical implantation) for 3 follow-up years. The study period costs were compared to costs incurred during the 1 year prior to GES.

During the study period, 3 patients in the MED group died (1 at home, 2? in the hospital) of intravenous access complications. No patients in the GES group died during the 3-year period.

Total Symptom Score

Prior to treatment, the GES and MED groups were not significantly different for the TSS (37.9+2.73 and 39.3+2.8 respectively). Overall, TSS for the GES group was significantly better than overall TSS for the MED group, $P < 0.017$.

Investigator-Derived Independent Outcome Measure Score

Prior to treatment, between-group comparison indicated that GES and MED groups were not significantly different with respect to IDIOMS (12.6+1.6 versus 11.0+0.71 respectively). With treatment, between-group comparison indicated that overall IDIOMS for the GES group was significantly better than overall IDIOMS for the MED group ($P < 0.017$).

Annual Healthcare Costs

Prior to treatment, GES and MED groups were not significantly different with respect to annual healthcare costs ($83,700 US ±27,000 versus $80,000 US ±26,700 respectively). With treatment, between- group comparison indicated that overall health care costs for the GES group declined over time (P <0.001) but not for the MED group (P =0.19).

Limitations to the study by Cutts et al. included:

- Very small sample size, which contains a subset of patients who were included in previous studies submitted to the FDA (WAVESS and Compassionate Use Study).
- The authors acknowledge that "this report is a preliminary study of a relatively small group of gastroparetic patients studied intensively in one center…".
- There may have been a difference in the socioeconomic status of the patients who received GES compared to MED. All the MED patients had been offered GES but had either declined it or did not have medical coverage to pay for the device.
- Higher mortality rate in the MED group.
- All patients in the study were reported to have been drug-refractory.
- No sample size calculation/discussion.
- The authors acknowledge that "IDIOMS is not standardized and requires extensive further evaluation to establish its psychometric properties versus other practitioner ratings and standardized measures of health related QoL."

Lin et al. (66) evaluated the daily use of prokinetics and antiemetics, hospitalizations, TSS for severity, SF-36 status for health related QoL and gastric emptying in 37 GP patients preoperatively and 1 year after undergoing GES implantation. All patients were previously included in studies submitted to the FDA: 8 patients were part of the WAVESS study and 29 were part of the CUESS study. The etiology of GP was insulin-dependent diabetes in 24 patients, idiopathic in 8 patients and postsurgical in 5 patients.

During the follow-up, patients were instructed to remain on a diet of small meals, low fat and low fibre. Other medications including antihypertensive drugs, diuretics, lipid lowering agents, nonsteroidal antiinflammatory drugs, antidepressants, insulin and laxatives, were not specifically changed and also were managed by other caregivers.

The mean (standard error of the mean [SEM]) number of prokinetic and antiemetic drugs used daily was significantly reduced at 1 year compared to baseline: 1.0(0.1) versus 0.6(0.1) and 1.2(0.2) versus 0.8(0.2), respectively (P<0.05).

Overall, TSS, nausea and vomiting scores were significantly reduced in patients continuing on medications and in patients off prokinetics or antiemetics at 1 year (P<0.05 compared to baseline). Patients off prokinetics had a significantly lower TSS at 1 year of GES than patients on prokinetics (P<0.05).

SF-36 scores for QoL were significantly improved in patients on both drugs (n=9) and off or reducing drug use (n=11) after1 year of GES (P<0.05).

Of the 37 patients, 20 patients were receiving nutritional support by either enteral feeding tubes or total parenteral nutrition (TPN) at baseline. At 12 months, the number of patients requiring some supplemental enteral tube feeding decreased from 19 to 7 (P<0.05) and no patient was receiving TPN.

For the year before GES therapy, patients spent an average (SEM) of 50(10) days (range 0 to 220) in hospital. Within 1 year of GES, hospitalizations decreased to 14 (3) days (range 0 to 69 days). The

authors reported that the major reason for hospitalization before GES was nausea and vomiting due to GP. After GES implantation, the reasons for hospitalization were glucose control in diabetes, recurrence of nausea and vomiting, feeding tube complications and concern about infection or injury at the pulse generator site (number of patients for each hospitalization not reported). Three patients (8%) had their GES removed at 3-, 10-, and 12-months postsurgery because of pocket infections.

Overall, GES did not significantly improve gastric emptying. The mean (SEM) gastric retention at 4 hours was 49.4% (5.1%) at baseline compared to 42.1% (5.9%) at 1 year (no *P* value reported). Eight patients (22%) had normalized gastric emptying at 1 year, however, 13 patients (35%) had more gastric retention than at baseline.

Limitations to the study by Lin et al. were:

- Reanalysis of the same set of patients reported in previous studies.
- Numerous inter- and intra-subanalyses and statistical comparisons that the study was never designed to test.
- Small sample size.
- Concurrent prokinetic/antiemetic therapy; it is unclear if the patients had treatment-resistant GP.
- The subjective nausea, vomiting and TSS severity scores were self-reported by the patient.

In 2006 Lin et al. (67) reported long-term outcomes in 55 (39 insulin dependent diabetes, 9 idiopathic, 7 postsurgical) patients with refractory GP. TSS, nutritional status, weight, hospitalizations , use of prokinetic and antiemetic drugs, glycosylated hemoglobin level (HbA1c, a blood test to determine if diabetes is under control) in patients with diabetes and adverse effects were evaluated at baseline, 1 year, and 3 years using an ITT and a per protocol analysis. Details regarding the diabetes patients (e.g., glycemic control, renal insufficiency, use of antidiabetes medication) were not reported.

The patients evaluated by Lin et al. (67) include the same patients that were involved with the WAVESS study. The authors stated "After the WAVESS study, we broadened the inclusion criteria to include patients with GP secondary to gastric surgery, specifically related to partial gastric resection, vagotomy or vagal nerve damage." (67) The inclusion criteria were the same as previously reported in WAVESS.

Each patient completed a symptom interview form with a 5-point categorical scale (0-4) which subjectively assessed the severity and frequency of 7 symptoms during the last 2 weeks before the interview: vomiting, nauseas, early satiety, bloating, postprandial fullness, epigastric pain, and burning. The sum of the severity and frequency ratings for each symptom subscore comprised the overall TSS for severity and frequency respectively.

For the ITT analysis, missing data were imputed by the authors as the last observation carried forward, the patient's baseline value, the maximum value of all participants in each visit, and the mean value of all participants in each visit.

Overall, 42 patients completed the 1-year follow-up and 37 patients completed the 3-year follow-up. Twenty-seven and 15 diabetes patients had HbA1c results available at 1 and 3 years respectively.

Of the 55 patients, 10 died of non-GES- related complications, 6 had the devices explanted, and 2 patients were lost to follow-up. The remaining 37 patients had the device activated for a mean of 45 months.

In comparison with baseline, TSS and 6 of the 7 symptom subscores (except for epigastric burning) were significantly reduced both in severity and in frequency at 1 year of GES, and were maintained beyond 3 years based on per protocol and ITT analysis. Both per-protocol and ITT analysis showed that hospitalizations days and the use of drugs (prokinetics and antiemetics) were all significantly reduced at 1

year and sustained at 3 years (P<0.05). The mean HbA1c levels in diabetes patients at 1 year (~8.8%) and 3 years (~8.6%) follow-up were significantly reduced compared to the baseline level (9.5%) using intent-to-treat analysis (P<0.05). The HbA1c levels were still above normal range (3.5% to 6%).

Limitations to the study by Lin et al. included:

- Case series single centre study
- Most patients were already included in the WAVESS study and the authors added more patients to the study because they added another indication for GES to be implanted in patients.
- Numerous subanalyses and statistical comparisons that the study was never designed to test.
- Details regarding the diabetes patients (e.g., glycemic control, renal insufficiency, use of antidiabetes medication) were not reported.
- The subjective nausea, vomiting and TSS severity scores were self-reported by the patient.
- It is unclear whether the authors used the data that was reported to the FDA or the data that was published by Abell et al. in 2003. (55)
- The authors stated "Future well controlled studies to investigate the efficacy of GES therapy and to clarify the major contributing mechanisms will be important and are currently being conducted."(67)

Canadian Costs

AHFMR (10) reported that the cost of implanting a GES in the United States for the treatment of GP is estimated to be $30,000 US. In Canada, the device costs approximately $10,700 Cdn; this does not include costs associated with physician training, implantation procedure, and device programming and maintenance. (10)

Ontario Context

There is no Schedule of Benefits code for GES.

There is no Canadian Classification of Health Interventions Index (CCI) procedure code for GES.

Since the ICD-10 diagnosis code for gastroparesis falls under K31.8 "Other specified diseases of the stomach and duodenum", it is impossible to determine how many patients in Ontario had discharge abstracts because of gastroparesis.

In 2005, there were less than 5 out-of-country requests for GES (for either consultation only or for surgery).

Gastroparesis in Ontario

The prevalence of severe, refractory GP is variably reported in the literature.

Using data from Abell and Minocha (11), AHFMR estimated that the prevalence of severe, symptomatic and medically refractory GP in the United States population was 0.017%. (10) Assuming a total Ontario population of 13 million (12), this would correspond to a budget impact of approximately $23.6 M Cdn ($10,700 Cdn x 2,210 patients) for the device cost alone.

The incidence of severe refractory GP estimated by the FDA is approximately 4,000 per year in the United States. This corresponds to about 150 patients in Ontario. Using expert opinion and FDA data, the incidence of severe refractory GP in Ontario is estimated to be about 20 to 150 per year. This corresponds to a budget impact of approximately $107,000 Cdn to $1.6M Cdn per year for the device cost alone.

Morbid Obesity in Ontario

An expert in the field estimated that there are approximately 160,000 to 180,000 people in Ontario who are morbidly obese. This would correspond to a budget impact of approximately $1.7B Cdn to $1.9B Cdn for the device cost alone (assuming 100% uptake). However, the uptake of GES for morbid obesity is unknown in relation to other types of bariatric surgery that are more effective.

Existing Guidelines Regarding the Use of the Technology

American Motility Society Task Force on Gastroparesis, April 2006

"While the results of these investigations are encouraging, the clinical benefits of GES have not been

unequivocally demonstrated or the site of action. A larger, longer duration, sham stimulated controlled multicentre trial of gastric electrical stimulation is ongoing in patients with GP. Optimal pulse parameters need to be defined and predictors of clinical improvement must be characterized."(29)

National Institute for Clinical Excellence (NICE), December 2004

"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." (30)

American Gastroenterological Association: Technical Review on the Diagnosis and Treatment of Gastroparesis, November 2004

Refractory GP

"There is no consensus regarding management of patients with GP who do not respond to simple antiemetic or prokinetic therapy or who develop severe drug induced side effects.

Managing the patient with refractory GP includes ensuing that GP is responsible for symptoms, optimizing current therapy and changing prokinetic agents if maximal doses of the current treatment program are inadequate.

For patients who are refractory to all attempts at pharmacotherapy, placement of a feeding jejunostomy and/or venting gastrostomy can be considered. Use of TPN should be temporary if possible due to the risk of complications. Newer therapies being evaluated are pyloric injection of botulinum toxin and gastric electric stimulation. Gastric resection usually is of limited value for most etiologies of GP." (3)

Gastric Electrical Stimulation

"Further investigation is needed to confirm the effectiveness of gastric stimulation in long term blinded fashion, which patients are likely to respond, the optimal electrode position, and the optimal stimulation parameters, none of which have been rigorously evaluated to date.

Future improvements may include devices that sequentially stimulate the stomach in a peristaltic sequence to promote gastric emptying.

This is an area of active investigation because the current therapy is suboptimal and existing treatments have not been well studied. Evidence based investigation will be required to better define appropriate approaches to this challenging condition." (3;49)

Centers for Medicare and Medicaid Services, United States, November 2003

Gastric electrical stimulation is used for the treatment of severe and medically intractable GP (both diagnoses, diabetes with neurological manifestations and gastroparesis are required for coverage) and is approved only when the following 3 conditions are met: (68)

1. The record established medical necessity by documenting severe, chronic GP, unresponsive to reasonable efforts of conventional medical therapy.
2. There is an affirmation that the FDA criteria for use of the investigational device exemption have been met.

3. There is an affirmation that the institution's institutional review board (IRB) has approved this procedure, has approved the surgeon doing the procedure and that the IRB's instructions or protocol are being followed.

When all of these conditions have been met, GES will be covered at a single, all-inclusive price (no separate fee for positioning gastroscopy or reprogramming, etc.).

Gastric electrical stimulation is not approved for the treatment of obesity.

American Society for Bariatric Surgery, United States, 2004

Future directions for clinical investigation, basic research and education include:

Controlled studies of new operative modalities (e.g., gastric pacing) and nonoperative modalities of treatment. (69)

Conclusion

As per the GRADE Working Group (54), overall recommendations consider 4 main factors.

- The tradeoffs, taking into account the estimated size of the effect for the main outcome, the confidence limits around those estimates and the relative value placed on the outcome.
- The quality of the evidence.
- Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects such as proximity to a hospital or availability of necessary expertise.
- Uncertainty about the baseline risk for the population of interest.

The GRADE Working Group also recommends that incremental costs of healthcare alternatives should be considered explicitly alongside the expected health benefits and harms. Recommendations rely on judgments about the value of the incremental health benefits in relation to the incremental costs. The last column in Table 7 shows the overall trade-off between benefits and harms and incorporates any risk/uncertainty.

For GP, the overall GRADE and strength of the recommendation is "weak" – the quality of the evidence is "low" (uncertainties due to methodological limitations in the study design in terms of study quality, consistency and directness), and the corresponding risk/uncertainty is increased due to a budget impact of approximately $107,000 Cdn to $1.6M Cdn for the device cost alone, while the cost-effectiveness of GES is unknown and difficult to estimate considering that there are no high-quality studies of effectiveness.

Overall, there is low-quality Level 2 evidence of the short-term effectiveness of GES for the reduction of weekly vomiting episodes compared to placebo for patients with severe refractory GP due to diabetes or idiopathic causes. Further evidence of effectiveness should be available in the future since there is a RCT underway that is examining the use of GES in patients with severe refractory GP associated with diabetes and idiopathic etiologies (ClinicalTrials.gov identifier NCT00157755).

For morbid obesity, the overall GRADE and strength of the recommendation is "weak" – the quality of the evidence is "low" (uncertainties due to methodological limitations in the study design in terms of study quality and consistency), and the corresponding risk/uncertainty is increased due to a budget impact

of approximately $1.7B Cdn to $1.9B Cdn for the device cost alone (assuming 100% uptake) while the cost-effectiveness of GES is unknown and difficult to estimate considering that there are no high quality studies of effectiveness. However, the true uptake of GES for morbid obesity is unknown in relation to other types of bariatric surgery (which are more effective).

Table 7: Overall GRADE and Strength of Recommendation (Including Uncertainty)

	Quality	Estimated Prevalence in Ontario	Cost-Effectiveness	Cost in Ontario	Risks/Burden	Benefits	Overall Grade & Strength of Recommendation
Severe, chronic refractory GP	Low	Incidence ~ 20 to 150	?	Cdn $107,000 to $1.6M	• Removal rate ~ 5-10% of cases due to infection, stomach perforation, device migration/erosion. • Cost effectiveness unknown. • Ongoing/lifetime monitoring of patient. • Battery change ~ 5 years. • Post hoc change in end point analysis. • Another RCT is underway.	Uncertain short/long- term benefits (reduced frequency of vomiting/nausea ; improved gastric emptying; quality of life).	Weak
Morbid obesity	Very Low	~ 160,000 to 180,000	?	Uptake not determined in relation to other types of bariatric surgery (which are more effective).	• Adverse effects – stomach perforation and lead dislodgment – difficult to determine rate given mid-study changes in surgical technique. • Cost - effectiveness and uptake unknown. • Ongoing/lifetime monitoring of patient. • Battery change ~ < 5 years?	Uncertain short/long-term benefits (EWL and improvement / resolution of comorbidities).	Weak

Appraisal

Survey of Provinces/Territories

The funding status of GES reported by other Canadian provinces and territories is shown in Table 8.

Table 8: Reported Funding Status of Gastric Electrical Stimulation in Canadian Provinces and Territories.

Province/Territory	Funding Status
Newfoundland	Not insured.
New Brunswick	Not insured, no request for coverage.
Prince Edward Island	Not insured.
Nova Scotia	Not insured.
Quebec	No response.
Ontario	Not insured.
Manitoba	Not an insured service.
Saskatchewan	Not insured.
Alberta	Not insured.
British Columbia	No response.
Yukon	Not insured, no request for coverage.
Northwest Territories	Not insured.
Nunavut	No response.

Survey of Some Insurers in United States

The funding status of GES by insurers in the United States is shown in Table 9.

Table 9: Funding Status of Gastric Electrical Stimulation by Some Insurers in the United States.

Insurer	Funding Status
CMS (68)	For the treatment of severe and medically intractable gastroparesis and will be approved only when the following 3 conditions are met: 1. The record establishes medical necessity by documenting severe, chronic gastroparesis. 2. Affirmation that FDA criteria for use of the investigational device exemption have been met. 3. Affirmation that the institution's IRB has approved the procedure, has approved the surgeon doing the procedure and that the IRB's instructions or protocol are being followed. * Both diagnoses (ICD-9-CM codes for diabetes with neurological manifestations AND gastroparesis are required for coverage.)
Aetna (70)	Medically necessary for the treatment of symptoms of nausea and vomiting from chronic gastroparesis that is refractory to medical management. Experimental and investigational as an initial treatment for gastroparesis, and for treatment of obesity and for other indications because their effectiveness for these indications has not been established.
Excellus BCBS (71)	Investigational for the treatment of any disease or condition, including but not limited to gastroparesis and morbid obesity.

Regence (72)	GES may be considered medically necessary in the treatment of chronic intractable nausea and vomiting secondary to GP of diabetic or idiopathic etiology when all 3 of the following criteria are met: 1. Significantly delayed gastric emptying as documented by standard scintigraphic imaging of solid food. 2. Patient is refractory or intolerant of 2 of 3 classes of prokinetic drugs and 2 out of 3 antiemetic drugs. 3. Patient's nutritional status is sufficiently low that TPN is medically necessary. GES is investigational for all other indications including but not limited to the treatment of obesity.
Cigna (73)	Investigational for all conditions (refractory gastroparesis or morbid obesity) at this time.
Care First BCBS (74)	Since it is a humanitarian device, patients determined to be candidates for gastric stimulation will receive individual case consideration for benefit coverage.

Appendix 1

Gastric Electrical Stimulation – Search Strategy

Search date: March 26, 2006
Databases searched: OVID Medline, In Process and Other Non-Indexed Citations, Embase, Cochrane Library, INAHTA

Database: Ovid MEDLINE(R) <1996 to March Week 3 2006>
Search Strategy:
---
1 exp Electric Stimulation Therapy/ (9928)
2 exp Gastroparesis/ (402)
3 exp gastrointestinal motility/ or exp gastric emptying/ (7717)
4 exp Obesity, Morbid/ (3003)
5 or/2-4 (10857)
6 1 and 5 (118)
7 (gastric adj1 stimulat$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (356)
8 5 and 7 (90)
9 ((stomach or duodenal or intestinal or gastric) adj1 (electric$ stimula$ or pacer$ or pacing or pacemaker)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (147)
10 enterra$.mp. (2)
11 ((gastroelectric$ or gastro-electric$) adj1 (stimulat$ or pacer$ or pacing or pacemaker)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (0)
12 6 or 8 or 9 or 10 or 11 (278)
13 limit 12 to (humans and english language and yr="2000 - 2006") (116)
14 (systematic review$ or meta-analysis or metaanalysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (22571)
15 13 and 14 (2)
16 13 (116)
17 limit 16 to (case reports or comment or editorial or letter or "review") (46)
18 16 not 17 (70)
19 15 or 18 (72)

Database: EMBASE <1980 to 2006 Week 12>
Search Strategy:
---
1 exp Electrostimulation/ (24245)
2 exp Stomach Paresis/ (1089)
3 exp Stomach Emptying/ (6777)
4 exp Stomach Motility/ (2874)
5 exp Morbid Obesity/ (2782)
6 or/2-5 (12105)
7 1 and 6 (143)
8 (gastric adj1 stimulat$).mp. [mp=title, abstract, subject headings, heading word, drug trade name,

original title, device manufacturer, drug manufacturer name] (1799)
9 6 and 8 (211)
10 7 or 9 (333)
11 ((stomach or duodenal or intestinal or gastric) adj1 (electric$ stimula$ or pacer$ or pacing or pacemaker)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (235)
12 enterra$.mp. (3)
13 ((gastroelectric$ or gastro-electric$) adj1 (stimulat$ or pacer$ or pacing or pacemaker)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (0)
14 or/10-13 (503)
15 limit 14 to (human and english language and yr="2000 - 2006") (120)
16 (systematic review$ or meta-analysis or metaanalysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (37397)
17 15 and 16 (4)
18 15 (120)
19 limit 18 to (editorial or letter or note or "review") (42)
20 Case Report/ (878938)
21 18 not (19 or 20) (70)
22 17 or 21 (74)

Appendix 2

Data Submitted to the United States Food and Drug Administration for Humanitarian Device Exemption Approval of Gastric Electrical Stimulation for the Treatment of GP

World Wide Anti-Vomiting Electrical Stimulation Study (WAVESS)

This study was a double blind randomized crossover study that enrolled a total of 33 patients. The study was designed to collect both safety and effectiveness data. (75)

Study Objective

The primary end point was a reduction in vomiting frequency as measured by patient diaries. The treatment was considered successful if a reduction in vomiting frequency by at least 80% was observed during the crossover period of the study with the ON mode stimulation compared to the OFF mode stimulation.

The secondary end points were quality of life, body weight, hypoglycemic attacks (diabetes group only), subjective symptoms documented by a clinical status interview, glycosylated hemoglobin and gastric emptying.

Inclusion/Exclusion Criteria

Inclusion criteria:

- Symptomatic gastroparesis lasting 1 year or more as documented by an initial gastric emptying test;
- Refractory or intolerant to at least 2 antiemetic and prokinetic drug classes;
- On stable medical therapy and if applicable stable nutritional support during the month prior to enrollment;
- Frequency of vomiting greater than 7 episodes per week, as documented with a baseline patient diary;
- Delayed gastric emptying defined by greater than 60% retention at 2 hours and greater than 10% retention at 4 hours as measured by standardized gastric emptying testing.

Exclusion criteria:

Organ transplant; organic obstruction; pseudoobstruction; prior gastric surgery; scleroderma amyloidosis; history of seizures; peritoneal or unstable dialysis; chemical dependency; pregnancy; primary eating or swallowing disorders; psychogenic vomiting; implanted electronic medical devices; age greater than 70 or less than18.

Study Design

The study was conducted in 2 phases:

1. Phase 1 was a double-blind crossover with evaluations prior to implantation, at 30 days and 60 days. Patients were randomly assigned to stimulation ON or OFF for the first month after implantation and were crossed to OFF or ON for the second month. Patients were blinded as to which stimulation sequence they received.

2. Phase 2 was an unblinded open-label study with follow-up at 6 and 12 months. After the crossover period was complete, the patients were asked which month of the crossover stimulation they preferred and the study blind was broken. The patient then received stimulation consistent with their preference.

A sample size calculation/justification was not reported in the FDA submission. However, in the subsequent publication in 2003, Abell et al. (55) stated that

> *"The initial study plan provided for an enrollment of 40 diabetes and 40 idiopathic patients. Because of slow recruitment, the sponsor stopped the study after enrollment of 33 patients in total. These 33 patients were randomized to Phase 1, continued to Phase 2 and form the basis of this report."*

The primary and secondary end points, except for gastric emptying, were measured at baseline, and 30 days, 60 days, 6 months, and 12 months postrandomization. Gastric emptying was measured at baseline and 6 and 12 months post randomization.

Effectiveness - Primary End point, Phase 1

There was no significant difference in the vomiting frequency with stimulation ON or OFF during the 2-month double-blind crossover study although both periods showed a decrease in vomiting when compared to baseline (Table 10).

Table 10: Vomiting Frequency in WAVESS Phase 1 (N=33).

Vomiting Episodes per Week (diaries)	Baseline	ON	OFF	Difference (OFF-ON)	% Difference
Mean (±SD)	47.6 ± 52.6	23.0 ± 35.5	29.0 ± 38.2	6.0 ± 22.4	21
Median	26.3	12.0	14.0	2.0	14.3

Source: United States.Food and Drug Administration. Summary of Safety and Probably Benefit: Enterra Therapy System. 1999. Available at: http://www.fda.gov/cdrh/pdf/h990014b.pdf

Effectiveness – Primary End Point, Phase 2

At the end of Phase 1, 21 patients preferred the ON mode, 7 preferred the OFF mode and 5 had no preference.

Although 33 patients completed the 2-month crossover period (Phase 1), data at 6 months was provided for only 25 patients. Some patients had the device turned to the ON mode immediately at the end of Phase 1, while others had the device turned ON later. By the end of the fourth month postrandomization, all 25 patients had the device turned ON. The vomiting frequency at 6 months was obtained from patients who received stimulation for at least 3 months. At the time the dataset was closed, 6-month follow-up data was available for 25 of the 33 patients (Table 11).

When vomiting frequency at 6 and 12 months was compared to baseline values for the idiopathic and diabetes GP patients, there were no statistically significant differences in vomiting frequency (no statistical test reported) (Tables 12 and 13). With this small sample size, failure to show any difference could have been due to a type 2 error.

Table 11: Vomiting Frequency in WAVESS Phase 2 (All Patients).

	Baseline	6 Months	% Difference	Baseline	12 Months	% Difference
Number of patients	25	25		15	15	
Mean number of episodes (+SD)	44.6±50.7	19.2±43.7	-57	42.7±53.9	10.1±9.8	-76
Median number of episodes	26.5	5.0	-81	18.5	4.5	-76
Number of patients with >50% vomiting reduction versus baseline, N (%)	-	17 (68)	-	-	14 (93)	-
Number of patients with >80% vomiting reduction versus baseline, N (%)	-	14 (56)	-	-	8 (53)	-

Source: United States.Food and Drug Administration. Summary of Safety and Probably Benefit: Enterra Therapy System. 1999. Available at: http://www.fda.gov/cdrh/pdf/h990014b.pdf

Table 12: Vomiting Frequency in WAVESS Phase 2 (Idiopathic Gastroparesis Patients).

	Baseline	6 Months	% Difference	Baseline	12 Months	% Difference
Number of patients	14	14		10	10	
Mean number of episodes (+SD)	32.7±44.4	12.1±25.1	-63	41.3±53.3	13.8±23.7	-67
Median number of episodes	22.5	3.0	-87	23.0	5.3	-77
Number of patients with >50% vomiting reduction versus baseline, N (%)	-	9 (64)	-	-	9 (90)	-
Number of patients with >80% vomiting reduction versus baseline, N (%)	-	8 (57)	-	-	5 (50)	-

Source: United States.Food and Drug Administration. Summary of Safety and Probably Benefit: Enterra Therapy System. 1999. Available at: http://www.fda.gov/cdrh/pdf/h990014b.pdf

Table 13: Vomiting Frequency in WAVESS Phase 2 (Diabetes Gastroparesis Patients)

	Baseline	6 Months	% Difference	Baseline	12 Months	% Difference
Number of patients	11	11		5	5	
Mean number of episodes (+SD)	59.8±56.1	28.2±60.1	-53	45.5±61.5	2.8±4.2	-94
Median number of episodes	28	6.0	-79	18.0	1.0	-94
Number of patients with >50% vomiting reduction versus baseline, N (%)	-	8 (73)	-	-	5 (100)	-
Number of patients with >80% vomiting reduction versus baseline, N (%)	-	6 (56)	-	-	3 (60)	-

Source: United States.Food and Drug Administration. Summary of Safety and Probably Benefit: Enterra Therapy System. 1999. Available at: http://www.fda.gov/cdrh/pdf/h990014b.pdf

Effectiveness – Secondary End Points

Overall, the study indicated trends toward improvement in most of the secondary end points (no statistical tests reported). With this small sample size, failure to show any difference could have been due to a type 2 error.

Compassionate Use Electrical Stimulation Study

Despite the Compassionate Use Electrical Stimulation Study (CEUSS) study being referred to many times in the literature (65;66;75;76), there are no published journal articles that are specifically and explicitly titled or identified as the "Compassionate Use Electrical Stimulation Study".

In addition to the WAVESS study, the "Compassionate Use Study" was submitted by the manufacturer to the FDA in 1999 for a humanitarian device exemption. (75) This study was an open label, nonrandomized study that included a total of 18 patients. The study was designed to provide safety information on gastric stimulation by treating patients with drug refractory GP who did not meet the entry criteria of WAVESS. The FDA submission stated "…adverse effects data were collected on patients with drug refractory gastroparesis of diabetes or idiopathic etiologies in 2 clinical studies conducted in the United States, Canada and Europe". As such, it is unclear which adverse effects reported in the submission were from WAVESS or the Compassionate Use Study. The FDA concluded that "data obtained from the WAVESS and Compassionate Use Studies revealed the same type of adverse events associated with other implantable electrical stimulation devices. These adverse events were treatable and did not cause significant morbidity and mortality."

Lin et al. (76) referred to the 2 studies (one a follow-up of the other) by Forster et al. (77;78) as being the CEUSS study. It is possible that CEUSS is a continuation of the Compassionate Use Study submitted to the FDA.

In 2003, Forster et al. (78) reported outcomes on 55 patients who underwent GES implantation for treatment of GP (39 diabetes, 9 postsurgical, 7 idiopathic) at a single centre. No inclusion or exclusion criteria were reported. Symptom assessments, gastric emptying and quality of life and weight were measured at baseline and at 6 and 12 months postoperatively.

Compared with baseline, at the 12-month follow-up:

- There was no significant change in gastric emptying (52 of the 55 patients and 36 of the 55 patients had this end point measured at baseline and at 12 months respectively). Details about the missing patient data were not reported by the authors.
- Total symptom score for both frequency and severity was significantly decreased ($P<0.05$). It is possible that this may be due to a placebo effect. Forty-one of 55 patients were evaluable for the 12-month follow-up. The WAVESS study showed no significant difference in vomiting frequency at 12-month follow-up.
- Quality of life was significantly increased ($P<0.05$). Forty-one of 55 patients were evaluable for the 12-month follow-up.
- Body weight was significantly increased. However, the magnitude of the difference was small - the mean (SEM) weight at baseline (n=55) was 64.5 kg (2.1); at 6 months (n=45) was 65.1 kg (2.0) and at 12 months (n=44) was 65.4 kg (1.9).
- BMI was significantly increased. However the magnitude of the difference was small - the mean (SEM) BMI at baseline (n=55) was 22.9 kg/m2 (0.7); at 6 months (n=45) was 22.3 kg/m2 (0.7); and at 12 months (n=44) was 23.3 kg/m2 (0.6).
- HbA1c in diabetes patients was significantly decreased. However the HbA1c was still above the acceptable limit of 7%. The mean (SEM) HbA1c at baseline (n=29) was 9.8% (0.49%); at 6 months (n=23) was 9.0% (0.56%); and at 12 months (n=24) was 8.5% (0.45%). Only 29 of the 39 diabetes patients at baseline had their HbA1c measured. It is unclear why HbA1c was not measured in all the diabetes patients at baseline.

Limitations to CEUSS were:

- According to the FDA, the study was designed to provide safety information on gastric stimulation by treating patients with drug refractory GP who did not meet the entry criteria of WAVESS.
- No inclusion/exclusion criteria, objectives or hypotheses were reported by the authors.
- Single-centre, case series, open-label study design. Not sham-controlled. It was not reported by the authors if patients were enrolled consecutively.
- Lack of explicit detail regarding missing data and patient dropouts (at baseline and the 6- and 12-month follow-up).

- Nine patients were initially part of the WAVESS study, 32 were part of the CEUSS study, and 14 received GES under the HDE protocol. The differences in patient inclusion criteria between CEUSS and the HDE protocol are unclear. It is unknown why only 9 patients from the WAVESS study were included in the analysis.
- There was a 75% follow-up for symptom scores and an 80% follow-up for BMI and weight at the 12-month follow-up.
- Patients were self-evaluated using subjective criteria to assess symptoms.
- Concurrent medication use.

Appendix 3

Gastric Electrical Stimulation for Gastroparesis: Studies of Lesser Quality than Abell et al. (55)

Abell et al. (79) conducted a 2-phase multicentre feasibility study (Gastric Electro-Mechanical Stimulation [GEMS]) on 38 patients with drug-refractory GP (idiopathic in 24, diabetes in 9 and postsurgical in 5 patients).

Phase 1 examined the effect of temporary GES between 2 and 4 weeks in order to determine if a patient was a responder. Phase 2 assessed the effect of GES for 12 months. Patients voluntarily had the device deactivated for 1 week at 6 months without blinding to assess change in symptoms with the device OFF compared to symptoms in the previous week with the device on.

Patients who experienced a reduction of at least 80% in their symptoms (frequency and intensity of vomiting and nausea) during Phase 1 were considered to be responders and eligible for enrollment in Phase 2. Patients enrolled within institutions in the United States were additionally required to show an improvement of at least 35% in their gastric emptying prior to inclusion into Phase 2.

Gastric emptying, symptom assessment, body weight, nutritional support and medications were evaluated at 3, 6, and 12 months after implantation of the leads and neurostimulator. Delayed gastric emptying was defined according to the criteria in place at each institution. The normal half-life and standard deviation values varied widely among centres. Analysis was performed on an ITT basis.

Prior to GES, the median weekly postprandial vomiting frequency was 21 episodes (range 0-210) and median weekly number of episodes of postprandial nausea was 21 (range 0-168). At baseline, 2 patients were unable to eat any solid food and 3 others could not quantify their nausea in terms of frequency as they continuously felt nauseated – these patients were excluded from further analysis on nausea.

At study entry, 20 patients were receiving one or more prokinetic drugs while the remaining 18 patients were not on prokinetic therapy since they previously failed to respond to them. Thirteen patients were receiving antiemetic drugs including 6 patients who were on more than 1 antiemetic drug. The remaining patients were treatment-resistant to antiemetic drugs. Eight patients were on a combination of prokinetic and antiemetic drugs. Fourteen patients were treatment-resistant to both prokinetic and antiemetic drugs and were on neither therapy.

Phase 1

During Phase 1, the median weekly vomiting episode frequency dropped from 21 at baseline to 0 episodes during GES. The median weekly number of episodes of nausea declined from 21 at baseline to 2 during GES. Gastric emptying improved in 8 patients.

Phase 2

Thirty–three of the 38 patients qualified for entry into Phase 2. Symptom data were available for 25 patients at 3 months, 22 for more than 6 months and 23 patients for more than 12 months. Partial data were available on 1 additional patient who was followed for more than 12 months and was unable to eat solid food during the study. Five patients did not meet the Phase 2 entry criteria because they could not eat during the study period and therefore did not vomit. Furthermore, 5 patients refused or were unable to

return for follow-up and 1 patient could not quantify the severity of her symptoms.
There was a reduction in the frequency of vomiting (decrease by more than 90% on average up to 1 year) and nausea (median weekly frequency decreasing from 28 episodes at baseline to 1 episode per week at 1 year).

At 1 year, gastric emptying was normalized in 7 patients, 6 showed no change and 2 worsened.

Several patients were over ideal body weight at baseline. The average weight gain for the 23 patients followed for 12 months was 8.4% ($P = 0.007$); 15 of 23 patients (65%) gained greater than 5% body weight, 3of 23 lost greater than 5% and the remaining 5 of 23 had no change.

Fourteen of 23 patients with 12-month follow-up were receiving either enteral or parenteral nutritional support at baseline. At 12 months, the number of patients receiving enteral support declined from 11 to 3 while the number of parenteral support declined from 3 to 2; these changes were not statistically significant.

The authors stated that with sustained GES, a substantial proportion of patients were able to decrease the use of prokinetic and or antiemetic drugs. The decrease in the number of patients on prokinetic drugs at 1 year compared to baseline was statistically significant ($P<0.05$). "The number of patients that managed without either type of drugs increased from 5 to 14 of the patients followed up to a year**."** It is unclear why these patients were on drugs if they were reported to have refractory GP.

OFF at 6 Months

The authors provided the following information regarding the patients who had the GES turned off for a week at the 6-month follow-up. It is unclear from the description of the analysis in the paper if the authors compared the OFF at 6-months results to the baseline data of the study, or to the ON at 6- months results.

According to the table on page 207 of the original article, when the GES was switched to OFF for a week at 6 months, there was a statistically significant decrease in the median weekly nausea and vomiting compared to baseline (nausea OFF at 6 months versus baseline: median 7 versus median 25, $P<0.002$; vomiting OFF at 6 months versus baseline: median 1 versus median 17.5, $P < 0.0005$). These data are suggestive of a placebo effect.

Adverse Events

Inadvertent deactivation of the pulse generator (occurring in 10 patients) was the most frequent adverse event. The authors stated that after the 10 patients switched to a different model of pulse generator, there were no further problems.

Four of the 33 pulse generators implanted were removed due to infection.

Two patients underwent a total gastrectomy due to one patient who expected to "…have a completely normal eating behaviour" and the other patient who had no change in vomiting and continued to lose weight requiring total parenteral nutrition.

Limitations to the study by Abell et al. (79) were:
- Case series; feasibility study.
- Not placebo-controlled.
- It is unclear to what extent there is patient overlap with WAVESS.
- It is unclear what baseline values were used to calculate Phase 2 results.
- The OFF 6-month results suggest a placebo response.

- It is unclear why some patients continued on drug therapy if they had treatment-resistant GP.

Abell et al. (80) followed up a subset (N=12) of the GEMS cohort and at 1 to 2 years and 5 years postimplantation and examined TSS severity, weekly vomiting frequency score, nutrition (BMI and route of nutrition) and overall health-related QoL measures. It is unclear how health-related QoL was measured but the authors stated that it "was measured by patient self-report as general or generic measures for nutrition quality of life and overall quality of life, scored -3 to +3 (worst to best) at long-term follow-up compared with baseline." The rationale for only selecting 12 patients from the GEMS cohort was not explained by the authors.

The median TSS changed from 37.1 at baseline to 15.8 at 1 to 2 years and 20.3 at 5 years (P<0.005 from baseline). The mean (SEM) weekly vomiting frequency score decreased from 3.9(0.1) at baseline to 1.4(0.6) at 1 to 2 years and to 1.7(0.5) at 5 years (P<0.05). The mean (SEM) weight changed from 69.9(3.6) at baseline to 72.7(6.4) at 1 to 2 years and to 71.4(5.9) at 5 years (P=0.8). The mean (SEM) BMI changed from 24.1(1) at baseline to 25.6(2) at 1 to 2 years and to 24.6(2) at 5 years (P=0.8).

Limitations to the study by Abell et al. (80) were:
- Reanalysis of data from patients included in a previous study.
- Unclear why only 12 of the original 38 GEMS patients were followed up.
- Lack of a standardized QoL scale.
- Unclear reporting of data.

McCallum et al. (81) examined 16 patients who had refractory postsurgical GP and were treated with GES. Clinical data were collected at baseline and after 6 and 12 months of GES and included: 1) severity and frequency of 6 upper GI symptoms by using a 5-point symptom interview questionnaire and TSS; 2) health-related QoL, including physical composite score and mental composite score; 3) a 4-hour standardized gastric emptying of a solid meal by scintigraphy; and 4) nutritional status.

A sample size calculation was not reported by the authors. It is not explicitly reported whether the study was prospective or retrospective in design.

Inclusion criteria consisted of:
- Documented diagnosis of GP for more than 1 year and refractoriness to antiemetics and prokinetics.
- More than 7 emetic episodes per week.
- In the setting of fundoplication where patients cannot vomit, then chronic daily nausea was the criterion
- Delayed gastric emptying (gastric retention great than 60% at 2 hours and greater than 10% at 4 hours).

Exclusion criteria consisted of:
- Organic obstruction or pseudo-obstruction
- Primary eating or swallowing disorders
- Chemical dependency
- Positive pregnancy test result or
- Psychogenic vomiting

In comparison to baseline, all 6 mean symptom severity subscores (vomiting, nausea, early satiety, bloating, postprandial fullness and epigastric pain) decreased by more than 50% at 6 months of GES. Both the mean TSS for severity and frequency were significantly reduced at 6 months of GES and sustained at 12 months compared to the initial baseline. The mean and standard error of the mean [SEM] results were as follows:

TSS for severity was 17.1[0.7] at baseline, 6.9 [1.3] at 6 months, and 8.6[1.5] at 12 months, P<0.05

compared to baseline for 6 and 12 months.
TSS for frequency was 19.2[0.7] at baseline, 7.9[1.3] at 6 months and 9.8[1.5] at 12 months, $P<0.05$ compared to baseline for 6 and 12 months.

The mean physical and mental component scores of the health-related QoL were reported to have significantly improved at 6 and 12 months ($P < 0.05$). The mean number of hospitalization days during the year (6[2], range 0-29 days) was significantly reduced compared with the prior year (31[13], range 0-200 days, $P < 0.05$). Gastric emptying was not significantly improved at 12 months. At implantation, 7 of the 16 patients required nutritional support with a feeding jejunostomy tube. After GES, 4 patients were able to discontinue jejunal feeding at 2, 4, 6, and 11 months after GES implantation, and 3 patients still required supplemental feeding at 12 months.

One person had the device removed after 12 months because of an infection in the pocket of the pulse generator.

Limitations to the study by McCallum et al. (81) were:
- Small case series and not placebo-controlled.
- Unclear whether the study was retrospective or prospective in design.
- Sample size calculation/justification not reported.
- The operations differed for all the patients, however all had received a procedure that involved either a known vagotomy or the potential for accidental injury to the vagus nerve.
- The authors stated that "a controlled clinical trial of GES for postsurgical GP patients (who are refractory to medical therapy) is indicated…" (81)

Van der Voort et al. (82) performed a prospective single centre study on the effects of GES on symptoms, gastric emptying (measured scintigraphically) and metabolic control (glycohemoglobin or HbA1c) in 17 insulin dependent patients with diabetes who had drug-refractory GP for more than 1 year. The authors stated that intensive therapy in patients with type 1 diabetes should aim to control HbA1c values to remain below 6.05% and can be used as a surrogate marker of sufficient long-term metabolic control in patients with diabetes.

Refractory GP was defined as vomiting frequency of more than 7 episodes per week, delayed gastric emptying (>60% retention at 2 hours and >10% at 4 hours) using scintigraphy after a solid meal, symptoms lasting longer than 12 months and refractoriness or intolerance to 2 of 3 classes of prokinetic drugs and 2 of 3 classes of antiemetics. The patients were allowed to continue their current antiemetic or prokinetic therapy during the study and were asked not to substantially alter their antidiabetes therapy.

All 17 patients were available for analysis at baseline, 6, and 12 months after device implantation. No adverse events were associated with GES at any follow-up.

Nausea and vomiting symptoms significantly decreased at 6 and 12 months of follow-up (vomiting: mean weekly frequency at baseline 26 [range 19-41], 6 months 3 [range 0-10], 12 months 4 [range 0-13]; nausea: mean weekly frequency at baseline 34 [range 21-49], 6 months 8 [range 1-18] and 12 months [12 [range 2-20]; $P < 0.01$ compared to baseline for all 6 and 12 month end points).

Gastric emptying rates at 6 and 12 months improved significantly compared to baseline values ($P < 0.05$).

The HbA1c values of the diabetes patients were significantly reduced at 6 months and 12 months compared to the baseline values ($P < 0.05$). In 5 and 4 patients, HbA1c levels fell below 6.05% at 6 and 12 months respectively. In 4 of the 17 patients, HBA1c was measured to be above 7% at 6 and 12 months.

Limitations to the study by Van der Voort et al. (82) were:
- Small case series design.
- No sample size calculation provided.
- No explicit primary outcome reported.
- Not placebo-controlled.
- Patients self-recorded their daily nausea and vomiting episodes.
- It is unclear if it was ensured that patients were optimally managed and euglycemic at the start of the study. No patient presented with a HbA1c value less than 7.5%. At the end of the study, only 5/17 patients had HbA1c below 6.05% at 6 months and only 4/17 had HbA1c below 6.05% at 12 months.
- Unclear how patients were selected (i.e., consecutively).
- Concurrent prokinetic/antiemetic therapy.

Lin et al. (83) retrospectively reviewed the effect of GES on 48 patients with diabetes and refractory GP at 6 and 12 months after implantation. Thirty-seven patients were evaluable for follow-up at 6 months and 28 patients at the 12-month follow-up (4 died, 4 had devices removed, and 12 were lost to follow-up).

Both the mean TSS for severity and frequency were significantly reduced at 6 months of GES (n=37) and sustained at 12 months (n=28) compared with baseline ($P<0.05$).

The mean health-related QoL physical and mental composite scores were significantly reduced at 6 (n=37) and 12 months (n=28) follow-up ($P<0.05$).

Twenty-four patients completed the gastric emptying test at 12 months. Five patients had normalized gastric emptying and the remainder of the patients continued to have delayed emptying, including 9 patients whose gastric retention worsened.

Hospitalization averaged 75[SEM 11] days (range 0-252 days) for the year prior to GES. This decreased to 23[SEM 4] days (range 0-75) days during the 1st year of GES ($P<0.05$).

There was a reduction in mean HbA1c levels from 9.4% at baseline to 8.7% at 6 months and 8.4% at 12 months ($P<0.05$ compared to baseline at 12 months follow-up). The number of patients who had this measured at each follow-up was not stated. At 12 months, 28 patients had symptom score data, and 24 patients had gastric retention data. The authors did not state whether the patients were being optimally treated for diabetes at baseline and whether there were changes to diabetes therapy during the course of the study. The normal range for HbA1c is 3.5% to 6%.

GES was removed in 4 patients; 3 due to infection at the local implantation site. Four patients died during the study follow-up period. An additional 5 patients died at 12 to 63 months postsurgery.

Limitations to the study by Lin et al. (83) were:
- Retrospective case series design.
- Not placebo-controlled.
- It is unknown to what extent patients were on concurrent medications.
- Large number of patients who were lost to follow-up.

Mason et al. (84) retrospectively reviewed 29 patients with refractory GP (24 type 1 diabetes and 5

idiopathic) who were referred for gastrectomy and received GES.

The outcomes of interest were need for supplemental nutrition, change in BMI and gastric emptying. Prior to GES implantation, "…unnecessary medications were discontinued and their preexisting medical conditions were optimized".

If it was noted at follow-up that the patient's symptoms were not relieved, the stimulating current was then incrementally increased by 1 milliamp per day until the symptoms were relieved. The maximum stimulating current was arbitrarily set at 10mA.

Follow-up results were available in 27 patients. The median follow-up was 20 months (range 4-37 months). Two patients were lost to follow-up. Three patients died of unrelated causes during the follow-up period: 2 died of complications related to renal failure at 12 and 18 months following implantation of the GES, and 1 died of a myocardial infarction at 17 months following implantation of the GES.

Three patients required additional procedures. One had erosion of the GES leads through the gastric mucosa at 6 months postoperatively. This required reoperation and replacement of the leads in the stomach wall. One patient requested removal of the GES owning to pain at the subcutaneous pocket site and the other patient had a total gastrectomy for failure to improve with GES.

Nineteen of the 29 patients were dependent on total or supplemental nutritional support preoperatively and none of these patients were dependent during the follow-up period ($P<0.001$). The median [standard deviation] BMI of the patients preoperatively was 22.9 [7.5] and this increased significantly ($P=0.006$) to 25.1 [7.45] at a median follow-up of 20 months.

Gastric emptying was measured in all of the patients preoperatively and in 15 (52%) of the 29 patients postoperatively. Seven of 15 patients normalized their gastric emptying postoperatively. Eight of the 15 patients continued to show abnormal gastric emptying. The median [interquartile range] preoperative gastric emptying rate of 0.17% [0.54%] per minute was significantly increased to 0.38% [0.26%] per minute postoperatively ($P<0.001$).

Limitations to the study by Mason et al. (84) were:

- Retrospective case series design.
- Differs from previous studies in that the stimulating current was titrated to control symptoms with a final median current level about 50% greater than initially used.

De Csepel et al.(85) prospectively assessed the safety and 6-month efficacy of GES in 16 consecutive patients with refractory GP (7 diabetes, 7 idiopathic, 1 the sequela of traumatic brain injury, and 1 a presumed vagotomy following Nissen fundoplication). Data were available from all patients at baseline and from 10 patients at at 6 or more months postoperatively. Of the 6 patients who were not evaluated, 5 patients were within 6 months of implantation and one was lost to follow-up.

Baseline and 6-month postoperative assessments of symptoms and QoL were done by self-administered questionnaires. Patients rated the severity and frequency of nausea and vomiting. Patients also completed the RAND 36 Health Survey 1.0.

The 10 patients with 6 or more months of follow-up showed on average a significant decrease in both nausea (P=0.006) and vomiting (P=0.004) compared to baseline. There was an improvement in their overall QoL (P=0.04).

Six of the 10 patients no longer required prokinetic drugs postoperatively.

Preoperatively, all patients showed delayed gastric emptying. Eight of the 10 patients with at least 6 months follow-up underwent postoperative assessment of gastric emptying. Six of the 8 patients demonstrated normalized gastric emptying.

Limitations to the study by de Csepel et al. were:

- Very small case series without complete follow-up.
- Subjective assessment of symptoms.
- Lack of a control group.
- Baseline results based on 16 patients; 6 or more months follow-up results based on 10 patients.
- If the patients all had refractory GP, it is unclear why 6 of the 10 patients no longer required drug treatment after receiving GES.

Appendix 4

Studies That Assessed Gastric Electrical Stimulation for Gastroparesis in the Alberta Heritage Foundation for Medical Research Report*

Study	Type of Study	Length of Follow-up	Description of Patients	Main Results	Limitations/Comments
Abell et al. (55)	Multicentre randomized placebo controlled crossover study. Phase 1. (WAVESS)	1 month	N=33. Diabetes and idiopathic GP. Average duration of GP symptoms = 6.3 years (range 1-28 years)	**Severity TSS**: not statistically significant. **Weekly vomiting frequency**: statistically significant decrease (but not statistically significant for separate etiologies). **Nausea**: NA. **Gastric emptying**: NA.	The protocol called for an enrollment of 40 diabetes and 40 idiopathic patients. Slow recruitment led to the sponsor stopping enrolment at 33 patients. 63 patients were screened; 30 did not meet the inclusion criteria. 2 patients lost to follow-up. 13 (39%) of patients unevaluable. Results between analysis for the FDA and published paper do not reconcile. FDA submission suggested a placebo effect. Subjective primary end point. No sample size calculation or justification.
Cutts et al. (65)	Comparative prospective study. (Patients from 2 FDA trials: WAVESS and CUESS)	3 years	N=18. Diabetes and idiopathic GP. Device Arm. N=9. Average duration of GP symptoms (SEM) = 7.2 years (2.3). Drug Arm. N=9. Average duration of GP symptoms (SEM) = 2.8 years (0.8).	**TSS:** statistically significant decrease in severity (for years 1, 2 and 3 in the GES arm). **Weekly vomiting frequency or severity**: NA. **Nausea**: NA. **Gastric emptying:** NA.	Very small sample size which contains a subset of patients who were included in previous studies (WAVESS and CUESS). GES patients had a longer symptom duration. All patients reported to be drug refractory. Possible difference in socioeconomic status between GES and Drug arms. All the patients receiving drugs had been offered GES but had either declined it or did not have medical coverage to pay for the device. No sample size calculation/justification.
Abell et al. (79)	Multicentre prospective case series. (GEMS)	1 year	Phase 1 N=38. Diabetes, idiopathic, and postsurgical GP. Phase 1 Average duration of GP symptoms = Females 5.1 years (range 1-20); Males 7.7 years (range 1-19). Phase 2 (open label) N=33.	**TSS:** Not an end point in the study. **Weekly vomiting frequency:** statistically significant decrease (Phase 1 and 2 at 3, 6, and 12 months). **Nausea**: Statistically significant decrease in frequency (Phase 1 and 2 at 3, 6, and 12 months). **Gastric emptying**: N=15. 7 normalized; 6 not changed; 2 worsened (statistical significance not determined).	Termed a feasibility study. Unclear how baseline measurements were calculated for phase 2. 5 patients could not eat at all during the study period; excluded from vomiting analysis. 5 patients refused follow-up and 1 patient who could quantify symptoms. Not intent to treat analysis. Unclear to what extent there is patient overlap with WAVEES. OFF 6 months results suggested a placebo response. Unclear why some patients continued on drug

					therapy if they had treatment- resistant GP.
McCallum et al. (81)	Prospective case series.	1 year	N=16. Postsurgical GP. Average duration of GP symptoms = 5.6 years (range 1 to 33).	**TSS:** Statistically significant decrease in frequency and severity (at 6 and 12 months). **Vomiting:** Statistically significant decrease in frequency and severity (at 6 and 12 months). **Nausea:** Statistically significant decrease in frequency and severity (at 6 and 12 months). **Gastric emptying:** N=13. 3 normalized; 6 not changed; 4 worsened at 12 months (statistical significance not determined).	Small case series. Unclear whether the study was retrospective or prospective in design. No sample size calculation. Subjective nausea and vomiting scores were self-reported by the patient.
Van der Voort et al. (82)	Prospective case series.	1 year	N=17. Diabetes (type 1) GP. Average duration of GP symptoms >1 year.	**TSS:** Not an end point in the study. **Weekly vomiting frequency:** statistically significant decrease (at 6 and 12 months). **Weekly nausea frequency:** statistically significant decrease (at 6 and 12 months). **Gastric emptying:** N=17. Statistically significant improvement (at 6 and 12 months).	Patients allowed to continue their current antiemetic or prokinetic therapy during the study and were asked not to substantially alter their antidiabetes therapy. Small sample size. Weight loss/gain not reported. Unreported how patients were selected.
Lin et al. (66)	Prospective case series. (patients from WAVESS and CUESS)	1 year	N=37. Diabetes (type 1), idiopathic and postsurgical GP. Average duration of GP symptoms = 9.4 years (range 1 to 33).	**TSS:** statistically significant decrease in severity (at 12 months for medication [prokinetics and antiemetics] ON and OFF). **Vomiting:** statistically significant decrease in severity (at 12 months for medication [prokinetics and antiemetics] ON and OFF). **Nausea:** NA. **Gastric emptying:** N=26. 8 normalized; 5 not changed; 13 worsened at 12 months (No statistically significant difference).	Reanalysis of the same set of patients reported in previous studies. Numerous inter-and intra-subanalyses and statistical comparisons that the study was never designed to test. Small sample size. Subjective nausea, vomiting, and TSS severity scores were self-reported by the patient.
Abell et al. (80)	Prospective case series. (subgroup from GEMS)	5 years	N=12. Diabetes and idiopathic GP. Average duration of GP symptoms not stated.	**Severity TSS:** statistically significant decrease (at 1 to 2 years and 5 years). **Weekly vomiting frequency:** statistically significant decrease (at 1 to 2 years and 5 years). **Nausea:** NA. **Gastric emptying:** NA. **Weight gain:** no significant increase (at 1 to 2 years and 5 years). **BMI:** no significant increase (at 1 to 2 years and 5 years).	Case series, subset reanalysis of data from patients in previous GEMS study. Unclear why this particular group of patients was chosen as a subset of GEMS – because had 5 year follow-up? Aim was to follow the nutritional status. Study reporting not of high quality. Lack of a standardized QoL scale.
Lin et al. (67)	Retrospective case series. (WAVESS, CUESS, and HDE study)	3 years	N=55. Diabetes (type 1), idiopathic and postsurgical GP. Average duration of GP symptoms = 6.2 years (range 1-33).	**TSS:** statistically significant decrease in frequency and severity (at 12 months and 3 years). **Vomiting:** statistically significant decrease in frequency and severity (at 12 months and 3 years). **Nausea:** statistically significant decrease in frequency and severity (at 12 months and 3 years). **Gastric emptying:** NA.	Case series. Most patients were already included in the WAVESS study and the authors added more patients to the study because they added another indication for GES to be implanted in patients. Numerous subanalyses and statistical comparisons that the study was never designed to test. Subjective nausea, vomiting and TSS severity

					scores were self-reported by the patient. It is unclear whether the authors used the data that was reported to the FDA or the data that was published by Abell et al. in 2003. Authors stated "Future well controlled studies to investigate the efficacy of GES therapy and to clarify the major contributing mechanisms will be important and are currently being conducted."
Lin et al. (83)	Retrospective case series (WAVESS – 3 patients)	1 year	N=48. Diabetes (type 1) GP. Average duration of GP symptoms = 5.9 years (range 1-20).	**TSS:** statistically significant decrease in frequency and severity (at 6 and 12 months). **Vomiting:** statistically significant decrease in frequency and severity (at 6 and 12 months). **Nausea:** statistically significant decrease in frequency and severity (at 6 and 12 months). **Gastric emptying:** N=24. 5 normalized; 10 not changed; 9 worsened at 12 months (statistical significance not determined).	Retrospective case series. High dropout - 12 patients lost to follow-up, 4 patients died, 4 patients had devices removed. It is unknown to what extent patients were on concurrent medications.
Mason et al. (84)	Retrospective case series	Median 20 months (range 4-37)	N=29. Diabetes (type 1) and idiopathic GP. Diabetes Median duration of GP symptoms = 2 years (range 1-10). Idiopathic Median duration of GP symptoms = 2.5 years (range 1-7).	**TSS:** NA. **Vomiting:** NA. **Nausea:** NA. **Gastric emptying:** N=15. 7 normalized; 2 not changed; 8 worsened post GES (statistical significance not determined).	Retrospective review. "Unnecessary medications were discontinued and their preexisting medical conditions were optimized." If the patient's symptoms were not relieved, the stimulating current was incrementally increased by 1mA per day until the symptoms were relieved.

*CUESS refers to Compassionate Use of Electrical Stimulation Study; GEMS, Gastric Electro-Mechanical Stimulation; HDE, Humanitarian Device Exemption; NA, Not Applicable; TSS, Total Symptom Score; WAVESS, Worldwide Antivomiting Electrical Stimulation Study.

Above table based on information in Alberta Heritage Foundation for Medical Research. Gastric electrical stimulation (Enterra Therapy System) for the treatment of gastroparesis [report on the Internet]. HTA Report # 37. January, 2006. Alberta Heritage Foundation for Medical Research. [cited 2006 June 21]. Available at: http://www.ahfmr.ab.ca/publications/

Appendix 5

Studies That Assess the Use of Gastric Electrical Stimulation in Patients with Morbid Obesity.

Study (year)	Study Type	Inclusion Criteria	Treatment	Primary Outcome of Study	Results/Comments
O-01 Trial (59)	Randomized double blind placebo controlled. N=103	BMI 40-55 kg/m2	One month after insertion, patients randomized to ON (treatment) or OFF (control). No dietary or behavioural advice or counseling were provided to the patients.	Percentage change in weight from baseline after 6 months of GES.	No statistically significant difference in weight loss between the study and control groups at the end of the 6 month randomized period. %EWL for the ON group was 1.3% and for the OFF group was 2.4%. Gastric luminal penetrations and lead dislodgements occurred with a high frequency early in the trial but decreased later as the technique became more familiar to the surgeons. Limitations/Comments: 1 lead device with pacing parameters that changed during the trial. Large dropout rate. No data regarding improvement /resolution of comorbidities. %EWL is much less than that reported after other bariatric surgery procedures. No sample size calculation/justification provided.
DIGEST Trial (59)	Nonrandomized open label study N=30	BMI 40-55 kg/m2 or 35-39 kg/m2 with one or more significant comorbidities. Pass a binge eating assessment and psychological evaluation.	Patients followed monthly for 24 months and required to complete the LEARN Behaviour Modification Program; Satiety and Dietary Analysis Questionnaire, attend monthly support group meetings, and have an assessment of the presence or absence of change in eating habits and weight loss.	% change in weight from baseline after 6 months of GES.	Results for the primary end point of the study (6 month follow-up) were not reported. At the 12 month follow-up, 71% of patients lost weight. The results for the Satiety and Dietary Analysis indicated that there was a significant reduction (P<0.05) in appetite and increases in both between meal and end of meal satiety between baseline and when the questionnaire was administered (n=29; follow-up interval not reported). Limitations/Comments:

			Quality of life measured by SF-36. Dietary counseling provided at clinic visits.		Small sample size – no calculation/justification reported. Results for primary end point not reported. %EWL is much less than that reported after other bariatric surgery procedures. No data regarding improvement /resolution of comorbidities. Follow-up interval for satiety questionnaire not reported. Variable programming of the GES device during the trial.
LOSS Study (35)	Prospective multicentre study. N=91	Morbidly obese patients.	Stimulation was activated 1 month postoperatively. It was suggested, but not mandatory, that patients follow the standard diet and behaviour modification programs established at each investigational centre. Patients were requested to appear at follow-up at 1, 2, 3, 4, 6, 8, 10, 12, 15, 18, 21, and 24 months after implantation.	Efficacy of GES?	The mean %EWL was 20% at 12 months after surgery and about 25% at 2 years after implantation. Patients with an initial BMI <40 kg/m2 prior to GES had a significantly greater weight loss after 21 months (32%EWL) than the group who had an initial BMII>40 kg/m2 (20%EWL, no *P* value was reported). It is unknown if this difference was also significant at other follow-up time points. <u>Limitations/Comments:</u> A "baroscreen" (a screening algorithm) was "retrospectively applied" to the patients to predict GES weight loss from pre-implant age, gender, BMI and Short Form 36 questionnaire responses. At the time of the LOSS study, a single lead was implanted on the lesser curvature of the stomach. However, at the time the article was published, Miller et al. reported that the investigational centres were evaluating different positions of the electrodes and some centres were using 2 leads. Weight loss after implantation with GES is less than weight loss resulting from other bariatric procedures such as Roux-en-Y gastric bypass, vertical banded gastroplasty and adjustable gastric banding (up to 80% EWL) Unclear details about patient dropouts. At baseline there were 91 patients, at 24 months, there were 25 patients available for follow-up (27% of the original patient group). It was not mandatory that patients follow the standard diet and behaviour modification programs established at each investigational centre. No details were reported regarding resolution or improvement of obesity related comorbidities.

Appendix 6

Gastric Electrical Stimulation for Morbid Obesity: Studies of Lesser Quality than the O-01 Trial

DIGEST Trial

This was a nonrandomized open-label study performed at 2 centres (N=30; 26 women and 4 men). (59) Inclusion criteria consisted of age 18-50 years and a BMI 40-55 kg/m2 or 35-39 kg/m2 with one or more significant comorbidities. Prior to enrollment, patients had to pass a binge eating assessment and a psychological evaluation. In addition to the exclusion criteria from the O-01 Trial, patients with binge eating disorders and those with HbA1c >6mg/dl were excluded.

Two weeks after insertion, all patients had their devices activated and programmed to the same parameters. On subsequent visits, the parameters were individualized and it was discovered that using high generator output caused most patients to develop symptoms such as nausea, cramping, bloating or the sensation of electrical stimulation. Programming was subsequently readjusted in these patients.

Patients were followed monthly for 24 months and were required to complete the LEARN Behaviour Modification Program; the Satiety and Dietary Analysis Questionnaire; attend monthly support group meetings; and have an assessment of the presence or absence of change in eating habits and weight loss. Quality of life was measured by the SF-36 Quality of Life questionnaire. Dietary counseling was provided at clinic visits. The primary efficacy end point was the percent change in weight from baseline after 6 months of stimulation.

The mean age was 39 years and mean BMI was 42 kg/m2. There were no major complications or deaths after implantation.

At the 12 month follow-up, 71% of patients lost weight: 54% of patients lost more than 10% EWL and 29% of patients lost more than 20% EWL. At the 16-month follow-up, the mean %EWL was 23%.

The results for the Satiety and Dietary Analysis Questionnaire indicated that there was a significant reduction ($P<0.05$) in appetite, and increases in both between meal and end of meal satiety between baseline and when the questionnaire was administered (n=29, follow-up interval not reported).

Limitations to the DIGEST Trial were:
- Small sample size; no sample size calculation/justification.
- Results for the primary end point were not reported (6-month follow-up data).
- Follow-up interval for the Satiety and Dietary Analysis Questionnaire was not reported.
- Variable programming of the GES device during the trial.
- Unclear why patients with binge eating disorders and HbA1c >6 mg/dl were excluded.

Screening Algorithm

In an effort to better select patients likely to respond to GES, a retrospective analysis of preoperative data and weight loss results from 224 GES patients (from both trials in the United States) was performed using a screening algorithm developed to exclude patients unable or unwilling to attempt eating restraint and who eat without regard to appetite cues.

For the O-01 Trial, the algorithm suggested retention of 17% of the study patients (these patients had >40% EWL at a mean follow-up of 29 months, while the rejected patients had a 4% excess weight gain). For DIGEST the algorithm selected 33% of the study patients who had more than 30% EWL at a mean follow-up of 16 months (the rejected patients had minimal success).

Limitations to the screening algorithm were:
- It is unknown where the 224 patients were drawn from (103+30=133, not 224).
- The algorithm was used on patients who had variable stimulation parameters applied during the course of treatment.
- No information on the extent of presurgical counseling or treatment for all the included patients.

European Laparoscopic Obesity Stimulation Survey (LOSS) study

■ Miller et al. (35) evaluated the efficacy of GES in 91 morbidly obese patients who were part of the prospective, multicentre, European Laparoscopic Obesity Stimulation Survey (LOSS) study.

A "baroscreen" (a screening algorithm) was "retrospectively applied" to the patients to predict GES weight loss from preimplant age, gender, BMI and Short Form 36 questionnaire responses. At the time of the LOSS study, a single lead was implanted on the lesser curvature of the stomach. However, at the time the article was published, Miller et al. reported that the investigational centres were evaluating different positions of the electrodes and some centres were using 2 leads.

Stimulation was activated 1 month postoperatively. It was suggested, but not mandatory, that patients follow the standard diet and behaviour modification programs established at each investigational centre. Patients were requested to appear at follow-up at 1, 2, 3, 4, 6, 8, 10, 12, 15, 18, 21, and 24 months after implantation.

The study group consisted of 62 women (68%) and 29 men (32%). The mean age was 41 years, mean weight was 116 kg and the mean BMI was 41 kg/m^2.

No deaths or severe perioperative or postoperative complications were reported. In 15 patients (15.4%) the battery became low, and in 13 of these patients the generator was exchanged after a mean of 20 months. In 2 patients (2.1%) the GES was removed because of "ineffectiveness" (length of time from implantation not reported) and 2 patients who underwent a generator exchange developed wound infections and the GES was removed (length of time from implantation not reported).

Four patients experienced no weight loss and had the GES removed; these patients received either a gastric bypass or a gastric banding procedure (it is unclear if the 2 previously mentioned patients who had the device removed due to "ineffectiveness" are included in these 4 patients).

The mean % EWL was 20% at 12 months after surgery and about 25% at 2 years after implantation (Table 14). Patients with an initial BMI of less than 40 kg/m2 prior to GES had a greater weight loss after 21 months (32%EWL) than the group who had an initial BMI of greater than 40 kg/m2 (20% EWL; no *P* value was reported). It is unknown if this difference was also significant at other follow-up time points.

Table 14: Weight Loss During the 24-Month Follow-up of the LOSS Study.

	Baseline	1 month	3 months	6 months	10 months	15 months	24 months
No. of Patients	91	90	84	74	62	45	25
%EWL	0	8	14	19	21	20	25
Standard error	0	0.9	1.4	1.9	2.3	2.8	3.7

Adapted from Miller K, Hoeller E, Aigner F. The implantable gastric stimulator for obesity: an update of the European experience in the LOSS (Laparoscopic Obesity Stimulation Survey) study. Treatments in Endocrinology 2006; 5(1):53-5, with permission from Wolters Kluwer Health.

The patients in whom the baroscreen was applied (n=50) achieved a significantly greater EWL (31.4%) compared to patients who did not undergo baroscreening (n=37, 15% EWL), $P<0.01$.

Limitations to the study by Miller et al. were:

- Unclear details about 66 patient dropouts. At baseline there were 91 patients, at 24 months, there were 25 patients available for follow-up (27% of the original patient group).
- No ITT analysis.
- Baroscreening was retrospectively assessed.

A number of substudies (86-90) were published that reported results from individual hospitals and countries that participated in the LOSS study. Only the study by Cigaina (90) reported on the status of preimplantation and postimplantation comorbidites in the patients who received GES.

Cigaina examined blood pressure and oral glucose tolerance test (OGTT) in a subset of the LOSS study (65 Italian patients). (90) Gastric emptying was also assessed.

Blood Pressure

Blood pressure was reported in a subsubset of the 65 patients over a follow-up duration of 19 months (n=23 at 19 months). It is unknown why only 35 of the 65 patients had presurgical blood pressure reported considering that all patients had their blood pressure measured weekly for the first month, monthly for the next 6 months, and then every 6 months thereafter. It is also unknown how the 35 patients were selected (i.e., were they all hypertensive?). Over the follow-up period, patients experienced a statistically significant decrease in blood pressure (ANOVA $P<0.001$) (Table 15).

Table 15: Percent Excess Weight Loss and Blood Pressure of Patients Before and After Implantation of GES*

	Presurgery n=35	1 month postsurgery n=35	7 months postsurgery N=33	13 months postsurgery N=30	19 months postsurgery n=23
% EWL		6.87 (6.60)	15.30 (8.32)	20.95 (8.14)	19.73 (11.09)
BP systolic	171 (38.54)	138 (21.36)	133 (9.54)	129 (12.35)	126 (9.38)
BP diastolic	104 (19.32)	86 (10.82)	86 (6.17)	83 (9.87)	81 (9.56)

* values expressed as mean (SEM)
%EWL: % excess weight loss is the
BP refers to blood pressure

Reproduced with permission from OBESITY SURGERY 2004;Vol. 14 Suppl. 1: S14-22; Cigaina V. Long-term follow-up of gastric stimulation for obesity: the Mestre 8-year experience.

Oral Glucose Tolerance test

The oral glucose tolerance Test was assessed preoperatively and after GES implantation (mean [SD] 182[25] days) in 22 of the 65 patients. It is unclear why only 22 of the 65 patients were given the OGTT (i.e.,were they all diabetes patients and insulin dependent?). The Homeostatic Model Assessment Insulin Resistance index (HOMA) was used to evaluate insulin resistance and the insulinogenic index was used to evaluate beta cell activity.

The mean (SD) HOMA index fell from 4.35(1.09) at baseline to 2.98(0.55) at 7 months after stimulation suggesting an improvement in insulin resistance ($P<0.01$). The improvement of the HOMA index correlated significantly with the weight loss (r=0.92, no *P* value reported). There was no significant difference in the insulinogenic index before or after implantation (no *P* value reported). The author did not report whether this was associated with a decrease in drug/insulin requirements. The mean plasma glucose at 0, 30, 60, 90, 120, 150, and 180 days was approximately the same before and after stimulation and weight loss (no data reported).

The author did not discuss the clinical significance of the OGTT results, but added that "… the role of weight loss and the influence of gastric stimulation on the HOMA-IR index require further investigation."

Gastric Emptying

Gastric emptying time (using Technetium-99) was studied in 19 of the 65 patients before implantation and 6 months after GES activation. It is unclear why only 19 of the 65 patients had GET measured (i.e., how were they selected?). There was no statistically significant difference in gastric emptying time before or after GES activation, nor was there any statistically significant correlation between emptying time and weight loss (no *P* value reported).

Limitations to the substudies by Cigaina were:

- All the limitations that apply to the LOSS study.
- Weight, blood pressure, OGTT and gastric emptying data were reported for a subset of the original 65 patients and it is unclear why/how these subsets were selected.

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