NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of gastroelectrical stimulation for gastroparesis

Gastroparesis is a long-term condition in which the stomach does not empty normally. In this procedure a device is inserted into a pocket near the stomach with contacts under the lining of the stomach. This device electrically stimulates the muscles that empty the stomach.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in May 2013.

Procedure name

- Gastroelectrical stimulation for gastroparesis
- Electrical stimulation for gastroparesis (nausea and vomiting secondary to gastroparesis)
- Local electrical stimulation for gastroparesis

Specialist societies

- British Society of Gastroenterology
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland.

Description

Indications and current treatment

Gastroparesis is a chronic disorder in which the stomach empties more slowly than normal (delayed gastric emptying) in the absence of any type of mechanical obstruction. The most common symptoms are nausea and protracted vomiting. Other symptoms include abdominal bloating, and, in severe cases, malnutrition.

Gastroparesis most commonly occurs in people with type 1 diabetes. It can also occur in other situations such as after abdominal surgery or in association with anorexia nervosa and abdominal migraine. Some cases are idiopathic. Conservative treatment options include modification of dietary intake and medical therapy with antiemetics or prokinetics. Treatment options for chronic intractable (drug-refractory) symptoms include jejunostomy tube insertion for feeding, gastrostomy tube insertion for stomach decompression, and pyloroplasty.

Gastroelectrical stimulation is an option for treating chronic, intractable nausea and vomiting secondary to gastroparesis.

What the procedure involves

Electrical stimulation is delivered through an implanted system that consists of a neurostimulator and 2 leads. With the patient under general anaesthesia, the stimulating electrode of each intramuscular lead is fixed to the muscle of the distal part of the stomach using either laparotomy or laparoscopy. The connector end of each lead is then attached to the neurostimulator, which is placed in a small pocket in the abdominal wall through a surgical incision. When the neurostimulator is turned on, electrical impulses are delivered. The rate and amplitude of stimulation can be adjusted wirelessly with a hand-held external programmer. Patients may need to return to hospital to adjust or reprogram the device to obtain better results.

Clinical assessment
A diagnosis of gastroparesis is usually made from a gastric-emptying scan using scintigraphy of a solid-phase meal. The test is usually performed 2 hours after ingestion of a radiolabelled meal. Retention of 10% of the meal in the stomach at 4 hours is considered abnormal.

Outcome measures

Gastroparesis cardinal symptom index
The gastroparesis cardinal symptom index (GCSI) is based on 3 subscales: post-prandial fullness/early satiety (4 items); nausea/vomiting (3 items) and bloating (2 items). Severity of each symptom item is scored on a scale ranging from 0 (none) to 5 (very severe). The total of 9 individual symptom scores range from 0 to 45.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to gastroelectrical stimulation for gastroparesis. Searches were conducted of the following databases, covering the period from their commencement to 22 May 2013: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good-quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with gastroparesis; patients with nausea and vomiting in diabetes.
Intervention/test	Gastroelectrical stimulation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 1765 patients from 2 systematic reviews[1, 2], 2 randomised controlled trials (crossover)[3,4] and 5 case series[4–8]. There may be some overlap of patients.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

The previous guidance was based on 251 patients from 1 randomised controlled trial (crossover), 6 case series, data from an unpublished UK study and safety data from the Food and Drug Administration (FDA). There may be some overlap of patients.

Table 2 Summary of key efficacy and safety findings on gastroelectrical stimulation for gastroparesis

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>O'Grady G (2009)[1]

Systematic review (with meta-analysis)
Search period: 1992–2008
Study population: patients with medically refractory gastroparesis.
n = 364; 13 studies (1 RCT, all others case series);
Age: not reported
Sex: not reported

Study selection criteria: Patients with medically refractory gastroparesis treated by high-frequency GES. External, temporary and/or low-frequency GES studies, studies reporting duplicate outcomes from a previously published study and small case series were excluded.

Technique: not reported

Follow-up: not reported.
(It was noted in the study that where outcomes were reported at multiple times, 12-month outcomes were preferred.)
Conflict of interest/source of funding: supported in part by grants.</td>
<td>Number of patients analysed: varied by outcomes
<table>
<tr><th>Outcomes; n (pre-GES)</th><th>Number of studies; n (post-GES)</th><th>WMD (95% CI)</th><th>p; I^2</th></tr>
<tr><td>TSS n=97</td><td>3; n=77</td><td>6.52 (1.32 to 11.73)</td><td>0.01;89%</td></tr>
<tr><td>VSS n=122</td><td>4; n=92</td><td>1.45 (0.99 to 1.91)</td><td><0.00001; 32%</td></tr>
<tr><td>NSS n=122</td><td>4; n=92</td><td>1.69 (1.26 to 2.12)</td><td><0.00001; 39%</td></tr>
<tr><td>SF-36 PCS n=110</td><td>4[a]; n=78</td><td>8.05 (5.01 to 11.10)</td><td><0.00001; 0%</td></tr>
<tr><td>SF-36 MCS n=110</td><td>4[a]; n=78</td><td>8.16 (4.85 to 11.47)</td><td><0.00001; 0%</td></tr>
<tr><td>Change in weight (kg) n=96</td><td>4[a]; n=75</td><td>3.68 (-0.23 to 7.58)</td><td>NS; 0%</td></tr>
<tr><td>Gastric emptying-2 hours n=97</td><td>4; n=90</td><td>23.15 (7.93 to 38.37)</td><td>0.003; 98%</td></tr>
<tr><td>Gastric emptying-4 hours n=135</td><td>4; n=86</td><td>12.67 (9.76 to 15.58)</td><td><0.01; 0%</td></tr>
</table>
[a] includes data from non-peer reviewed publications. All significant changes were in favour of GES compared to pre-GES or sham GES (for TSS outcome).
Need for enteral or parenteral nutritional support:
Odds ratio: 5.53 (2.75 to 11.13); p<0.00001; I^2=27% (n=184 post-GES; 8 studies) [includes data from a conference abstract]; Need for nutritional support reduced from 44% (96/216) of patients at baseline to 11% (21/184) of patients at follow-up.</td>
<td>Complications
(reported in 10 of the 13 studies)

Device removal and/or replacement (because of a complication): 8.3% (22/265) of patients.
Reasons for device removal (n):
• infection (8);
• erosion through the skin (6);
• pain at implantation site (4);
• perforation of the stomach by the stimulation lead (2);
• device migration (1); and
• small bowel infarction related to volvulus around the devices wires (1).

It was reported that minor complications (not needing device removal or not reported frequently) were not presented in the systematic review.</td>
<td>Follow-up issues:
• Loss to follow-up ranged from 7% to 36%.
Study design issues:
• Searches conducted on databases including Medline and EMBASE.
• Quality assessment using Grading of Recommendations Assessment, Development and Evaluation scheme (this scheme is typically used to assess the quality of a particular outcome across studies, not to rate the quality of individual studies). Study quality was considered to be 'low' for most studies.
• Severity scores ranged from 0 (absent) to 4 (extremely severe). TSS is a sum of severity scores for 6 symptoms. Authors noted that the included studies used a variety of different scoring systems to evaluate change in symptoms (including unvalidated scales) and QoL; therefore a number of results could not be included in the summary statistics.
• Gastric emptying</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

Study details	Key efficacy findings	Key safety findings	Comments
			assessed using standardised radionucleotide scans of a solid meal. **Study population issues:** • Concurrent use of pharmacological therapy was reported. **Other issues:** • 2 studies included in the meta-analysis were included in the previous guidance, including 1 RCT (Abell 2003). The RCT (involving sham stimulation) was a crossover trial; phase 1 (RCT) lasted 2 months and for the remaining 10 months all patients were treated by GES.

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Chu H (2012)[2]
Systematic review (with meta-analysis)

Search period: 1995–2011
Study population: patients with DG (52%), IG (38%) or PSG (10%)
n = 601; 10 studies (2 crossover RCTs; all others case series)
Age: not reported
Sex: not reported

Study selection criteria: Full-text papers which included patients who were treated by GES >1 month, reported severity symptom scores on a scale of 0(absent) to 4(extremely severe) and reported data for TSS, VSS, NSS or gastric emptying were included. Studies with duplicate data or reporting on temporary GES were excluded.

Technique: not reported

Follow-up: range 12 months to 4 years

Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: varied by outcomes

Severity scores (for all patients)
<table>
<tr><td>Outcome (n pre-GES; number of studies)</td><td>WMD (95% CI); I^2 (n post-GES)</td></tr>
<tr><td>TSS (n=485; 6)</td><td>6.80 (4.04 to 9.57); 92.0% (n=425)</td></tr>
<tr><td>VSS (n=320; 5)</td><td>1.42 (1.22 to 1.62); 53.3% (n=291)</td></tr>
<tr><td>NSS (n=320; 5)</td><td>1.47(1.82 to 2.11); 85.6% (n=291)</td></tr>
</table>
Difference between pre- and post-GES severity scores were significant (p<0.00001) for all groups.

TSS - subgroups
<table>
<tr><td>Group (n pre-GES; number of studies)</td><td>WMD (95% CI); I^2 (n post-GES)</td></tr>
<tr><td>DG (n=180; 4)</td><td>8.96 (6.08 to 11.84); 68.6% (n=169)</td></tr>
<tr><td>IG (n=65; 3)</td><td>7.53 (5.35 to 9.70); 52.9% (n=58)</td></tr>
<tr><td>PSG (n=34; 2)</td><td>8.30 (5.48 to 11.12); 0% (n=33)</td></tr>
</table>
Difference between pre- and post-GES severity scores were significant (p<0.00001) for all subgroups.

Gastric emptying – 2 hours
<table>
<tr><td>Group (n pre-GES; number of studies)</td><td>WMD (95% CI) (n post-GES)</td><td>p; I^2</td></tr>
<tr><td>all patients (n=380; 6)</td><td>22.60 (11.82 to 33.37) (n=350)</td><td>p<0.0001; 96.8%</td></tr>
</table>
</td>
<td>Complications (8 studies reported complications)
• Infection (3.9%)
• Lead or device migration (2.7%)
• Complications of peptic ulcer disease, penetration of the electrode into the lumen of the stomach, skin erosion after abdominal wall trauma and small bowel obstruction caused by the wires (1.2%)
• Pain at implantation site (0.7%)</td>
<td>Study design issues:
• English and non-English language publications were searched in EMBASE, PubMed, ISI Web of Science and Google Scholar.
• Study quality was reported to be ‘low’ to ‘moderate’ (not assessed using a quality assessment tool).
• Authors noted that if trials included both temporary and permanent GES, data for patients treated by permanent stimulation were selected and that data reported at the latest time point was chosen.
• Authors noted there may be a greater representation of responders because some patients who lacked symptom response had their device removed.

Other issues:
• 2 RCTs with uncontrolled prospective follow-up were included in the meta-analysis; 1 RCT was included in the previous guidance (Abell 2003) and the</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

Study details	Key efficacy findings	Key safety findings	Comments

DG (n=137; 4)	29.44 (10.10 to 48.77); (n=131)	p=0.003; 98.5%
IG (n=36; 2)	10.00 (-4.70 to 24.70) (n=31)	NS; 96.1%
PSG (n=30; 2)	15.66 (10.11 to 21.21) (n=27)	p<0.00001; 0%

Gastric emptying – 4 hours

Group (n pre-GES; number of studies)	WMD (95% CI) (n post-GES)	p; I^2
all patients (n=408; 7)	13.04 (7.44 to 18.64) (n=378)	<0.00001; 87.4%
DG (n=137; 4)	21.50 (10.70to 32.31) (n=131)	0.0001; 93.1%
IG (n=36; 2)	6.92 (3.00 to 10.83) (n=31)	0.0005; 32.4%
PSG (n=30; 2)	29.10 (-17.94 to 76.14) (n=27)	NS; 85.8%

other RCT (McCallum 2010)[3] is included in table 2.

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>McCallum RW (2010)[3]

Phase I: prospective case series (1.5 months: device ‘on’ in all patients);

Phase II: Randomised (crossover) (6 months: device ‘on’ or ‘off’ for 3 months each);

Phase III: prospective case series (4.5 months: device ‘on’ in all patients)

USA (8 centres)

Recruitment period: not reported

Study population: patients with refractory nausea and vomiting secondary to DG; symptoms for a mean of 5.9 years and median vomiting frequency of 16.8 episodes per week.

n = 55

Age: mean 38 years

Sex: 66% female

Patient selection criteria: ≥18 years, symptomatic needing treatment for >1 year with gastric retention of 10% at 4 hours or >60% at 2 hours.

Technique: GES (Enterra Therapy System, Medtronic, Inc.) inserted using either laparoscopy or laparotomy. Device was programmed to standardised parameters (5 mA, 14 Hz, 330 µs, cycle on 0.1 s, cycle off 5 s) and adjusted at follow-up at 7.5 months.

Follow-up: 12 months</td>
<td>Number of patients analysed: varied for outcomes

Reduction in WVF
<table><tr><td>Timing</td><td>median % reduction (p value)</td></tr><tr><td>6 weeks (n=35)</td><td>57% (p<0.001) (reduced from median 19.5 episodes at baseline to median 4.75 episodes at 6 weeks)</td></tr><tr><td>During crossover phase (‘on’ vs ‘off’ state) (n=32)</td><td>0% (NS)</td></tr><tr><td>1 year (n=36) completed cases[a]</td><td>67.8% (p<0.001) (reduced from median 19.5 episodes at baseline to median 4.3 episodes at 1 year)</td></tr></table>[a] the per-protocol (n=29) and intention-to-treat (n=39) analyses were also reported and were significant (p<0.001).

Responders (defined as having a 50% or greater reduction in WVF from baseline to 12 months): 69.4% (25/36); p=0.01

Severity symptom scores - at 12 months (mean [SD]); (n=39)<table><tr><td></td><td>Baseline</td><td>Follow-up[a]</td></tr><tr><td>Vomiting</td><td>3.0 (1.2)</td><td>1.9 (1.3)</td></tr><tr><td>Nausea</td><td>3.2 (0.9)</td><td>2.0 (1.4)</td></tr><tr><td>Early satiety</td><td>2.4 (1.2)</td><td>1.5 (1.4)</td></tr><tr><td>Bloating</td><td>2.2 (1.3)</td><td>1.4 (1.4)</td></tr><tr><td>Postprandial fullness</td><td>2.7 (1.1)</td><td>1.5 (1.4)</td></tr><tr><td>Epigastric pain</td><td>2.1 (1.6)</td><td>1.2 (1.5)</td></tr><tr><td>Epigastric burning</td><td>1.5 (1.4)</td><td>1.2 (1.4)</td></tr><tr><td>TSS</td><td>17.1 (5.8)</td><td>10.7 (7.6)</td></tr></table>[a] difference in severity of score was significant (p≤0.001) except for epigastric burning.

• Baseline and follow-up scores for frequency of symptoms were also reported. All scores were significantly improved except for epigastric burning.

• There were no significant differences in frequency and severity</td>
<td>Adverse events: 732 events

Therapy- or device-related events : 6.1% (45); 15 considered serious:

• 7 device-related events: lead migration/dislodgements (3), device migrations (2), implant site haematoma (1), implant site infection (1; device removed)

• 8 events considered ‘therapy-related’ (caused by implantation procedure or associated with presence of device); within 2 weeks of the procedure.

• 5.6% (93/55) patients needed surgical intervention.

Patient-related (related to underlying or new diagnosis) events: 687 (438 considered serious)

• Hospitalisations: gastroparesis-related 32.8% (225 events; 40 patients)

• Other serious patient-related events: ketoacidosis (21), vomiting (10),haematemesis (8), hypoglycaemia (7) and hypertension (7).

Mortality (1 year): 12.7% (7/55) patients. Causes: cardiovascular (5) infection of knee/septicaemia (1), and cerebral aneurysm (1); none related to the device or therapy.</td>
<td>Follow-up issues:
• Of 55 patient enrolled, 10 were not randomised (reasons: device explant because of infection [1]; lost to follow-up [1]; patient refused [2]; medical condition prohibiting randomisation [3]; deaths [3]); 29% (16/55) lost to follow-up at 12 months.
Study design issues:
• Randomisation by 1:1 stratified by centre in a block size of 4; allocation concealment by sealed envelopes. Sample size calculation showed 32 patients were needed for analysis to detect a significant difference (p=0.05) at 80% power. Patients and investigators blinded to device setting during the crossover period.
• Primary aim was to show there was a reduction in WVF when the device was turned ‘on’ during the blinded crossover phase; a 25% reduction in WVF when device was ‘on’ compared with ‘off’ was considered clinically significant.
• WVF recorded by patients in a 28-day diary. Severity symptoms rating: 0 (absent)</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Conflict of interest/source of funding: All authors received funding from Medtronic, Inc. and sponsored by the manufacturer. Medtronic, Inc. also involved in study design and statistical analysis.</td>
<td>symptoms scores between ‘on’ and ‘off’ state except for vomiting (higher severity) during the ‘on’ state (n=36; p=0.02) and postprandial fullness (higher frequency in the ‘off’ state (n=36; p=0.01)
Short Form-36 QoL (n=38)
<table>
<tr><td></td><td>Baseline</td><td>Follow-up</td><td>p</td></tr>
<tr><td>PCS</td><td>29.5 (7.0)</td><td>36.4 (10.0)</td><td><0.001</td></tr>
<tr><td>MCS</td><td>33.5 (12.5)</td><td>40.4 (13.9)</td><td>0.009</td></tr>
</table>
Improvement was reported in the remaining 8 domains and was significant (p<0.05).
Gastric retention (%, median [IQR]) (n=28)
<table>
<tr><td></td><td>Baseline</td><td>Follow-up</td></tr>
<tr><td>2 hours</td><td>76.5 (50.4–91)</td><td>51 (37–69)</td></tr>
<tr><td>4 hours</td><td>46.5 (25–70.5)</td><td>20.5 (9.5–33)</td></tr>
</table>
Difference between baseline and follow-up was statistically significant (p<0.001).
There was no significant change in BMI or glycosylated haemoglobin (improved glucose control is an efficacy outcome in patients with diabetic gastroparesis).</td>
<td></td>
<td>to 4 (extremely severe, needing bed rest).
• Gastric emptying assessed using scintigraphy and low-fat test meal.
Study population issues:
• ‘No significant differences’ reported between the groups at baseline.
• 42% patients needed oral, enteral or parenteral support.
Other issues:
• Patients needed to be on prokinetic agents for at least 30 days before baseline and remain on it through completion of the crossover period.</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

Study details

McCallum RW (2014)[4]

USA (8 centres)

Recruitment period: 2002-8

Study design: **crossover RCT**

Study population: patients with chronic vomiting in ID-GP, mean 7.7 years of GP, median vomiting frequency of 17.3 episodes per week.

Patient selection criteria: ≥18 years, symptomatic needing treatment for >1 year with gastric retention of 10% at 4 hours or >60% at 2 hours, associated with GP of ID aetiology unresponsive/intolerant to drugs for a month, symptomatic and at least 7 episodes of vomiting in a week on a 28 day baseline dairy.

n=32

Age: mean 39 years

Sex:19% (6/32) male

Technique: GES (Enterra Therapy System, Medtronic, Inc.) inserted using either laparoscopy or laparotomy. Device was programmed to standardised parameters (5 mA, 14 Hz, 330 µs, cycle on 0.1 s, cycle off 5 s) and adjusted at follow-up at 7.5 months.

The stimulator was turned ON for 11/2 months followed by double-blind randomisation to consecutive 3-month crossover periods with the device either ON or OFF. ON

Key efficacy findings

Number of patients analysed: n=25

Reduction in weekly vomiting frequency (WVF) at 1½ months

During the initial unblinded ON period prior to randomisation, there was a median reduction in WVF of 61.2% (P < 0.001) at 1½ month compared with baseline (n=25) with a median WVF of 17.3 episodes at baseline and 5.5 episodes at 1½ months. The mean TSS for frequency was also decreased (14.6%, p<0.001) from 21.4 to 16.1 points.

Reduction in WVF and TSS in crossover phase (for 3 months)

	n	ON state	OFF state	p value
Median WVF	20	6.4	9.8	1.000
Frequency of TSS (mean±SD)	21	16.0±6.29	17.19±6.98	0.932
Severity of TSS (mean±SD)	21	12.10±5.83	13.81±6.95	0.556

Within patient median reduction in WVF was 17% (P > 0.10). 75% of patients preferred the ON vs OFF period (P = 0.021).

Reduction in WVF at 12 months

	n	Baseline	12 months (with ON stimulation)	Median % reduction	p value
Completed cases	18	17.3 episodes	2 episodes	87.1%	<0.001
Per-protocol*	19	17	2.3	85.3	<0.001
ITT	27	21.84	4	80.9	0.003

* included the patient with missing dairy data.

Improvements in GP symptoms, QOL, gastric emptying and days of hospitalisation at 12 months

	n	**Baseline**	**12 months**	**p value**
Frequency of	19	21.74±5.16	13±7.92	<0.001

Key safety findings

Adverse events	% (n)
Total events	170
Patient related events*	85 (145/170)
Therapy or device related	14 (24/170)
Serious adverse events 1 paraesthesia [resolved with device reprogramming], 1 lead migration/dislodgement and 1 migration of neurostimulator [required surgical intervention)	3
Deaths at 1 year (1 due to sudden cardiac arrest, other unknown)	6.3% (2/32)
Infections of leads and/or neuro-stimulator pocket	0
Explants	0

*70 were serious events. 58% of these were GP-related hospitalisations that occurred 41 times in 11 patients. Other events reported more than once were hypertension, infection or complications of feeding tube and headache.

Comments

Follow-up issues:

- Of 32 patient enrolled 5 were not randomised (reasons: 2 withdrew consent, 1 non-compliant, 2 exited due to study closure) and 2 patients withdrew consent after randomisation.
- 25 patients completed the crossover phase and 21 finished 1 year of follow-up (2 died, 1 exited due to medical condition, 1 exited due to study closure).

Study design issues:

- A prospective, multicenter, double-blinded, randomised, crossover study. Patients were randomised in a masked fashion.
- Primary aim was to show there was a reduction in WVF when the device was turned 'on' compared with OFF period.
- WVF recorded by patients in a 28-day diary. Severity symptoms rating: 0 (absent) to 4 (extremely severe, needing bed rest).
- Gastric emptying assessed using scintigraphy and low-fat test meal.
- Most subjects showed a

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

Study details	Key efficacy findings	Key safety findings	Comments
stimulation was followed in unblinded fashion for another 4.5 months. **Follow-up: 1 year (n=21)** Conflict of interest/source of funding: All authors received funding from Medtronic, Inc. and study sponsored by the manufacturer. Medtronic, Inc. also involved in study design and statistical analysis.	<table><tr><td>TSS (mean±SD)</td><td></td><td></td><td></td><td></td></tr><tr><td>Severity of TSS (mean±SD)</td><td>19</td><td>18.05±6.34</td><td>1.16±1.42</td><td>0.114</td></tr><tr><td>QOL –PCS (mean±SD)</td><td>19</td><td>32.66±8.8</td><td>37.86±13.28</td><td>0.043</td></tr><tr><td>MCS (mean±SD)</td><td>19</td><td>34.11±11.67</td><td>41.27±12.29</td><td>0.001</td></tr><tr><td>Gastric retention at 2 h (median)</td><td>16</td><td>63.5</td><td>49</td><td>0.016</td></tr><tr><td>gastric retention at 4h (median)</td><td>16</td><td>26</td><td>16.5</td><td>0.236</td></tr><tr><td>Days in hospital (median)</td><td>19</td><td>2</td><td>0</td><td>0.006</td></tr></table> Individual scores for vomiting, nausea, early satiety, bloating, postprandial fullness and epigastric pain were also decreased significantly from baseline to 12 months for both frequency and symptom scores ($p<0.05$). There was no significant reduction in frequency or severity symptom scores of epigastric burning at 12 months ($p=0.154$ and 0.114). Statistically significant SF 36 survey scores ($p<0.05$) were reported in the physical functioning, role physical, vitality, social functioning and mental health domains.		large reduction in WVF from baseline at 1½ months at which time they were randomised to either ON or OFF period for 3 months each. **Study population issues:** • 'No significant differences' reported between the groups at baseline. • 10 patients needed oral, enteral or parenteral support. **Other issues** • Authors state that 'lack of wash out period' between the ON and OFF periods compromised the data obtained and masked the GES effects. • The 'carry over effect' induced by GES for first 1½ months in all and 4½ months in half of the patients remains a confounding factor.

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

Study details	Key efficacy findings	Key safety findings	Comments
McCallum RW (2011)[5] **Case series** USA Recruitment period: not reported Study population: patients with drug-refractory severe gastroparesis for median of 3.5 years. 64% DG, 22% IG and 14% had PSG. n = **221** Age: median 38 years Sex: 74% female Patient selection criteria: IG, DG and PSG patients for >1 year, delayed solid gastric emptying assessed using scintigraphy (>60% retention at 2 hours and >10% at 4 hours). Technique: GES (Enterra Therapy System, Medtronic) placement by open laparotomy. Device programmed to standardised parameters (5 mA, 14 Hz, 330 µs, cycle on 0.1 s, cycle off 5 s) and adjusted during last 2 years of follow-up. Follow-up: **range 12–131 months** Conflict of interest/source of funding: 2 authors have participated in teaching and consulting activities sponsored by Medtronic, Inc. Financial support	Number of patients analysed**: varied by outcomes** **Individual symptom scores** (n=188) ; mean (SD) | | Baseline | Follow-up | |---|---|---| | Vomiting | 3.0 (1.2) | 1.4 (1.3) | | Nausea | 3.5 (1.6) | 1.6 (1.3) | | Early satiety | 2.9 (1.1) | 1.5 (1.3) | | Bloating | 2.8 (1.2) | 1.4 (1.3) | | Postprandial fullness | 2.8 (1.1) | 1.4 (1.2) | | Epigastric pain | 2.5 (1.3) | 1.3 (1.3) | | Epigastric burning | 2.1 (1.4) | 0.8 (1.1) | p<0.0001 compared with baseline **TSS-subgroups** (over 1 to 10 years) | | DG (n=114); | IG (n=43); | PSG (n=31); | |---|---|---|---| | Baseline: mean (SD) | 19.8 (5.0) | 18.6 (5.8) | 19.1 (3.4) | | Follow up: mean (SD)[a] [timing] | 8.7 (6.0) [at 54 months] | 9.7 (6.2) [at 57 months] | 10.9 (7.6) [at 63 months] | | % improvement | 55 | 47 | 48 | | Proportion of patients with >50% reduction of TSS (n=197) | 58 | 48 | 53 | [a] change was significant (p<0.001) compared with baseline. **Weight change** (mean [SD]); (n=124) Baseline: 149 lbs (41); At follow-up: 162 lbs (43); (change was significant; p<0.05) **Need for supplemental nutrition** (%[n]) (total parenteral nutrition, total parenteral nutrition and jejunostomy; gastrostomy-jejunal tubes) | | DG (n=142) | IG (n=48) | PSG (n=31) |	**Death**: 12% (26)-none GES therapy-related; 13 died within 1 year; timing unclear for remaining patients. **Device explanted**: n=24 (1 to 43 months after procedure) Reasons: • infection at the pulse generator or electrode sites (13); timing ranged from less than 2 months to 4 years after procedure; • lack of symptom improvement (6); • lead dislodgements (2); • small bowel obstruction caused by wires (1); • penetration of electrode into lumen of the stomach (1); and • associated with peptic ulcer disease (1). **Device repositioned or replaced:** n=10 (timing unclear) • lead dislodgement secondary to trauma or twisted wires (4); • depleted battery (4); and • device migration (2). **Additional procedures:** 10 patients needed a total gastrectomy (because of unimproved vomiting episodes and hospitalisations); in 3 patients this was within 1 year of implantation of the device. No malfunctioning of the GES system was reported.	**Follow-up issues:** •85% (188/221) of patients had at least 1 year of follow-up. 10 patients were lost to long-term follow-up. **Study design issues:** •Retrospective review •Severity of symptom assessed on scale from: 0 (absent) to 4 (extremely severe, needing bed rest) for 7 symptoms; graded by patients. •TSS was sum of the severity ratings. •Gastric emptying assessment based on 4-hour scintigraphic technique with a standardised solid meal. •Response rate calculation included all gastrectomy patients, patients who had devices removed because of efficacy and all patients who died after 6 months (n=197). •**Study population issues:** Patients were instructed to continue medications and changes to diet. **Other issues:** •TSS and gastric emptying outcomes reported in the Chu (2012)[2] meta-analysis included in table 2. •The study broadened the inclusion criteria following the Worldwide Anti-

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

Study details	Key efficacy findings	Key safety findings	Comments
by Medtronic, Inc.			Vomiting Electrical Stimulation Study (Abell 2003 study; included in the O'Grady (2009)[1], Chu (2012)[2] and in the original guidance) to include patients with gastroparesis secondary to gastric surgery, specifically partial gastric resection, vagotomy or vagal nerve damage. • Some patients included in this study are included in the studies reporting 5 years follow-up in the systematic reviews[1-2].

Baseline	34 (48/142)	47 (22/48)	35 (11/31)
Follow up	6 (3/48)	27 (6/22)	18 (2/11)

Gastric retention (median %[IQR]) (n=119)

	DG (n=75)	IG (n=20)	PSG (n=24)
2 hours baseline	70.5 (53.0-86.0)[a]	63 (43.0-71.0)	80.5 (68.0-92.0)[a]
2 hours follow-up	68.0 (45.0-84.0)	60.5 (53.5-78.0)	65.0 (35.5-86.0)[b]
4 hours baseline	39.5 (21.0-68.0)[a]	30.5 (10.0-40.0)	48.0 (33.0-73.0)[a]
4 hours follow-up	30.0 (9.0-57.0)	20.5 (6.2-55.5)	40.0 (4.5-73.0)[b]

[a] p<0.05 compared with IG group at baseline.
[b] p<0.05 compared with baseline.

Glycosylate levels: mean HbA_{1c} levels reduced from 8.5% at baseline to 78% at last follow-up (results reported for n=37 patients with diabetes for whom data were available for >1 year).

Use of medications: reduced after 1 year (p≤0.05) in all patient groups.

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

Study details	Key efficacy findings	Key safety findings	Comments
Zehetner J (2013)[6] **Comparative case series** USA Recruitment period: 2003-12 Study population: patients with medically refractory and/or PSG. n = **103** (72 GES; 31 laparoscopic subtotal or total gastrectomy) Age: median 42 years (GES); median 53 years (gastrectomy). Sex: 66% female Patient selection criteria: gastroparesis (DG, IG, PSG) diagnosed using a 4-hour nuclear gastric-emptying study. Technique: GES (Enterra Therapy system, Medtronic) implantation done either laparoscopically or by mini-incision. Follow-up: **median 33 months (GES); median 27 months (gastrectomy)** Conflict of interest/source of funding: one author is a consultant for manufacturer (Medtronic, Inc). The other authors have no conflicts of interest.	Number of patients analysed: varied for different outcomes **Treatment effect** | | GES | Gastrectomy | |---|---|---| | Symptoms improved[a] | 63% (38/60) | 87% (26/30) | | Symptoms same(estimated from graph) | 15% | 10% | [a] p=0.02 **Median GCSI scores** There was no significant difference in the median total GCSI scores for patients treated by GES compared with gastrectomy group (primary or secondary) (numbers not reported).	| **Complications** | GES (n=72) | Gastrectomy (n=31) | |---|---|---| | Death <30 days[a] | 2.7% (2) because of small bowel infarction and heart failure. | 3.2% (1) because of myocardial infarction. | | Other complications (<30 days)[b]. | Atrial fibrillation (1). | Wound infection (2); sepsis (2); atrial fibrillation (1). | | Other complications (>30 days)[a] | Infection (n=3; needing device removal); deaths (n=10; 3 to 72 months; unrelated to device). | small bowel infarction (n=1). | [a] no significant difference; [b] overall difference: p=0.02 **Treatment failure** •Treatment failure was reported in 26% (19/72) of patients treated by GES. Reasons were: failure to respond (14); device infections needing removal (3), device malfunction (1) and damage to device (1). • Of the 14 patients who failed to respond to GES, 1 patient had device removed and 13	**Study design issues:** • Retrospective review. • Symptom severity assessed using GCSI (total of 9 individual symptoms); score 0-45. • Proportion of patients with symptoms reported. Postoperative outcome evaluated by classifying symptoms as 'improved', 'same' or 'worse'. **Study population issues:** • Aetiology: 63% DG, 25% IG, 12% PSG. • There was significant difference between the groups in relation to preoperative symptoms: vomiting and dehydration (higher proportion in patients treated by GES); bloating and early satiety (higher proportion in patients treated by gastrectomy). • In the GES group patient were significantly (p<0.01) younger, higher proportion of patients with diabetes, had shorter operating time and a shorter median

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

Study details	Key efficacy findings	Key safety findings	Comments
		were switched to a subtotal gastrectomy for persistent symptoms. 11 patients subsequently reported symptom improvement and 2 died at 22 and 72 months (unrelated to procedure). **Worsening of symptoms** (estimated from graph) **GES**: 20%; **Gastrectomy:** 3%.	length of stay.

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

Study details	Key efficacy findings	Key safety findings	Comments
Timratana P (2013)[7] **Case series** USA Recruitment period: 2001-11 Study population: patients with medical refractory IG (55%) or DG (49%). n = **113** (2 revision procedures) Age: mean 40 years Sex: 91% female Patient selection criteria: >18 years who have failed medical management or unable to tolerate medications and have undergone 4-hour gastric emptying study. Those who have undergone prior gastric surgery excluded. Technique: laparoscopic placement of GES (Enterra Therapy System, Medtronic). Adjustments were made to device settings (3 volts and 0.1 s on cycle) at set time points or as needed. Follow-up: **mean 27 months** Conflict of interest/source of funding: 2 authors have received honoraria from various manufacturers; 3 have no conflicts of interest. No financial support received.	Number of patients analysed: **113** **Symptom improvement** Symptom improvement was reported in 80% (91/113) patients. Complete or partial resolution of symptoms (80%) was reported in both IG and DG groups. There were lower numbers of patients with nausea, vomiting, and pain symptoms following the procedure in both DG and IG groups (significant change; p<0.01). The change in number of patients with bloating was not significant (numbers not reported). **Need for supplemental nutrition** Type of access (timing) / n / n (at follow-up) Enteral (before GES) / 20 / 6 Parenteral (before GES) / 4 / 0 Enteral (placed concomitantly with GES or after the procedure) / 14 / 5 **Change in BMI** There was no significant change in BMI in DG or IG groups.	Death: n=4 patients with DG (timing 1 to 26 months after GES); related to underlying disease Device-related adverse events: 7% (8) • Stimulator malfunction: n=2; (1 secondary to electrical malfunction and 1 lead fracture) • Battery depletion: n=6 (mean 75 months after procedure) Additional complications (timing unclear): • Pacer removal: 6% (7) • Pacer infection: 3% (3) • Device migration (malposition): 5% (6) • Device, lead or wire malfunction: 2% (2) • Wire erosion: 3% (3); needed replacement in 1 • Skin necrosis: n=1; (needed device removal)	**Study design issues:** • Retrospective review of prospective collected data. • Change in symptoms based on clinician interview and reduction or cessation of medications. **Study population issues:** • Higher proportion of females in the IG group. Significantly longer duration of gastroparesis and cardiac comorbidities in patients with DG. • Patients remained off all narcotics and pro-motility agents for 2 weeks before 4-hours solid gastric emptying study. **Other issues:** • Results of the adverse events were compared to open GES (McCallum [2011][4]). A significantly higher proportion of device migration (malposition) was reported in the current study.

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

Study details	Key efficacy findings	Key safety findings	Comments
Keller DS (2013)[8] **Case series** USA Recruitment period: 2000-11 Study population: patients with refractory gastroparesis; IG (54%); DG (44%); not reported (2%) n = **266** Age: mean 38 years Sex: 80% female Patient selection criteria: patients >18 years with documented delayed gastric emptying on scintigraphy. Technique: under general sedation, GES implanted mainly by mini-laparotomy. Follow-up: **mean 39 months** Conflict of interest/source of funding: not reported	Number of patients analysed: **233** **Symptom improvement** (n=74) 70% reported improved symptoms of pain, bloating and nausea. Device was explanted in 2 patients whose symptoms improved. In patients with higher BMI there was higher likelihood of need for revision surgery for the GES subcutaneous pocket (Odds ratio 4.45).	**Death:** n=2 (treatment failure; unrelated complications of nephrotic syndrome; timing after 30 days; no further details) **Device explanted:** 12%(27) Reasons: n No relief of symptoms 11 Mechanical device issues 9 Persistent infection 4 Stimulator eroded through skin 3 **Revisions/complications:** 15%(34) Reasons: n Revision of stimulator in subcutaneous pocket 21 Incisional hernia repair 4 Battery failure 3 Laparotomy for small bowel obstruction 2 Lead erosion 2 Colectomy for colitis 1 Enterocutaneous fistula (no further details) 1 **Nutritional support:** Additional procedures needed in 19%(45) of patients (needed 77 procedures) Procedures / Number of procedures Jejunostomy 33 Central access for total parenteral nutrition 21 Gastrostomy tube insertion 19 Combined gastrostomy-jejunostomy tube insertion 4	**Follow-up issues:** • 12% (33/266) patients excluded from analysis because of unavailable medical records. **Study design issues:** • Retrospective review. • Treatment before and after GES placement were not standardised (especially regarding the need for nutritional support) • Data on symptoms based on medications, and assessment of QoL and symptom severity assessed on questionnaires; numbers not reported. **Study population issues:** • 36% of patients were overweight or severely obese. **Other issues:** • Additional complications (needing readmission) were reported in 14 patients. These are not reported here because there was some overlap with the safety events reported under revision procedures.

Abbreviations used: CI, confidence interval; DG, diabetic gastroparesis; GES, gastroelectrical stimulation; GCSI, Gastroparesis Cardinal Symptom Index; I^2,test for heterogeneity; IG, idiopathic gastroparesis; IQR, interquartile range; MCS, mental component score; NS, not significant; NSS, nausea severity score; PCS, physical component score; PSG, post-surgical gastroparesis; QoL, quality of life; TSS, total symptom severity score; VSS, vomiting severity score; WMD, weighted mean difference; WVF, Weekly vomiting frequency.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>O'Loughlin PM (2013)[9]

Case series
UK
Recruitment period: 2008–10
Study population: patients with gastroparesis refractory to medical therapy

n = 17
Age: median 46 years
Sex: 47% female

Patient selection criteria: patients with ongoing symptoms of gastroparesis despite dietary changes and medical therapy with abnormal gastric emptying.
Technique: GES device (Enterra, Medtronic) inserted via open technique.

Follow-up: median 14 months

Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 14

Mean GCSI score
<table>
<tr><th></th><th>Pre-GES</th><th>Post-GES</th></tr>
<tr><td>Abdominal pain</td><td>3.1</td><td>1.5</td></tr>
<tr><td>Bloating</td><td>3.0</td><td>2.0</td></tr>
<tr><td>Nausea</td><td>4.1</td><td>2.1</td></tr>
<tr><td>Vomiting</td><td>3.1</td><td>1.1</td></tr>
</table>
Mean reduction in total GCSI score was 51%; from 13.4 at baseline to 6.4 after the procedure (Z=0.0013).

Patient satisfaction
'Most' patients described an improvement in quality of life and some specifically noting a reduction in sick leave.

Change in medication use (n=14)
Median number of prescribed medications reduced form a median of 3.5 before the procedure to 1.5 after the procedure.</td>
<td>Device removal : n=3
• Gastric perforation related to an episode of vomiting (2 months after procedure) was reported in 1 patient; leading to removal of device and repair of the perforation.
• Device removal was reported in another patient because of discomfort related to the implant and poor clinical response (timing unclear).
• One patient is awaiting device removal because there has been no improvement in symptoms and the patient is aware of the presence of the device.

Device recalibrations: needed in 2 patients.

Pain and discomfort (for 2 weeks after the procedure) in the abdominal wall was reported when lying directly on the device (numbers not reported).</td>
<td>Follow-up issues:
• 3 patients did not respond to questionnaire (including 1 patient waiting to have device removed).

Study design issues:
• Retrospective review of a prospectively collected database in a single centre.
• Gastric emptying study assessed using either solid or liquid scintigraphy (n=16) or barium emptying (n=1)
• Symptom severity assessed using questionnaire based on GCSI. Symptom score on a 6 category scale ranging from (nil or never) to (very severe or always).

Study population issues:
• Aetiologies: DG (53%), IG (41%) and PSG (6%)</td>
</tr>
</table>

Efficacy

Symptom scores

A systematic review of 364 patients with 13 studies (including a randomised controlled trial and prospective case series) reported improvement in the total symptom severity, vomiting severity and nausea severity scores in patients treated by gastroelectrical stimulation. The study reported improvement in total symptom severity score (compared with baseline or sham procedure) based on a meta-analysis of 3 studies with 77 patients (weighted mean difference [WMD] 6.5 [95% confidence interval {CI} 1.3 to 11.7]; p=0.01; I^2=89% indicating significant heterogeneity), improvement in vomiting severity score (compared with baseline) based on meta-analysis of 4 studies with 92 patients (WMD 1.5 [95% CI 1.0 to1.9]; p<0.00001; I^2=32%) and improvement in nausea severity score (compared with baseline) based on meta-analysis of 4 studies with 92 patients (WMD 1.7 [95% CI 1.3 to 2.1]; p<0.00001; I^2=39%). Length of follow-up was not reported but 12-month outcomes were preferred[1].

A meta-analysis of 4 studies including 169 patients with diabetic gastroparesis treated by gastroelectrical stimulation (part of a systematic review of 10 studies including 2 crossover randomised controlled trials and 8 case series with 601 patients) reported improvement in total symptom severity score (weighted mean difference 8.96 [95% CI 6.1 to 11.8]; p<0.00001; I^2=68.6%). A meta-analysis of 3 studies including 58 patients with idiopathic gastroparesis treated by gastroelectrical stimulation reported improvement in total symptom severity score (weighted mean difference 7.5 [95% CI 5.4 to 9.7]; p<0.00001; I^2=52.9%). A meta-analysis of 2 studies including 33 patients with post-surgical gastroparesis treated by gastroelectrical stimulation reported improvement in total symptom severity score (weighted mean difference 8.3 [95% CI 5.5 to 11.1]; p<0.00001; I^2=0%). Length of follow-up was unclear in all the analyses[2].

Quality of life

The systematic review of 364 patients reported a significant improvement in Short Form-36 (SF-36) physical component score (WMD 8.1 [95% CI 5.0 to 11.1]) and the mental component score (WMD 8.16 [95% CI 4.9 to 11.5]) based on meta-analyses of 4 studies with 78 patients. The difference was statistically significant (p<0.00001) for both outcomes with no heterogeneity. Length of follow-up was not reported but 12-month outcomes were preferred[1].

A crossover trial of 55 patients reported a significant improvement in SF-36 physical component score from 29.5 (standard deviation [SD] 7.0) at baseline to 36.4 (SD 10.0) at 12-month follow-up (n=38; p<0.001) and in mental component score from 33.5 (SD 12.5) at baseline to 40.4 (SD 13.9) at 12-month follow-up (n=38; p=0.009)[3].

Gastric emptying

The systematic review of 601 patients reported a significant improvement in gastric emptying at 2 hours (based on a meta-analysis of 6 studies with 350 patients): WMD 22.6 (95% CI 11.8 to 33.4); p<0.0001; I^2=96.8% indicating significant heterogeneity. Subgroup analysis showed there was a significant improvement in gastric emptying at 2 hours in patients with diabetic gastroparesis (n=131; WMD 29.4 [95% CI 10.1 to 48.8]; p=0.003; I^2=98.5%) and patients with post-surgical gastroparesis (n=27; WMD 15.7 [95% CI 10.1 to 21.2]; p<0.00001; I^2=0% indicating no heterogeneity). The change in gastric emptying was not significant in patients with idiopathic gastroparesis[2].

A meta-analysis of 7 studies including 378 patients with diabetic, idiopathic or post-surgical gastroparesis treated by gastroelectrical stimulation (part of a systematic review of 601 patients) reported a statistically significant improvement in gastric emptying at 4 hours (assessed using standardised radionucleotide scans of a solid meal): weighted mean difference 13.0 (95% CI 7.4 to 18.6); p<0.00001; I^2=87.4% indicating significant heterogeneity. Subgroup analysis showed that the improvement was statistically significant in patients with diabetic or idiopathic gastroparesis but not in patients with post-surgical gastroparesis. Length of follow-up was unclear in all the analyses[2].

A randomised controlled trial of 32 patients with gastroparesis of idiopathic origin reported that there was a significant reduction in weekly vomiting frequency from 61.2% to 87% (p<0.001) and improvements in gastroparesis symptoms, gastric emptying and days of hospitalisation (p<0.05) at 1 year follow-up[4].

Weight gain

The systematic review of 364 patients showed no statistically significant change in weight (based on meta-analysis of 4 studies with 75 patients): WMD 3.7 (95% CI −0.2 to 7.6); I^2=0%. Length of follow-up was not reported but 12-month outcomes were preferred (includes data from a conference abstract)[1].

A case series of 221 patients showed a significant weight change from mean 149 pounds at baseline to 162 pounds at follow-up (p<0.05) in 124 patients; follow-up ranged from 12 to 131 months[5].

Need for nutritional support

In the systematic review of 364 patients, a meta-analysis of 8 studies including 184 patients with gastroparesis treated by gastroelectrical stimulation reported a reduction in need for nutritional support from 44% (96/216) patients at baseline to 11% (21/184) at follow-up; odds ratio 5.5 (95% CI 2.8 to 11.1); p<0.00001; I^2=27%. Length of follow-up was not reported but 12-month outcomes were preferred[1].

Safety

Death

Death (within 30 days) was reported in 3% (2/72) of patients treated by gastroelectrical stimulation due to small bowel infarction and heart failure, and 3% (1/31) of patients treated by gastrectomy due to myocardial infarction, in a comparative case series of 103 patients[6].

Gastric perforation

Gastric perforation related to an episode of vomiting (2 months after the procedure) was reported in 1 patient in a case series of 17 patients; the device was removed and the perforation repaired[9].

Device removal

Device removal was reported in 11% (24/221) of patients in the case series of 221 patients (timing ranged from 1 to 43 months after the procedure). Reasons were infection at the pulse generator or electrode sites (13 patients), lack of symptom improvement (6 patients), lead dislodgements (2 patients), small bowel obstruction caused by wires (1 patient), penetration of electrode into lumen of the stomach (1 patient) and 'associated with peptic ulcer disease' (1 patient)[4]. Erosion through the skin (in 6 patients), device migration (in 1 patient) and pain at implantation site (in 4 patients) resulting in device removal or replacement (timing unclear) were reported in a systematic review of 364 patients[1].

Skin erosion

Erosion through the skin because of the stimulator (leading to device removal) was reported in 1% (3/266) of patients treated by gastroelectrical stimulation in a case series of 266 patients[8].

Lead erosion

Lead erosion (leading to a revision procedure) was reported in less than 1% (2/233) of patients in the case series of 266 patients[8].

Infection

Infections at the pulse generator or electrode sites (leading to device removal) were reported in 6% (13/221) of patients in the case series of 221 patients[5].

Treatment failure

Treatment failure was reported in 26% (19/72) of patients treated by gastroelectrical stimulation in a case series of 103 patients. Reasons included failure to respond (14 patients), device malfunction (1 patient) and damage to the device (1 patient). The device was removed in 1 patient, and 13 patients whose symptoms failed to respond were treated by gastrectomy. Eleven patients subsequently reported symptom improvement and 2 patients died at 22 and 72 months (unrelated to the procedure)[6].

Battery failure

Battery failure resulting in device replacement was reported in 2% (4/221) of patients in the case series of 221 patients (timing unclear)[5].

Validity and generalisability of the studies

- Studies in table 2 included adults with idiopathic gastroparesis or gastroparesis associated with diabetes or surgery.
- Most of the studies reported permanent gastroelectrical stimulation.
- Gastric emptying was assessed mainly using scintigraphy.
- The CE mark for the device (Enterra Therapeutic System) is indicated for the treatment of chronic intractable (drug-refractory) nausea and vomiting secondary to gastroparesis.

Existing assessments of this procedure

A clinical guideline developed by the American College of Gastroenterology (2013)[10] concluded that gastric electrical stimulation 'may relieve symptoms, including weekly vomiting frequency, and the need for nutritional supplementation, based on open-label studies'. The guideline recommended that 'GES [gastric electrical stimulation] may be considered for compassionate treatment in patients with refractory symptoms, particularly nausea and vomiting. Symptom severity and gastric emptying have been shown to improve in patients with DG [diabetic gastroparesis], but not in patients with IG [idiopathic gastroparesis] or PSG [post-surgical gastroparesis]. (Conditional recommendation, moderate level of evidence)'

The Ontario Health Technology Assessment Series (2009)[11] evidence update concluded that findings from an earlier review in 2006 remained unchanged: '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).'

The Alberta Heritage Foundation for Medical Research (2006)[12] concluded that 'The current evidence, based on an average of 12 months of follow-up on the safety and efficacy of GES for patients with idiopathic GP or GP associated with diabetes or surgery who tolerated the implanted device, is not adequate to support the routine use of this procedure. It would, however, be considered a last-resort treatment after all conventional treatment regimes had failed to control symptoms of nausea and vomiting. The research on GES for GP associated with other conditions has yet to be done.'

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) Horizon scanning prioritising summary (2006)[13] concluded that 'Notwithstanding the lack of randomised controlled trials, in the context of a common condition associated with considerable morbidity where current

therapies have significant limitations and side effects, the available evidence regarding the Enterra system provides sufficient encouragement and the potential to improve the symptoms and overall quality of life of patients with gastroparesis to warrant the conduct of more robust randomised multicentre research, including an economic evaluation. It is not recommended that this procedure be used outside the context of a clinical trial protocol.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Gastroelectrical stimulation for gastroparesis (current guidance). NICE interventional procedure guidance 103 (2004). Available from http://guidance.nice.org.uk/IPG103

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or royal college. The advice received is their individual opinion and does not represent the view of the society.

Dr Philip Bliss, Dr Adam Farmer, Mr Sri Kadirkamanathan (British Society of Gastroenterology).

- One specialist adviser has performed this procedure and 2 have never performed this procedure.
- Two specialist advisers stated that this procedure is established, and 1 stated that this is a novel procedure and is of uncertain safety and efficacy.
- Comparators: medical therapy, supplemental feeding, endoscopic injection of botulinum toxin or total gastrectomy (1 specialist adviser noted that gastrectomy is an option but should not be considered as a real alternative). All 3 specialist advisers stated that fewer than 10% of specialists engaged in this area of work perform this procedure.
- Key efficacy outcomes: reduction in symptoms (vomiting, nausea and bloating), reduced need for or stopping nutrition support, improvements in nutritional status and reduction in hospital admission.

- Adverse events reported in literature: lead migrations, lead dislodgments, haematoma, device explant because of infection, need for surgical intervention and superficial infection.
- Anecdotal adverse events: infection at subcutaneous pocket, local infection, lead disconnected, pain at site of insertion of subcutaneous stimulation device and ‘pins and needles’ sensation from the stimulation device.
- Theoretical adverse events: lead migration, electrode displacement and generic adverse effects of any surgical procedure (risk of general anaesthesia, post-operative chest infection, wound infection or thromboembolic events).
- Two specialist advisers stated that the procedure is likely to be carried out in fewer than 10 specialist centres in the UK and 1 stated the procedure is likely to be carried out in a minority of hospitals, but at least 10.
- Two specialist advisers stated the potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is minor and 1 stated the potential impact would be moderate.

Patient commentators’ opinions

NICE’s Public Involvement Programme sent 50 questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers), and 1 questionnaire was sent to a patient who contacted NICE directly. NICE received 27 completed questionnaires.

The completed questionnaires represented patients aged between 16 and 88 (mean = 48, median = 45). 22 patients (81%) were female and 5 patients (19%) were male.

Overall people were very positive about the procedure in improving the way their stomach empties. All patients stated they would have the procedure again and also would recommend the procedure to another patient with gastroparesis.

Issues for consideration by IPAC

- This guidance is being reviewed as a result of a formal request.
- Ongoing trials:
  - NCT00903799 Medico-economic Evaluation of ENTERRA Therapy Clinical efficacy and efficiency of gastric electrical stimulation (Enterra) for refractory nausea and/or vomiting. Type: randomised controlled trial (device activated or not); location: France; estimated enrolment: 220; study start date: June 2009; estimated study completion date: November 2015 (ongoing but not recruiting participants).
  - NCT00568373 Gastric pacemaker implantation for gastroparesis (HUD) Gastric electric stimulation-Enterra Therapy for the treatment of chronic intractable (drug-refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology. Type: case series; location: USA; estimated enrolment: 40; study start date: June 2007; estimated study completion date: January 2014.

References

1. O'Grady G, Egbuji JU, Du P et al. (2009) High-frequency gastric electrical stimulation for the treatment of gastroparesis: a meta-analysis. World Journal of Surgery. 33 (8):1693–1701.

2. Chu H, Lin Z, Zhong L et al. (2012) Treatment of high-frequency gastric electrical stimulation for gastroparesis. Journal of Gastroenterology and Hepatology. 27 (6):1017–26.

3. McCallum RW, Snape W, Brody F et al. (2010) Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association 8: 947–54.

4. McCallum, R. W., Sarosiek, I., Parkman, H. P., Snape, W., Brody, F., Wo, J., and Nowak, T(2013). Gastric electrical stimulation with Enterra therapy improves symptoms of idiopathic gastroparesis. Neurogastroenterology and Motility.25 (10) 815-e636.

5. McCallum RW, Lin Z, Forster J et al. (2011) Gastric electrical stimulation improves outcomes of patients with gastroparesis for up to 10 Years. Clinical Gastroenterology and Hepatology. 9 (4):314–9.

6. Zehetner J, Ravari F, Ayazi S et al. (2013) Minimally invasive surgical approach for the treatment of gastroparesis. Surgical Endoscopy 27: 61–6.

7. Timratana P, El-Hayek K, Shimizu H et al. (2013) Laparoscopic gastric electrical stimulation for medically refractory diabetic and idiopathic gastroparesis. Journal of Gastrointestinal Surgery 17: 461–70.

8. Keller DS, Parkman HP, Boucek DO et al. (2013) Surgical outcomes after gastric electric stimulator placement for refractory gastroparesis. Journal of Gastrointestinal Surgery 17: 620–6.

9. O'Loughlin PM, Gilliam AD, Shaban F et al. (2013) Pre-operative gastric emptying time correlates with clinical response to gastric electrical stimulation in the treatment of gastroparesis. Surgeon Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland 11: 134–40.

10. Camilleri M, Parkman HP, Shafi MA et al. (2013) Clinical guideline: management of gastroparesis. American Journal of Gastroenterology; 108: 18–37

11. Medical Advisory Secretariat (2009) Gastric electrical stimulation (GES): an evidence update. Ontario Health Technology Assessment Series; 9 (Suppl. 1): 1–9 [accessed 5 October 2013]

12. Moga C and Harstall (2006) Gastric electrical stimulation (Enterra therapy system) for the treatment of gastroparesis. HTA Report 37

13. Enterra therapy gastric electrical stimulation (GES) system for the treatment of the symptoms of medically refractory gastroparesis. Horizon Scanning Report ASERNIP-S 2006

Appendix A: Additional papers on gastroelectrical stimulation for gastroparesis

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Abell T, Lou J, Tabbaa M, Batista O, et al. (2003) Gastric electrical stimulation for gastroparesis improves nutritional parameters at short, intermediate, and long-term follow-up. Journal of Parenteral & Enteral Nutrition 27(4):277–81.	N= 12 Follow up=5 years	Total symptom score and weekly vomiting frequency significantly improved from baseline.	Included in table 2 of the original overview. Larger studies included in table 2.
Abell TL, Van Cutsem E, Abrahamsson H et al. (2002) Gastric electrical stimulation in intractable symptomatic gastroparesis. Digestion 66(4):204–12.	N= 33 (uncontrolled) Follow up=12 months	Median vomiting frequency, total symptom score, physical and mental composite scores and gastric emptying (2 and 4 hours) significantly improved from baseline to 6 months and 12 months follow-up.	Included in table 2 of the original overview. Larger studies with longer follow-up included in table 2.
Abell T, McCallum R, Hocking M et al. (2003) Gastric electrical stimulation for medically refractory gastroparesis. Gastroenterology 125(2):421–8.	N= 33(Randomised phase: stimulation either 'on' or 'off' for 1 month and crossed over to other mode for 1 month) Follow up= 1 month	Median weekly vomiting frequency was 13.5 during the 'off' phase and 6.8 during the 'on' phase.	Included in table 2 of the original overview. Larger studies with longer follow-up included in table 2.
Abell TL, Johnson WD, Kedar A et al. (2011) A double-masked randomized, placebo-controlled trial of temporary endoscopic mucosal gastric electrical stimulation for gastroparesis. Gastrointestinal endoscopy 74(3):496-503	N= 58 (crossover trial of two consecutive, 4-day sessions) Follow up=72 hours	An overall treatment effect of a slight, non-significant daily decrease in average vomiting scores, -0.12 (-0.26 to 0.03; p = 0.116), was observed (pooled stimulation effects across sessions).	Larger studies with longer follow-up included in table 2.
Al-Juburi A, Grander S, Barnes J et al. (2005) Laparoscopy shortens length of stay in patients with gastric electrical stimulators Journal of the Society of Laparoendoscopic Surgeons 9:305-10	N=36 (18 laparoscopy vs 18 laparotomy) Follow up= mean 29 months in the laparoscopy group and mean 43 months in the laparotomy group	Laparoscopic placement is associated with shorter length of stay. Patients who underwent laparotomy had higher vomiting scores.	Compares different techniques.
Anand C, Al-Juburi A, Familoni B et al. (2007) Gastric electrical stimulation is safe and effective: a long-term study in patients with drug-refractory gastroparesis in three regional centers.	N=214 Follow up=median 4 years	87% were alive and had significantly reduced gastrointestinal symptoms, and improved health-related quality of life, with evidence of improved gastric emptying, and 90% of the patients had	Studies with longer follow-up included in table 2. Included 33 patients with temporary device.

Digestion 75:83-9.		a response in at least 1 of 3 main symptoms. Device explanted, usually for pocket infections, were later reimplanted successfully. There were no deaths directly related to the device.	
Anarparthy R, Pehlivanov N, Grady J et al. (2009) Gastroparesis and gastroparesis-like syndrome: response to therapy and its predictors. Digestive Diseases and Science 54(5):1003-10.	N= 69 Follow up=3 years	71% (49/69) were responders. Higher global GCSI score, bloating subscale score, and severity of stomach distension presentation correlated with an unfavourable response.	Large studies included in table 2.
Andersson S, Ringström G, Elfvin A et al. (2011) Temporary percutaneous gastric electrical stimulation: a novel technique tested in patients with non-established indications for gastric electrical stimulation. Digestion 83:3-12.	N= 27 Follow up= 6 months	Four of 7 patients improved with increased stimulation. Twenty of the 22 responders received a permanent GES implant, 90% of them still being responders at last follow-up.	Larger studies (for patients with established indications) included in table 2.
Ayinala S, Batista O, Goyal A et al. (2005) Temporary gastric electrical stimulation with orally or PEG-placed electrodes in patients with drug refractory gastroparesis. Gastrointestinal endoscopy 61:455-61.	N=13 Follow up= unclear	For patients receiving temporary gastric electrical stimulation demonstrated a rapid, significant, and sustained improvement in vomiting frequency score results similar to those with permanent stimulation.	Larger studies included in table 2.
Becker JC, Dietl KH, Konturek JW et al. (2004) Gastric wall perforation: a rare complication of gastric electrical stimulation. Gastrointestinal endoscopy 59:584-6.	N=1 Follow up= 41 months	Electrode perforation of the gastric wall was reported 41 months after implantation. The electrode was replaced.	Larger studies included in table 2.
Brody F, Nam A, Drenon E et al. (2007) Laparoscopic insertion of gastric electrodes for electrical stimulation Journal of laparoendoscopic and advanced surgical techniques. 17(1):1-6	N= 31 Follow up= unclear	Two patients developed cellulitis at the generator site (treated with antibiotics).	Larger studies included in table 2.
Brody F, Vaziri K, Saddler A et al. (2008) Gastric electrical stimulation for	N=50 Follow up=median 28 months	The total symptom severity score (19.05±8.04) decreased significantly at 6 months	Included in Chu (2012)[2] systematic review in table 2.

gastroparesis. Journal of the American College of Surgeons. 207(4):533-8.		(12.92 ± 7.41, p < 0.001) and 12 months (14.05 ± 8.28, p < 0.01). Similarly, total frequency score (20.39 ± 8.08) decreased significantly at 6 months (15.01 ± 7.37, p < 0.01) and 12 months (15.71 ± 7.40, p < 0.05). At 12 months (n = 27), gastric retention at 2 hours was decreased significantly from 66% ± 21% to 50% ± 22% (p < 0.04) and normalised in 11 of 27 patients. The severity of symptoms was reduced in all patients with normal gastric retention postoperatively. Finally, gastric retention at 4 hours was reduced by 14%, but the difference was not significant.	
Cutts TF, Luo J, Starkerbaum W et al (2005) Is gastric electrical stimulation superior to standard pharmacologic therapy in improving GI symptoms, healthcare resources, and long-term healthcare benefits? Neurogastroenterology and Motility 17: 35-43	N=18 (9 GES vs 9 intensive medical therapy) Follow up= 3 years	The TSS score decreased from 37.9 to 23.4 in patients treated by GES and from 39.3 to 34.8 in patients treated by medical therapy (the difference was not significant).	Larger studies included in table 2.
De CJ, Shapsis A, and Jordan C. (2005) Gastric electrical stimulation: a novel treatment for gastroparesis. Journal of the Society of Laparoendoscopic Surgeons / Society of Laparoendoscopic Surgeons 9 (3): 364-7.	N=1 Follow up= 6 months	Two months after the procedure, the patient was symptom free with unrestricted diet and improved glycaemic and haemoglobin levels. At 6 months follow-up, normal pattern of gastric emptying (2 hours) was reported.	Larger studies included in table 2.
De CJ, Goldfarb B, Shapsis A et al. (2006) Electrical stimulation for gastroparesis: Gastric motility restored. Surgical endoscopy: ultrasound and interventional techniques 20 (2): 302-6.	N=16 Follow up= 6 months	Discomfort because of the proximity of stimulator to the inferior costal margin and stimulator explanation for overlying skin erosion caused by abdominal wall trauma were reported.	Included in Chu (2012)[2] systematic review included in table 2.
Elfvin A, Gothberg G, Lonroth H et al. (2011) Temporary percutaneous	N=3 Follow up= 24 months	All 3 patients were responders to temporary stimulation	Larger studies included in table 2.

and permanent gastric electrical stimulation in children younger than 3 years with chronic vomiting. Journal of Pediatric Surgery 46 (4): 655-61.		and were subsequently implanted with permanent device. A reduction in vomiting >50% was reported.	
Filichia LA and Cendan JC. (2008) Small case series of gastric stimulation for the management of transplant-induced gastroparesis. Journal of Surgical Research.148 (1):90-3.	N=13 Follow up= mean 12 months	11 patients reported an improvement in quality of life.	Larger studies included in table 2.
Forster J, Sarosiek I, Lin Z, Durham S, et al. (2003) Further experience with gastric stimulation to treat drug refractory gastroparesis. American Journal of Surgery; 186(6):690–5.	N= 55 Follow up= 12 months	Total symptom score and quality of life scores significantly improved ($p<0.05$) at 6 and 12 months.	Included in table 2 of original overview. Larger studies included in table 2.
Forster J, Sarosiek I, Delcore R, Lin Z, et al. (2001) Gastric pacing is a new surgical treatment for gastroparesis. American Journal of Surgery; 182(6):676–81.	N=25 Follow up=upto 12 months	There was a significant change from baseline to 3 months	Included in table 2 of original overview. Larger studies included in table 2.
Gourcerol G, Leblanc I, Leroi AM et al. (2007) Gastric electrical stimulation in medically refractory nausea and vomiting. European Journal of Gastroenterology and Hepatology. 19(1):29-35.	N=15 (8 patients had delayed gastric emptying in; 7 patients had normal emptying). Follow up= 6 months	Gastrointestinal Quality of Life Index and nausea/vomiting scores improved in patients with normal and delayed gastric emptying.	Included in O'Grady (2009)[1]systematic review included in table 2.
Gourcerol G, Chaput U, Leblanc I et al. (2009) Gastric electrical stimulation in intractable nausea and vomiting: assessment of predictive factors of favorable outcomes. Journal of the American College of Surgeons.209 (2):215-21.	N=33 Follow up=6 months	In multivariate analysis, baseline quality of life and appetite alterations were predictive of improvement; previous history of gastric surgery was associated with failure.	Larger studies included in table 2.
Gourcerol G, Huet E, Vandaele N et al. (2012) Long term efficacy of gastric electrical stimulation in intractable nausea and vomiting. Digestive and Liver Disease 44:563-8.	N=31 Follow up= mean 80 months	Quality of life showed 27% improvement ($p<0.01$) and 56% of patients showed improvement at 5 years. Device was explanted because of lack of improvement in 6 patients and 1 patient	Larger studies included in table 2.

		died.	
Gourcerol G, Ouelaa W, Huet E et al. (2013) Gastric electrical stimulation increases the discomfort threshold to gastric distension. European Journal of Gastroenterology & Hepatology 25:213-7.	N=9 Follow up=6 months	Gastroelectrical stimulation increased gastric maximal tolerable volume to distension from 522 ml (SD 64) at baseline to 628 ml (SD60) at follow-up.	Larger studies included in table 2.
Hannon MJ, Dinneen S, Yousif O et al. (2011) Gastric pacing for diabetic gastroparesis-does it work? Irish Medical Journal 104(5):135-7	N=4 Follow up= 9 months to 3 years	There was no improvement in glycaemic control following GES.	Larger studies included in table 2.
Hyman P, Schropp K, Sarosiek et al. (2009) Feasibility and safety of gastric electrical stimulation for a child with intractable visceral pain and gastroparesis. Journal of Pediatric Gastroenterology and Nutrition.49 (5):635-8.	N=1 Follow up=37 months	At follow-up, the patient continued to receive J-tube feedings and had weekly episodes of pain and retching lasting 12-24 hours. No device complications.	Larger studies included in table 2.
Islam S, Vick LR, Runnels MJ et al. (2008) Gastric electrical stimulation for children with intractable nausea and gastroparesis. Journal of Pediatric Surgery.43 (3): 437-42.	N=9 Follow up= range 8 to 42 months	There was sustained improvement in symptoms and improved quality of life in 7 patients.	Larger studies included in table 2.
Jayanthi, N. V., Dexter, S., and Sarela, A. (2013) Gastric electrical stimulation for treatment of clinically severe gastroparesis. Journal of Minimal Access Surgery. 9 (4) 163-167.	Study design = case series (audit) n=71 FU= median 10 months(range 1-28 months (n=31)	We conducted a clinical audit of consecutive gastroparesis patients, who had been selected for GES, from May 2008 to January 2012. Delayed gastric emptying was diagnosed by scintigraphy of >=50% global improvement in symptom-severity and well-being was a good response. Results: There were 71 patients (51 women, 72%) with a median age of 42 years (range: 14-69). The aetiology of gastroparesis was idiopathic (43 patients, 61%), diabetes (15, 21%), or post-surgical (anti-reflux surgery, 6 patients; Roux-en-Y	Larger studies with longer follow-up included.

		gastric bypass, 3; subtotal gastrectomy, 1; cardiomyotomy, 1; other gastric surgery, 2) (18%). At presentation, oral nutrition was supplemented by naso-jejunal tube feeding in 7 patients, surgical jejunostomy in 8, or parenterally in 1 (total 16 patients; 22%). Previous intervention included endoscopic injection of botulinum toxin (botox) into the pylorus in 16 patients (22%), pyloroplasty in 2, distal gastrectomy in 1, and gastrojejunostomy in 1. It was decided to directly proceed with permanent GES in 4 patients. Of the remaining, 51 patients have currently completed a trial of temporary stimulation and 39 (77%) had a good response and were selected for permanent GES, which has been completed in 35 patients. Outcome data are currently available for 31 patients (idiopathic, 21 patients; diabetes, 3; post-surgical, 7) with a median follow-up period of 10 months (1-28); 22 patients (71%) had a good response to permanent GES, these included 14 (68%) with idiopathic, 5 (71%) with post-surgical, and remaining 3 with diabetic gastroparesis. Conclusions: Overall, 71% of well-selected patients with intractable gastroparesis had good response to permanent GES at follow-up of up to 2 years.	
Lahr CJ, Griffit J, Subramony C et al. (2013) Gastric electrical stimulation for abdominal p ain in patients with symptoms of	N=68 Follow up = mean 275 days	After permanent GES, mean symptom scores (abdominal pain, early satiety, distension, nausea and vomiting) significantly improved	Larger studies included in table 2.

gastroparesis The American Surgeon 457-64.		from baseline to follow-up (p<0.001).	
Lin ZY, McCallum RW, Schirmer BD et al. (1998) Effects of pacing parameters on entrainment of gastric slow waves in patients with gastroparesis. American Journal of Physiology; 274(1 Pt 1):G186–91.	N=13	Gastric pacing at a frequency up to 10% higher than the intrinsic gastric slow wave frequency and with an amplitude of 4 mA and a pulse width of 300 ms is able to completely entrain the gastric slow wave and normalize gastric dysrhythmias in patients with gastroparesis.	Included in appendix A of original overview. No relevant efficacy outcomes. Larger studies included in table 2.
Lin Z, Forster J, Sarosiek I et al. (2003) Treatment of gastroparesis with electrical stimulation. Digestive Diseases and Sciences; 48(5):837–48.		Most of these studies seem to indicate that LFS is able to normalize gastric dysrhythmias and entrain gastric slow waves and accelerate gastric emptying. On the other hand, HFS has no effect on gastric emptying but is able to significantly reduce symptoms of nausea and vomiting in gastroparetic patients	Included in table 2 of original overview.
Lin Z, Forster J, Sarosiek I et al. (2004) Treatment of diabetic gastroparesis by high-frequency gastric electrical stimulation. Diabetes Care.27 (5):1071-6.	N=48 Follow up=12 months	4 patients has device removed (3 to 17 months after procedure) because of infection at pulse generator pocket site. 12 patients needed nutritional support at baseline and only 4 needed supplemental enteral feeding at follow-up.	Included in O'Grady (2009)[1] systematic review
Lin Z, Forster J, Sarosiek I et al. (2004) Effect of high-frequency gastric electrical stimulation on gastric myoelectric activity in gastroparetic patients. Neurogastroenterology and Motility; 16(2):205-12.	N=15 Follow up=3 months	Symptom severity of nausea and vomiting reduced from baseline to 3 months (p<0.01) but there was no significant change in gastric retention.	Included in table 2 in the original overview. Larger studies included in table 2.
Lin Z, McElhinney C, Sarosiek I et al. (2005) Chronic gastric electrical stimulation for gastroparesis reduces the use of prokinetic and/or antiemetic medications and the need for hospitalizations.	N= 37 Follow up= 1 year	Mean total symptom severity reduced, overall quality of life significantly improved; with higher quality of life in patients off antiemetics.	Larger studies included in table 2.

50: 1328-34.			
Lin Z, Sarosiek I, Forster J et al. (2006) Symptom responses, long-term outcomes and adverse event beyond 3 years of high-frequency gastric electrical stimulation for gastroparesis. Neurogastroenterology and Motility. 18: 18-27	N= 55 Follow up= 3 years	Significant improvement in symptoms was maintained for more than 3 years. Six patients had device removed.	Larger studies included in table 2.
Lin Z, Hou Q, Sarosiek I et al. (2008) Association between changes in symptoms and gastric emptying in gastroparetic patients treated with gastric electrical stimulation. Neurogastroenterology and Motility.20 (58): 464-70.	N=63 Follow up= 1 year	Improvements in vomiting, nausea and epigastric pain were significantly correlated with reduction in 4-hour gastric retention between baseline and 12 months.	Larger studies included in table 2.
Liu RC, Sabnis AA, and Chand B. (2007) Erosion of gastric electrical stimulator electrodes: Evaluation, management, and laparoscopic techniques. Surgical Laparoscopy, Endoscopy and Percutaneous Techniques. 17(5): 438-41.	N=2 Follow up=16 and 21 months after procedure	Gastric stimulator electrode erosion through the gastric wall at 16 and 21 months after procedure.	Larger studies included in table 2.
Maranki JL, Lytes V, Meilahn JE, et al. (2008) Predictive factors for clinical improvement with Enterra gastric electric stimulation treatment for refractory gastroparesis. Digestive Disease and Sciences; 53:2072–8.	N=29 Follow up= mean 148 days	At follow-up, 14 of 28 patients felt improved, 8 remained the same, and 6 worsened. Adverse events included 1 incidence of deep vein thrombosis because of central line placement, 2 syncopal episodes.	Included in O'Grady(2009)[1] and Chu (2012)[2] systematic reviews. Larger studies included in table 2.
Mason RJ, Lipham J, Eckerling G et al. (2005) Gastric electrical stimulation: An alternative surgical therapy for patients with gastroparesis. Archives of Surgery. 140(9):841-8.	N=29 Follow up= median 20 months	Nutritional support was discontinued in 19 patients. Additional procedures were needed in 4 patients (because of poor outcome in 3 patients).	Included in O'Grady(2009)[1] systematic review and interim report of Zehetner (2013)[5] included in table 2.
McCallum RW, Chen JD, Lin Z et al. (1998) Gastric pacing improves emptying and symptoms in patients with gastroparesis. Gastroenterology. Mar; 114(3):456-61.	N=9 Follow up= 1 to 3 months	Gastric retention time (mean 2 hours) reduced form 77% to 56.6% ($p<0.05$).	Included in table 2 of original overview. Larger studies included in table 2.

McCallum R, Lin Z, Wetzel P et al. (2005) Clinical response to gastric electrical stimulation in patients with postsurgical gastroparesis. Clinical Gastroenterology and Hepatology. 3(1): 49-54.	N=16 Follow up=12 months	Device was removed in 1 patient because of infection (12 months after procedure), device replaced because electrodes were detached (23 months after procedure). Physical and mental component quality of life scores significantly improved at 6 and 12 months ($p<0.05$).	Larger studies included in table 2.
McKenna D, Beverstein G, Reichelderfer M et al. (2008) Gastric electrical stimulation is an effective and safe treatment for medically refractory gastroparesis. Surgery. 144 (4): 566-74.	N=19 Follow up= mean 38 weeks	Frequency of vomiting decreased in 75% of patients with diabetic gastroparesis and all patients with idiopathic gastroparesis within 6 weeks. Mean total symptom severity scores improved signification up to 1 year.	Larger studies included in table 2.
Musunuru S, Beverstein G, and Gould J. (2010) Preoperative predictors of significant symptomatic response after 1 year of gastric electrical stimulation for gastroparesis. World journal of surgery. 34(8):1853-8.	N=25 Follow up=6 months	4 patients with idiopathic gastroparesis did not improve more than 20% at 1 year. All patients with diabetic gastroparesis had a durable symptomatic improvement.	Larger studies included in table 2.
Ong, C. and Logarajah, V. (2013). Gastric pacing in a child with severe gastroparesis and review of the literature. Proceedings of Singapore Healthcare.21 (3) pp 205-208.	n = 1 Case report	A case of a 13-year-old girl with life-long severe idiopathic gastroparesis who was successfully treated by gastric pacing.	Larger studies with longer follow-up included.
Pinto DA, Kaidar-Person O, Cho M et al. (2008) Laparoscopic placement of a gastric stimulator for the treatment of gastroparesis: A pilot study technique and results. Surgical Laparoscopy, Endoscopy and Percutaneous Techniques.18(2):144-50.	N=7 Follow up=2 to 10 months	All patients indicated reduction of symptoms. There were no conversions or complications.	Larger studies included in table 2.
Reddymasu SC, Lin Z, Sarosiek I et al. (2010) Efficacy of gastric	N=18 (patients with normal gastric	No adverse events related to GES. Reduction in symptoms	Larger studies included in table 2.

electrical stimulation in improving functional vomiting in patients with normal gastric emptying. Digestive diseases and sciences.55(4): 983-7.	emptying) Follow up=12 months	and improvement in quality of life was reported at 1 year.	
Sibartie V, Quigley EM, O'Donnell A et al. (2005) Gastric electrical stimulation: a report of two cases. Irish Medical Journal. 98(10):245-6.	N=2 Follow up= 6 months	Reduction in symptoms and improvement in quality of life was reported at 6 months.	Larger studies included in table 2.
Teich S, Mousa HM, Punati J et al. (2013) Efficacy of permanent gastric electrical stimulation for the treatment of gastroparesis and functional dyspepsia in children and adolescents. Journal of Pediatric Surgery 48:178-83.	N=16 Follow up= 0.5 to 23 months	There was significant improvement in severity and frequency of vomiting and nausea.	Larger studies included in table 2.
Ullah S, Arsalani-Zadeh R, Sedman P et al. (2011) Temporary gastric neuromodulation for intractable nausea and vomiting Annals of the Royal College of Surgeons of England 93:623-8.	N=6 Follow up= 7 days	Improvements in symptom scores and in quality of life (mental and physical component) scores were reported.	Larger studies included in table 2.
Van Der Voort IR, Secker JC, Dietl KH et al. (2005) Gastric electrical stimulation results in improved metabolic control in diabetic patients suffering from gastroparesis. Experimental and Clinical Endocrinology and Diabetes.113 (1): 38-42.	N= 17 Follow up=12 months	Weekly vomiting and nausea frequencies decreased significantly and gastric retention rates improved significantly.	Included in Chu (2012)[2] systematic review. Larger studies included in table 2.
Velanovich V. (2008) Quality of life and symptomatic response to gastric neurostimulation for gastroparesis. Journal of Gastrointestinal Surgery.12(10):1656-63.	N=42 Follow up=median 12 months	Eleven patients had no response or had worsening symptoms. There was significant improvement in health transition and social functioning domain.	Included in O'Grady (2009)[1] systematic review. Larger studies included in table 2.

Appendix B: Related NICE guidance for gastroelectrical stimulation for gastroparesis

Guidance	Recommendations
Interventional procedures	**Gastroelectrical stimulation for gastroparesis (current guidance). NICE interventional procedure guidance 103 (2004)** 1.1 Current evidence on the safety and efficacy of gastroelectrical stimulation for gastroparesis does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake gastroelectrical stimulation for gastroparesis should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear, written information. Use of the Institute's Information for the public is recommended. • Audit and review clinical outcomes of all patients having gastroelectrical stimulation for gastroparesis. 1.3 The procedure should only be performed in specialist gastroenterology units with expertise in gastrointestinal motility disorders. 1.4 Current evidence on the efficacy of the procedure relates mainly to relief from nausea and vomiting, which occurs in some patients. There is little evidence that the procedure improves gastric emptying. Further research will be useful, and the Institute may review the procedure upon publication of further evidence.

Appendix C: Literature search for gastroelectrical stimulation for gastroparesis

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	11/12/2013	Issue 12 of 12, December 2013
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	11/12/2013	Issue 4 of 4, October 2013
HTA database (Cochrane Library)	11/12/2013	Issue 11 of 12, November 2013
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	11/12/2013	Issue 4 of 4, October 2013
MEDLINE (Ovid)	11/12/2013	1946 to November Week 3 2013
MEDLINE In-Process (Ovid)	11/12/2013	December 10, 2013
EMBASE (Ovid)	11/12/2013	1974 to 2013 Week 49
PubMed	11/12/2013	n/a
JournalTOCS	11/12/2013	n/a

MEDLINE search strategy

1 Gastroparesis/
2 gastropares*.tw.
3 ((gastric or stomach) adj3 (stases or stasis or empty*)).tw.
4 Gastric Emptying/
5 ((gastric or stomach) adj3 (paresis or paraly*)).tw.
6 or/1-5
7 gastroelectric*.tw.
8 GES.tw.
9 Electric Stimulation/
10 Electric Stimulation Therapy/
11 (((electric* or gastric*) adj3 stimulat*) or pulse*).tw.
12 (electrotherap* or electrostimulat*).tw.
13 Electrodes, Implanted/
14 (implant* adj3 (neurostimulat* or stimulat* or electrod*)).tw.
15 (gastric adj3 (pacemaker* or pacing* or pacer*)).tw.
16 Implantable Neurostimulators/
17 neurostimulat*.tw.
18 (high adj3 frequen* adj3 stimul*).tw.

19 medtronic.tw.
20 enterra*.tw.
21 or/7-20
22 6 and 21
23 animals/ not humans/
24 22 not 23
25 limit 24 to ed=20120930-20130531