

Horizon Scanning in Surgery: Application to Surgical Education and Practice

**Implantable gastric stimulation device for
glycemic control and/or obesity management**

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Disclaimer

This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment that is based on a search of studies published in the peer-reviewed literature. This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

This report is not intended to be used as medical advice or to diagnose, treat, cure or prevent any disease, nor should it be used for therapeutic purposes or as a substitute for a health professional's advice. The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) does not accept any liability for any injury, loss or damage incurred by use of or reliance on the information.

Objective

This horizon scanning assessment provides short, rapidly completed, 'state of play' documents. These provide current information on technologies to alert clinicians, planners, and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can then assist clinicians, planners, and policy makers to control and monitor the introduction of new health technologies as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

This report is a preliminary summary of the safety, effectiveness and cost-effectiveness of implantable gastric stimulators for glycemc control and/or obesity management.

Acronyms

ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
DEA	Drug Enforcement Agency
DIAMOND	Diabetes improvement and metabolic normalization device
DIGEST	Dual implantable gastric electrical stimulation trial
EWL	Excess weight loss
FDA	Food and Drug Administration
HbA1c	Glycated hemoglobin
IGS	Implantable gastric stimulation
LOSS	Laparoscopic obesity stimulation survey
NHLBI	National Heart, Lung, and Blood Institute
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
SHAPE	Screened health assessment and pacer evaluation
WHO	World Health Organization

Introduction

Background

Obesity

Obesity is defined by the World Health Organization (WHO) as a body mass index (BMI) of at least 30 kg/m² (WHO 2013a). The etiology of obesity is highly complex, including genetic, psychological, physiologic, environmental, social, and economic factors. The food environment has shifted over time to promote overeating; high calorie foods are affordable and easily accessible in large portion sizes (Wright & Aronne 2012). At the same time, levels of physical activity have decreased. While 62 per cent of adults in the United States of America (USA) report engaging in recommended levels of activity, only 10 per cent of adults actually comply with exercise guidelines when levels are measured by accelerometry (Tucker, Welk & Beyler 2011). Other factors that contribute to increasing rates of obesity include sleep debt, drug-induced weight gain, decline in cigarette smoking, endocrine disruptors, and an aging population (Wright and Aronne 2012). In addition, the populations with the highest obesity rates tend to have the lowest incomes and to be the least educated (Drewnowski 2012).

The health burden of obesity is largely a result of the increased risk of comorbidities such as diabetes, cardiovascular disease, and cancer. For example, for every 5 kg/m² increase in BMI in men, the risk of developing colon cancer and esophageal cancer increases by 24 per cent and 52 per cent, respectively. The same change in BMI for women increases the risk of endometrial cancer by 59 per cent, gall bladder cancer by 59 per cent, and post-menopausal breast cancer by 12 per cent (Wang et al. 2011). Obesity is also associated with an increase in nonfatal, but disabling and costly, disorders such as osteoarthritis, sleep apnea, and asthma (Wang et al. 2011).

Diabetes

Diabetes is a group of diseases characterized by high levels of blood sugar (hyperglycemia). Diabetes mellitus type 1 is caused by autoimmune destruction of the insulin-producing pancreatic cells. Diabetes mellitus type 2 is a metabolic disorder in which insulin is produced but is not used effectively. Type 2 is the most common form of diabetes and accounts for about 95 per cent of cases in adults (Centers for Disease Control and Prevention 2012). Pre-diabetes is a condition in which blood glucose levels are higher than normal but are not high enough for the individual to be considered diabetic. People with pre-diabetes have an increased risk of developing diabetes. It is thought that up to 33 per cent of the adult population in the USA have pre-diabetes, although less than 10 per cent of these individuals have been diagnosed with the condition (Centers for Disease Control and Prevention 2012).

Diabetes is diagnosed by measuring either the percentage of glycated hemoglobin (HbA1c) in the blood or the level of plasma glucose in the blood after fasting for at least eight hours. The American Diabetes Association guidelines state that the criteria for a diagnosis of diabetes is an HbA1c level of at least 6.5 per cent or a fasting plasma glucose level of at least 126 mg/dL (7 mmol/L). Pre-diabetes is defined as an HbA1c level of between 5.7 and 6.4 percent or a fasting plasma glucose level of between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L). As diabetes is characterized by hyperglycemia, glycemic control is fundamental to the management of the disease (American Diabetes Association 2013).

The health effects associated with hyperglycemia can be severe. In the short term, diabetes is characterized by weight loss and increased thirst and hunger. The long-term effects include damage to the heart and blood vessels (leading to heart disease and stroke), eyes (leading to blindness), kidneys (leading to renal failure), and nerves (leading to impotence and foot disorders or possibly amputation) (WHO 2013b).

Weight loss has been recognized as a key factor in the control and prevention of coronary heart disease, hypertension, type 2 diabetes, and other chronic degenerative diseases (Pasanisi et al. 2001). Sustained weight loss of 10 per cent of body mass has been shown to reduce blood glucose levels, which is associated with reducing the risk of developing hypertension, increasing blood levels of high-density lipoproteins, and reducing levels of low-density lipoproteins and triglycerides (American Diabetes Association et al. 2008; Pasanisi et al. 2001). Patients with pre-diabetes can delay or prevent the onset of type 2 diabetes by losing between five and seven per cent of their body weight and performing 150 minutes per week of moderate exercise (Centers for Disease Control and Prevention 2012).

Burden of disease

Obesity

The increased prevalence of obesity is a worldwide health concern. In 2008, 502 million adults were estimated to be obese (WHO 2013a). In 2009–10, 33 per cent (78 million) of adults and 17 per cent (12.5 million) of youth in the USA were obese (Ogden et al. 2012a; Ogden et al. 2012b; Wright and Aronne 2012). Between 2000 and 2010, the prevalence of obesity in the USA rose from 28 per cent to 36 per cent among men and from 33 per cent to 36 per cent among women (Ogden et al. 2012a). Non-Hispanic blacks have the highest age-adjusted obesity rate (50%), compared with Mexican Americans (40%), Hispanics (39%) and non-Hispanic whites (34%) (Ogden et al. 2012a).

Treatment of obesity and related conditions was estimated to cost US\$147 billion in 2008, of which roughly half was publicly funded. This equates to 2.8 per cent of total healthcare expenditure, and has risen from US\$78.5 billion in 1998 (Finkelstein et al. 2009; Trogdon et al. 2012; Wang et al. 2011). These increasing costs are almost entirely a result of treating the diseases associated with obesity (Finkelstein et al. 2009). In addition to medical costs, the indirect costs of obesity, such as reduced years of disability-free life, early retirement, work absenteeism, and reduced productivity, are substantial (Wang et al. 2011).

Diabetes

In 2007, 17.5 million Americans were diagnosed with type 2 diabetes, 6.3 million people were estimated to have undiagnosed diabetes, and nearly 57 million Americans were estimated to have pre-diabetes. The total estimated cost of type 2 diabetes was estimated to be between US\$160 billion and US\$190.5 billion per annum in 2007 (Dall et al. 2010; Finkelstein et al. 2009).

People aged over 60 years are far more likely to develop diabetes, with a prevalence of 16.9 per cent compared with 1.8 per cent among people aged between 20 and 39 years. The prevalence of diabetes is highest among people who are overweight (6%) or obese (13%) compared with people who have a BMI lower than 25 kg/m² (4%) (Cheung et al. 2009). Significantly higher rates

of diabetes occur among Mexican Americans (12%) and non-Hispanic black Americans (13%) than among non-Hispanic white Americans (6%) (Cheung et al. 2009).

Technology

Implantable gastric stimulation (IGS) is a potentially safer alternative to current surgical treatments for glycemic control and obesity management as it is reversible and does not alter the gastrointestinal anatomy (Shikora et al. 2009). IGS is indicated for patients with a BMI greater than 35 kg/m² who have failed to achieve sustained weight loss through diet and exercise and who are likely to respond to postoperative nutritional counseling and education (CADTH 2005; Shikora & Storch 2005).

IGS is a minimally invasive procedure that stimulates the gastric wall with electrical pulses to induce satiety and reduce appetite (Shikora & Storch 2005). The electrical stimulator system comprises one or more bipolar electrocatheters (gastric leads) and a gastric pacemaker (a battery with a microcircuit, similar to a cardiac pacemaker) (Cigaina & Hirschberg 2007). The leads are implanted in the anterior gastric wall by laparoscopic or open surgery under general anesthesia and are secured in place with sutures. The ends of the leads are brought out of the abdominal cavity and connected to the pacemaker, which is placed subcutaneously in the upper left quadrant of the abdomen (Shikora et al. 2009). Endoscopy is performed to ensure that the leads do not penetrate the lumen of the stomach, and X-rays are used to document the final position of the leads and pacemaker (Shikora et al. 2009).

Post-procedural adverse events may include lead dislodgement and gastric perforation. Gastric perforation may occur when the lead is placed so deeply that it penetrates the mucosa. Both lead dislodgement and gastric perforation necessitate further surgery to remove and re-implant the leads (Shikora & Storch 2005).

The mechanism by which IGS induces weight loss is not yet understood. There are two hypotheses:

- a) Stimulation using short pulse widths may induce gastric distension. In turn, this may activate stretch receptors and inhibit postprandial antral contractions, thereby slowing gastric emptying and causing an increased feeling of satiety (Mizrahi, Ya'acov & Ilan 2012; Xing & Chen 2004).
- b) Electrical stimulation may alter the pattern of secretion by enteroendocrine cells of gastrointestinal peptides that regulate digestion, food intake, and metabolism (Korner et al. 2011; Mizrahi et al. 2012). For example, IGS may reduce the levels of ghrelin, a hunger-stimulating peptide. Ghrelin levels increase after diet-induced weight loss and potentially contribute to poor long-term maintenance of weight loss (De Luca et al 2004).

Stage of development

Since its inception in the mid-1990s, a number of clinical trials of IGS for the management of obesity and hyperglycemia have been completed in the USA and Europe. These trials tested the efficacy of the Tantalus™ (MetaCure, Inc., Orangeburg, NY, USA), Enterra® (Medtronic, Inc., Minneapolis, MN, USA), Transcend® (formally Transneuronix, Inc., Mount Arlington, NJ, USA, now Medtronic) or Diabetes Improvement and Metabolic Normalization Device (DIAMOND)

(MetaCure Inc., Orangeburg, NY, USA) systems (Shikora et al. 2009). More than 700 patients have been implanted with Transcend[®] for obesity management (Medtronic 2005). The first device implanted for diabetes management occurred in June, 2005. In the same year, Transneuronix Inc. was acquired by Medtronic (Medtronic 2005).

Regulatory approval

IGS devices are not registered with the US Food and Drug Administration (FDA) for the management of obesity or diabetes. In 2000, the Enterra[®] system was approved by the FDA under a Humanitarian Device Exemption for the treatment of chronic intractable nausea and vomiting secondary to diabetic and idiopathic gastroparesis (FDA 2000). According to its manufacturer, the DIAMOND system has had CE approval since 2007 to treat obesity and type 2 diabetes with obesity and is commercially available in selected centers in Europe (Miners 2011).

Current clinical trials

Seven clinical trials that were either recently completed or currently recruiting patients were registered in clinicaltrials.gov. No additional trials were registered in Australian New Zealand Clinical Trial Registry or WHO International Clinical Trial Registry.

Table 1: Current clinical trials

Trial Identifier Country	Study design	Trial status	Device (manufacturer)	N	Estimated completion date
NCT00200018 USA	Multicenter Randomized controlled trial	Complete	Enterra [®] System (Medtronic, Inc.)	46	February 2007
NCT00200083 USA	Multicenter Randomized controlled trial	Complete	Transcend [®] II (Medtronic, Inc.)	190	January 2009
NCT01448785 International	Multicenter Randomized controlled trial	Recruiting	Abiliti [™] system (IntraPace, Inc.)	165	January 2015
NCT01303302 International	Multicenter Randomized controlled trial	Recruiting	Tantalus [™] II (MetaCure, Inc.)	40	May 2015
NCT00779363 USA	Case series	Complete	Tantalus [™] II (MetaCure, Inc.)	14	November 2009
NCT01539850 Germany	Case Series	Complete	OMS 102 device (IntraPace, Inc.)	34	September 2011
NCT01823705 International	Case series	Ongoing	Exillis Implantable Gastric Electrical Stimulator (Medtronic, Inc.)	30	September 2016

Resource: clinicaltrials.gov (accessed on 15 July 2013)

Current treatment and alternatives

Contemporary treatments for obesity can be classified as lifestyle modification (behavior modification, diet and meal replacement therapy), pharmaceutical (orlistat, lorcaserin, and a combination of phentermine and topiramate) or bariatric surgery. Each of these approaches has unique limitations.

Diet and lifestyle modification

Traditionally, the first step in obesity management is a calorie restriction diet, often in combination with increased physical activity. While it is recognized that a restricted calorie diet, regardless of macronutrient content, will result in short-term weight loss (Freedman, King & Kennedy 2001; Sacks et al. 2009; Wadden et al. 2012), weight regain is a problem for virtually all dietary and behavioral interventions for obesity, with 50 per cent of patients returning to their baseline weight five years after treatment (Wadden, Butryn & Byrne 2004). Current methods of lifestyle modification, when used as sole treatments for obesity, may be ineffective (Padwal & Majumdar 2007).

Pharmaceutical therapy

When lifestyle modification strategies alone are ineffective in managing obesity, pharmacotherapy can be considered for patients with a BMI greater than 30 kg/m² or for those with a BMI greater than 27 kg/m² who have comorbidities such as type 2 diabetes, hypertension, or obstructive sleep apnea (NHLBI 1998). Three drugs are currently approved by the US FDA for the long-term treatment of obesity (orlistat, lorcaserin, and a combination of phentermine and topiramate); there are also numerous appetite suppressants (the most common being phentermine) which are approved only for short-term use (<12 weeks) and are classified as controlled substances by the Drug Enforcement Agency (DEA) due to the potential for abuse (Bray 2003).

Orlistat is a potent gastrointestinal and pancreatic lipase inhibitor which prevents the breakdown of ingested triglycerides (Kaplan 2010). This reduces dietary fat absorption by up to 30 per cent (Padwal & Majumdar 2007). As of 2007, orlistat is available to adults as an over the counter medication (FDA 2013). The adverse effects of orlistat include fatty and oily stool and fecal urgency (Padwal & Majumdar 2007).

Lorcaserin, an agonist of the serotonin 2C receptor, modulates food intake by increasing satiety and decreasing hunger (Fidler et al. 2011; Smith et al. 2010). It is approved by the US FDA as an adjunct to a reduced-calorie diet for chronic weight management (FDA 2012a). It is classified as a Schedule IV drug (DEA 2013b) and is available only by prescription. The most common side effects of lorcaserin are headache, dizziness and nausea. Serious side effects are rare (Fidler et al. 2011; O'Neil et al. 2012; Smith et al. 2010).

In 2012, the US FDA approved a combination of phentermine and topiramate as an adjunct to a reduced-calorie diet for chronic weight management in obese adults (FDA 2012b). Phentermine increases the release of norepinephrine and is approved for short-term weight loss. The combination is classified as a Schedule IV drug (DEA 2013a) and has been available by prescription only since 2012. The most common side effects associated with

phentermine/topiramate are dry mouth, paresthesia, constipation, insomnia, and dizziness (FDA 2012b).

Surgery

Bariatric surgery is indicated for severely obese patients (BMI >40 kg/m² or BMI >35 kg/m² with comorbidities) in whom other weight loss methods have failed (Mechanick et al. 2013; NHLBI 1998). Bariatric surgery procedures may be classified as: restrictive, where the size of the stomach is reduced (e.g. gastric banding, gastroplasty and sleeve gastrectomy); malabsorptive, where the anatomy of the small intestine is modified (e.g. biliopancreatic diversion); or mixed (e.g. gastric bypass) (Mechanick et al. 2013). Minimally invasive laparoscopic surgery is becoming more common for bariatric procedures (Nguyen et al. 2011). There were 124,838 bariatric surgery procedures performed in the USA in 2008, most commonly gastric bypass (69% of procedures) followed by laparoscopic gastric banding (29% of procedures) and gastroplasty (2% of procedures) (Nguyen et al. 2011).

A recently published meta-analysis of 31 randomized controlled trials (RCTs) on bariatric surgery found that all surgical methods resulted in clinically significant weight loss one year after surgery (Padwal et al. 2011). The mean reduction in BMI was 11.2 kg/m² after biliopancreatic diversion, 10.1 kg/m² after sleeve gastrectomy, 9.0 kg/m² after gastric bypass, between 5.0 and 6.4 kg/m² after gastroplasty, and 2.4 kg/m² after adjustable gastric banding. All procedures sustained this weight loss in medium-term (up to seven years) follow-up (O'Brien et al. 2006). Gastric bypass and biliopancreatic diversion induced type 2 diabetes remission in between 75 and 95 per cent of patients (Mingrone et al. 2012). Adjustable gastric banding induced type 2 diabetes remission in between 53 and 70 per cent of patients (Dixon et al. 2012).

Although bariatric surgery is a successful method for treating obesity, these procedures are associated with a number of complications (Lee, Kelly & Wassef 2007). Complications of gastric bypass and biliopancreatic diversion include gastric leak (occurring in 0.4–0.9% of patients), ulcer (1–11%), small bowel obstruction (3%), and incisional hernia (6.6–18%). Complications of gastric banding procedures include band slippage (5.5%), pouch enlargement (5.5%), obstruction (2%), band erosion (3%), infection (1%), gastric leak (4%), and esophageal or gastric perforation (0.5%) (Lee, Kelly & Wassef 2007).

Literature review

Search criteria

Keyword/MeSH terms utilized:

(Gastric stimulation device OR gastric electrical stimulation OR gastric pacing OR implantable gastric stimulator) AND (weight loss OR glycemc control)

Databases utilized:

PubMed and the Cochrane Database of Systematic Reviews

Inclusion criteria

Inclusion criteria for eligible studies are listed in Table 2.

Table 2 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Randomized controlled trials, non-randomized comparative studies, case series studies
Patient	Patients require obesity management or glycemc control
Intervention	Implantable gastric stimulation
Comparator	Bariatric surgery, pharmaceutical treatment, diet or lifestyle modification, placebo or no treatment
Outcome	Safety: adverse events, such as gastric perforation, lead dislodgement, infection, hematoma, reflux, and hernia Efficacy: excess weight loss, appetite, satiety, quality of life, HbA1c and blood glucose levels
Language	English only

Included studies

Five trials reported in four papers were included (refer to Appendix B for the exclusion process): two RCTs (Shikora et al. 2009; Shikora & Storch 2005) and three case series studies (Bohdjalian et al. 2009; De Luca et al. 2004; Shikora & Storch 2005). A summary of the characteristics of the included studies is given in Table 3. Each study was assigned a level of evidence according to the National Health and Medical Research Council (NHMRC) hierarchy of evidence (Appendix A). A summary of the patient characteristics at baseline is given in Table 4.

Table 3 Characteristics of included studies

Study/Location	Study type	Level of Evidence	Intervention	No. of patients	Duration of follow-up	Loss to follow up
Obesity						
Shikora and Storch 2005 O-01 trial USA	Randomized, double blind, placebo controlled trial	II	IGS activated IGS deactivated	103*	29 months	67%*
Shikora et al. 2009 SHAPE trial USA	Randomized, double blind, placebo controlled trial	II	IGS activated IGS deactivated	96 94	12 months	7% 3%
Shikora and Storch 2005 DIGEST trial USA	Prospective case series	IV	IGS activated	30	14 months	23%
De Luca et al. 2004 LOSS trial Europe	Prospective case series	IV	IGS activated	69	15 months	71%
Obesity and glycemic control						
Bohdjalian et al. 2009 Europe	Prospective case series	IV	IGS activated	24	12 months	13%

* Only combined group data was available

Table 4 Patient demographics and selection criteria of the included studies

Study	Baseline patient demographics	Inclusion criteria	Exclusion criteria
Shikora and Storch 2005 O-01 trial	Mean age (range)*: 40 years (23–54) Sex distribution* 16 men, 87 women* Mean weight (range)*: 129 kg (84–183 kg)* Mean BMI (range): 46 kg/m ² (38–56)*	18–50 years BMI 40–55 kg/m ²	Pregnancy, lactation, previous bariatric surgery, other implanted electrostimulation devices, gastrointestinal motility disorders, peptic ulcer disease, other significant comorbidities (including diabetes)
Shikora et al. 2009 SHAPE trial	Mean age ± SD Placebo: 44 years ± 11 IGS: 43.7 years ± 10.7 Range: 27–50 years* Sex distribution Placebo: 15 men, 79 women IGS: 9 men, 87 women Mean BMI ± SD Placebo: 41.5 kg/m ² ± 4.8	18–65 years BMI 35–55 kg/m ² Acceptable performance in pre-screening: Baroscreen algorithm (Medtronic), psychological assessment (as for bariatric surgery) and	Pregnancy, lactation, previous bariatric surgery, previous operations on the stomach, other implanted electrostimulation devices, gastrointestinal motility disorders, peptic ulcer disease, other significant comorbidities (including poorly controlled diabetes)

	IGS: 40.6 kg/m ² ± 4.3 Range: 35–55 kg/m ² *	a binge eating survey	
Shikora and Storch 2005 DIGEST trial	Mean age (range): 39 years (27–50) Sex distribution: 4 men, 26 women Mean BMI (range): 42 kg/m ² (34–55 kg/m ²)	18–50 years BMI 40–55 kg/m ² or 35–39 kg/m ² with significant comorbidity** Adequate performance in binge eating and psychological evaluations	Pregnancy, lactation, previous bariatric surgery, other implanted electrostimulation devices, gastrointestinal motility disorders, peptic ulcer disease, patients with binge eating disorder, HbA1c >6 mg/dL, other significant comorbidities (including diabetes)
De Luca et al. 2004 LOSS trial	Mean age (range): 41 years (18–65 years) Sex distribution: 20 men, 49 women Mean baseline weight (range): 115.0 kg (65–160 kg) Mean BMI (range): 41 kg/m ² (35–57 kg/m ²)	18–65 years Use of adequate birth control methods BMI 35–40 kg/m ² with documented co-morbidity or 40–45 kg/m ² Able and willing to travel to clinical site for designated follow-up	Pregnant or lactating, prior bariatric surgery, prior stomach surgery, other implantable electrostimulation device, untreated or risk for developing gastric ulcer, weight loss medication, ulcerogenic medication, history of cardiac arrhythmia or severe cardiac disease, severe weight related comorbidity, any serious health condition (not related to obesity), patients the physician considers unwilling or unable to fulfill requirements of study, use of an investigational agent or device within 30 days prior to implant
Bohdjalian et al. 2009	Mean age: 50.0 years Sex distribution: 9 men, 15 women Mean BMI: 41.9 HbA1c: 8.0% waist circumference: 130.7 cm weight: 123.7 kg blood pressure: 139 mmHg triglycerides: 199 mg/dL FPG: 183 mg/dL	18–60 years Type 2 diabetes mellitus HbA1c range 6.5%–9.7% BMI 33.3–49.5 kg/m ² Obesity present for >5 years	Medication for weight loss within last 3 months, severe eating or mobility disorders, prior bariatric surgery, any other significant medical or psychiatric condition that may have impaired ability to comply with study procedures

* only combined group data was available

** one patient entered the trial with a BMI of 34 kg/m² due to weight loss between screening and device implantation

Shikora and Storch (2005) O-01 trial, USA

The first major research trial conducted in the United States to investigate IGS as a treatment for obesity was the O-01 trial, which began in February 2000 (Shikora & Storch 2005). The O-01 trial was a randomized, double blind, placebo-controlled trial. Patients were included if they had a BMI of between 40 and 55 kg/m² and were aged between 18 and 50 years. The single-lead device, Transcend[®] 2000 (Transneuronix, Inc., Mount Arlington, NJ, USA), was implanted laparoscopically in all enrolled patients under general anesthesia. An intra-operative endoscopy was performed in all cases to check for lead perforation. The mean operating time was 73.2 minutes (range 22 to 150 minutes). Most patients were discharged from hospital on the day of surgery. One month after device insertion, patients were randomly assigned to the treatment

group (device activated) or the control group (device not activated). The primary endpoint was the percentage change in weight after six months of stimulation. At this six-month point, the patients in the control group had their devices activated and all patients were followed up for the remainder of the trial (up to 29 months).

By the end of the trial, 69 patients had withdrawn, (only combined group data was available), with the main reasons being lead dislodgement (where the patient elected for removal rather than replacement) and desire for another bariatric operation.

Shikora et al. (2009) SHAPE trial, USA

The Screened health assessment and pacer evaluation (SHAPE) trial was a randomized, double-blinded, placebo-controlled trial on the use of IGS as a treatment for obesity. The double-lead device, a Transcend[®] II IGS 2002 (Medtronic, Inc., Minneapolis, MN, USA), was implanted laparoscopically under general anesthesia. Upper endoscopy was used to identify any cases of lead perforation. Operating time and duration of hospital stay was not reported. Two weeks after insertion, the devices were activated in 96 patients and set at such a level that no effects were felt from the device; in 94 patients, the devices remained inactivated. All patients were instructed to consume a diet with a 500 kcal deficit per day and to attend monthly support meetings. The primary outcome was the per cent of excess weight loss (EWL) at 12 months. By the 12 month follow-up, seven patients from the treatment group and three patients from the control group had withdrawn from the study, either because of a missed appointment or study attrition.

Shikora and Storch (2005) DIGEST trial, USA

The Dual Implantable Gastric Electrical Stimulation Trial (DIGEST) was a case series study on the use of IGS as a treatment for obesity. The double-lead Transcend[®] II IGS 2002 device (Transneuronix, Inc., Mount Arlington, NJ, USA) was implanted in the manner reported by Shikora et al. (2009). Intra-operative endoscopy was used to identify any cases of lead perforation. Two weeks after insertion, the devices were activated in all patients and set at such a level that the patients felt no effects from the device. The primary endpoint was the percentage change in weight after six months of stimulation. By the 14-month follow-up, seven patients had withdrawn, but the reasons for this were not provided.

De Luca et al. (2004) LOSS trial, Europe

The Laparoscopic Obesity Stimulation Survey (LOSS) was a case series study on the use of IGS as a treatment for obesity. The device used was a Transcend[®] IGS (Transneuronix, Inc., Mount Arlington, NJ, USA), which was implanted in the manner described by Shikora et al. (2009). The mean surgery time was 58.5 minutes (range 37 to 85 minutes). All patients had their devices activated one month after implantation, with uniform stimulation parameters for the first six months and an increase in pulse amplitude and pulse width, varying from patient to patient, occurring at the six-month follow-up. The primary outcome of the study was the difference in the per cent of EWL between the baseline and the six-month follow-up. By the 15-month follow-up, 49 patients had withdrawn from the study. The reasons for this were not provided.

Bohdjalian et al. (2009) Europe

Bohdjalian et al. (2009) report the results of a case series study on the safety and feasibility of IGS for the treatment of obesity and glycemic control. The triple-lead Tantalus[™] system was implanted laparoscopically under general anesthesia. Six weeks after insertion, the device was activated in all patients. Patients received information and advice about a healthy diet but were not required to undertake a specific diet or form of behavior control. The primary outcome of the

study was the difference in weight and level of glycemic control between baseline measurements and the 12-month follow-up. By the 12-month follow-up, three patients had withdrawn from the study, with one lost to follow-up at week 13 and two patients refusing device replacement at weeks 28 and 32.

Critical appraisal

The appraisal of the methodology of the included studies was informed by elements of the Cochrane manual (Higgins 2005) and the Consolidated Standards Of Reporting Trials statement (Schulz, Altman & Moher 2010).

Both of the RCTs were triple-blind; however, neither RCT adequately reported methods of randomization or allocation concealment (Shikora et al. 2009; Shikora & Storch 2005). Only the SHAPE trial (Shikora et al. 2009) defined that numbers would be analyzed on an intention-to-treat basis rather than per protocol. Shikora et al. (2009) was also the only study to provide an a priori analysis of the statistical power of the study. The majority of trials had unacceptably high dropout rates (>10% for short-term follow-up). All studies reported clear patient selection criteria, adequately defined the primary study outcomes and described the interventions.

While all studies stated, a priori, the duration of the trial, three studies (the DIGEST, SHAPE, and LOSS trials) failed to report outcomes to the final follow-up period. Shikora and Storch (2005) reported that the DIGEST trial was 24 months long; however, outcomes were reported only until the 14-month follow-up. Shikora et al. (2009) indicated that the results for the 12 to 24 month follow-up from the SHAPE trial would be reported separately; however, this later report was not identified in the search. De Luca et al. (2004) reported that patients were followed up 36 months after device activation; however, outcomes were reported only up to the 15-month follow-up.

Two studies reported that the trial was supported by the IGS device manufacturer. The SHAPE trial (Shikora et al. 2009) was sponsored by Medtronic/Transneuronix and the sponsor developed the trial protocol in consultation with the investigators, compiled and analyzed the data (which was provided to the principal investigators), and reviewed the report before submission. The authors disclosed their individual conflicts of interests. In Bohdjalian et al. (2009), MetaCure supported the research by a research grant. De Luca et al. (2004) and Shikora and Storch (2005) did not report the presence or absence of a conflict of interest.

Safety and efficacy

Safety

The adverse events occurring from IGS that occurred in the five included trials are listed in Table 5.

Table 5 Adverse events following implantable gastric stimulation

	Shikora and Storch (2005) O-01 trial (N=103) No. of patients (%)	Shikora and Storch (2005) DIGEST trial (N=30) No. of patients (%)	Shikora et al. (2009) SHAPE trial (N=190) No. of patients (%)	De Luca et al. (2004) LOSS trial (N=69) No. of patients (%)	Bohdjalian et al. (2009) (N=21) No. of patients (%)
Lead dislodgement	20 (19%)	NR	2 (1%)	NR	NR
Complete dislodgement	12 (12%)	NR	NR	NR	NR
Partial dislodgement	8 (8%)	NR	NR	NR	NR
Gastric perforation	20 (19%)	NR	26 (14%)	7 (10%)	NR
Pocket infection	NR	NR	1 (0.5%)	NR	NR
Retained needle	NR	1 (3%)	NR	1 (1%)	NR
Pain at stimulator site	NR	NR	NR	1 (1%)	10 (48%)
Postoperative hematoma	NR	NR	NR	NR	5 (24%)
Abdominal pain, heartburn or reflux	NR	NR	NR	NR	4 (19%)
Hernia of scar/wound dehiscence	NR	NR	NR	NR	3 (14%)
Atrial fibrillation	NR	NR	NR	NR	2 (10%)
Hypoglycemia	NR	NR	NR	NR	2 (10%)
Device pocket stimulation	NR	NR	NR	NR	1 (5%)
Lead connection failure	NR	NR	NR	NR	1 (5%)
Left diaphragm paresis	NR	NR	NR	NR	1 (5%)

NR: Not reported

The O-01 trial (Shikora & Storch 2005) reported 20 cases of lead dislodgement, 17 of which occurred in the first 41 patients. In response to this high dislodgement rate, the surgical technique was changed and the leads were fixed with sutures or a surgical clip. Following this change in procedure, only three lead dislodgements were observed for the remaining 62 patients. Perforation of the stomach during lead implantation occurred in 20 patients and was identified by gastroscopy immediately following implantation. Perforation resulted in lead replacement. No cases of perforation resulted in leakage of gastric content, infection, hemorrhage, or other clinical manifestations.

The DIGEST trial (Shikora & Storch 2005) (and all subsequent trials) utilized the modified lead implantation technique developed in the O-01 trial. Consequently, no lead dislodgements

occurred in DIGEST. No other major complications were observed; however, a lead needle was retained in one patient who required a subsequent laparoscopy to retrieve it.

The most common adverse event in the SHAPE trial (Shikora et al. 2009), occurring in 26 patients, was gastric perforation at the time of device implantation. In all cases, the device was withdrawn and reinserted. None of the perforations led to gastric leak, infection, or bleeding. No deaths or major complication occurred.

De Luca et al. (2004) reported seven gastric perforations occurring at the time of lead implantation. In all cases, the device was withdrawn and reinserted. One patient required surgery to recover a retained lead needle. One patient experienced pain at the pacemaker site, which was managed with nonsteroidal anti-inflammatory drugs.

Bohdjalian et al. (2009) reported a total of 29 adverse events occurring in 24 patients. It was noted that, due to device battery exhaustion after an average of eight months, 17 patients underwent device replacement. This increased the chances of adverse events relating to the device pocket as it involved reopening of the pocket scar.

Efficacy

The data from the two RCTs on the efficacy of IGS with regards to weight loss is summarized in Table 6. The efficacy data from the case series studies is summarized in Table 7.

Weight loss

Table 6 RCT data—response to treatment with implantable gastric stimulation

	Mean per cent of excess weight loss		
	IGS	Placebo	P value
Shikora and Storch 2005 (O-01 trial)			
6 month follow-up	1.3%	2.4%	NR
Shikora et al 2009 (SHAPE trial)			
6 month follow-up	13.3%	11.4%	0.184
12 month follow-up	12.2%	11.9%	0.682

Table 7 Case series data—response to treatment with implantable gastric stimulation

	Mean per cent of excess weight loss
Shikora and Storch 2005 (DIGEST trial)	
6 month follow-up	NR
14 month follow-up	19%
De Luca et al 2004 (LOSS trial)	
1 month follow-up	8.6% (SE=0.91)
3 months follow-up	15.8% (SE=1.38)
6 months follow-up	17.8% (SE=1.98)
10 months follow-up	21.0% (SE=2.64)
15 months follow-up	21.0% (SE=3.78)
Bohdjalian et al 2009	
Week 20	5.8 kg or 4.7%
Week 52	4.5 kg or 3.7%

NR: not reported

Shikora and Storch (2005) O-01 and DIGEST trials

The O-01 trial reported no statistical difference in weight loss between the study and control groups six months after randomization (Table 6). At six months post-implantation, the control group had their devices switched on and the subsequent results were compared to baseline measurements. At 12 months post-implantation, the mean EWL was 2.5 per cent, while 23 per cent of patients had lost a clinically significant amount of weight (>5% EWL). For this 23 per cent, the mean per cent of EWL was 10 per cent. The number of patients completing the 12-month follow-up was not reported. At 29 months follow-up, 69 patients had withdrawn from the study; however, the remaining 34 patients reached a mean 20 per cent EWL.

In the DIGEST trial, 71 per cent of the 30 patients had lost weight at the 12-month follow-up (54% had lost >10% EWL and 29% had lost >20% EWL). At the 14-month follow-up, mean EWL was 19 per cent. Shikora and Storch (2005) reported that the results differed greatly between the two investigative sites. Patients recruited at Site 1 of the DIGEST trial had a mean 30 per cent EWL, whereas those recruited at Site 2 had no change in weight from the baseline. It was suggested that this discrepancy occurred because the patients at Site 2 had been rejected by their insurer for other bariatric surgery procedures in addition to poor support group compliance or poor program stability. All patients in the DIGEST trial filled in a Satiety and Dietary Analysis Questionnaire. The results showed that IGS produced a mean reduction in appetite of 14 per cent ($p=0.04$), and a mean increase in between-meal and end-of-meal satiety of 60 per cent ($p=0.004$) and 89 per cent ($p<0.001$), respectively, compared to baseline values.

Data from both the O-01 and DIGEST trials suggested that some patients responded vigorously to the IGS treatment, whereas others did not respond at all. A screening algorithm was developed based on perioperative patient demographics such as age, sex, body weight, BMI, and responses to a quality of life questionnaire. This algorithm was used in both trials to predict the patients who would respond to treatment. For the O-01 trial, the screening algorithm selected only 18 per cent of enrolled patients; these patients achieved 20 per cent EWL at 19 months and 32 per cent EWL at 29 months. In contrast, the excluded group gained 4 per cent of their excess weight at 29 months. The difference between the two groups was statistically significant ($p<0.01$). For the DIGEST trial, the screening algorithm selected 33 per cent of enrolled subjects. At the 12-month follow-up, these patients had achieved a 31 per cent EWL compared with 1 per cent EWL for patients rejected by the algorithm ($p<0.01$).

Shikora et al. (2009) SHAPE trial

The SHAPE trial prescreened all participants with the Baroscreen screening algorithm developed by Medtronic, Inc. subsequent to the O-01 and DIGEST trials. Only candidates predicted to achieve at least 15 per cent EWL were considered for enrolment. Of a total of 4802 candidates, 1315 were selected by the Baroscreen tool; 190 patients were ultimately enrolled in the trial. No statistical differences were found in the per cent of EWL between the intervention and control groups at the six-month follow-up (13% compared to 11 % respectively, $p=0.68$) or the 12-month follow-up (12.2% compared to 11.9 % respectively, $p=0.68$). In addition, there was no statistical difference in the number of patients who achieved more than 20 per cent EWL by the 12-month follow-up (25 patients in the intervention group and 15 in the control group; $p=0.07$). The authors hypothesized that the lack of a statistically significant difference between the two groups may have been due to the screening algorithm selecting a control group that was inclined to achieve weight loss regardless of the treatment received.

De Luca et al. (2004) LOSS trial

De Luca et al. (2004) reported a mean 21 per cent EWL among 43 patients at the 10-month follow-up, compared with baseline values, which were maintained at the 15-month follow-up. At the six-month follow-up, appetite was significantly lower than before treatment ($p < 0.001$), and after-meal satiety and between meal-satiety was significantly higher ($p < 0.01$). The average number of meals being consumed had fallen from 3.4 meals per day at baseline to 2.1 meals per day at the six-month follow-up ($p < 0.001$). The levels of ghrelin were measured in a subgroup of 19 patients at the six-month follow-up. There was no significant difference in levels of the hormone before or after weight loss.

Bohdjalian et al. (2009)

Bohdjalian et al. (2009) observed mean weight loss of 4.7 per cent, compared with baseline, at the 20-week follow-up ($p < 0.05$), which was largely sustained at the 52-week follow-up (3.7%, $p < 0.05$). In a subgroup of patients taking oral medication for diabetes ($n = 11$), mean body weight had decreased by 4.7 per cent at the 52-week follow-up ($p < 0.05$). In contrast, patients taking insulin for diabetes ($n = 6$) did not achieve a significant weight loss. Results from a Three-Factor Eating Questionnaire conducted at baseline and week 52 showed that cognitive control had increased, while disinhibition and hunger had decreased ($p < 0.05$ in all cases). In addition, ghrelin and triglyceride levels were both significantly lower after treatment with IGS.

Glycemic control

In the single study that measured markers of glycemic control in 21 patients, levels of HbA1c were lower by a mean of 0.6 per cent at week 20 ($p < 0.05$) and by a mean of 0.5 per cent at week 52 ($p < 0.05$) (Bohdjalian et al. 2009). For the subgroup of patients ($n = 11$) taking oral medication for diabetes, HbA1c levels had decreased by 1.5 per cent at 14 weeks ($p < 0.05$) and by 0.9 per cent at 52 weeks ($p < 0.05$). The subgroup of patients taking insulin ($n = 6$) had no significant change in HbA1c levels after treatment. The mean levels of fasting plasma glucose in all 21 patients decreased from 183 mg/dL before treatment to 148 mg/dL one year after ($p < 0.05$).

Cost impact

No studies were identified that assessed the cost-effectiveness of IGS therapy as a treatment for obesity or glycemic control.

Due to similarities between the Medtronic, Inc. Enterra[®] system, which is used to treat gastroparesis, and the Transcend[®] device in terms of size, placement, and implantation procedure, the cost of the Enterra[®] system can be used to estimate the costs associated with implanting the Transcend[®] device. The cost of implanting the Enterra[®] system in the USA is estimated to be US\$30,000 in 2011 (Bortolotti 2011; Health Quality Ontario 2006). In Canada, the device alone cost CN\$10,700 in 2006, which does not include costs associated with implantation or device programming and maintenance (Moga & Harstall 2006). A recent study estimated the costs associated with implanting the Tantalus[™] system at US\$16,800¹ in 2009 (Sanmiguel et al. 2009). These devices are considered experimental treatments for both obesity and diabetes and are generally not covered by insurance companies in the USA (Harvard Pilgrim Health Care 2010).

¹ <http://www.oanda.com/currency/historical-rates/> average Euro to USD rate = 1.4, (accessed 16 September 2013)

Clinical practice guidelines and consensus statements

A search for relevant clinical practice guidelines was conducted using various resources (Appendix C), which did not reveal any guidelines relevant to the use of IGS as a treatment for obesity or hyperglycemia.

A National Institute for Health and Care Excellence (NICE) guideline on the treatment of gastroparesis stated that the implantation of IGS devices should only be performed in specialist gastroenterology units (NICE 2004). This advice may also apply to the implantation of IGS devices for glycemic control and obesity management.

According to general guidelines on the management of obesity and type 2 diabetes, bariatric surgery of any kind is recommended only for patients with a BMI greater than 40 kg/m² or greater than 35 kg/m² where significant comorbidities are present (ICSI 2011). No one bariatric surgery technique is considered superior to another (ICSI 2011). Any surgery should be considered as an adjunct in the overall treatment plan for obesity, and only patients who are aware of the risks associated with the procedure should be considered for treatment. In addition, patients should be evaluated for psychological readiness and post-surgical lifestyle commitment prior to undergoing surgery (MQIC 2011).

Training and education impact

No studies were identified that assessed the impact of IGS on surgical training and education. Due to similarities between the Transcend[®] device and Medtronic's Enterra[®] system for gastroparesis it is reasonable to assume that the training required for these devices is similar. Prior to prescribing IGS for the first time, physicians should receive appropriate training by specialists in the implantation techniques, operational characteristics, and functions of the IGS system. Programming of the device should be provided by (or provided under the supervision of) a physician or by other experienced medical personnel who are familiar with the programming software (Moga & Harstall 2006).

Summary

The increased prevalence of obesity and type 2 diabetes is a worldwide health concern. For many obese patients, lifestyle modification is ineffective in achieving sustained weight loss. Pharmaceutical and surgical strategies are increasingly being used to achieve weight loss; however, they are associated with many adverse effects.

IGS is a reversible, minimally invasive technology that, unlike bariatric surgery, does not alter the anatomy of the gastrointestinal tract. It is thought to induce weight loss by disrupting gastric motility and/or hormone secretion, although the exact mechanism is unknown. The current assessment included evidence from two RCTs and three case series that assessed the safety and efficacy of IGS as a treatment for obesity and glycemic control. Four of the studies used either a first or second generation Transcend[®] device; one study used a Tantalus[™] device.

Safety outcomes were reported in 413 patients across five studies. The most commonly reported adverse event was gastric perforation (13%, 53 patients); however, none of these cases led to a major complication. Lead dislodgements were common in earlier studies, but this issue was largely resolved by altering the surgical technique. Other complications, predominantly from one case series study, included hematoma, pain, reflux, diaphragm paresis, and hernia. The maximum length of follow-up for all studies was 29 months. The length of follow-up in the included trials may not have been long enough for issues such as lead migration or lead erosion to present.

The included studies provide inconclusive results in terms of the efficacy of IGS for the management of obesity. Two RCTs, the O-01 trial (n=103) with 29 months follow-up and the SHAPE trial (n=190) with 12 months follow-up, showed no difference in weight loss between patients with the device on and those with the device off. The SHAPE trial used a screening algorithm to select patients most likely to succeed at losing weight. The selected patients lost weight whether the device was activated or not, suggesting that these patients were either highly susceptible to the placebo effect or highly motivated and would have lost weight without formal interventional assistance. When the screening algorithm was retrospectively applied to the O-01 trial, patients who were not selected by the algorithm gained an average of 4.4 per cent of excess weight while being treated by IGS. Overall, these results suggest that the device is not particularly effective for weight loss in either patient subpopulation.

Case series data (including the longer follow-up data from the RCTs that converted to case series) show a 20 per cent EWL up to 29 months; however, the dropout rate was very high in some studies, with many patients (49 patients in the LOSS trial and 69 patients in the O-01 trial) opting not to replace the device when lead dislodgement or battery failure occurred. The devices failed between 8 and 29 months after treatment. Replacement of the device increases the risk of infection and wound site adverse events so an apparent lack of durability in these devices is an issue. It is not known if any weight loss is maintained beyond 29 months.

Results from one case series study (Bohdjalian et al. 2009) showed that IGS leads to a 0.5 per cent reduction in HbA1c levels at the 12-month follow-up.

The ability to draw firm conclusions about the safety and efficacy of this technology is limited by a number of factors. There were limitations in all of the included studies, particularly around defining the methods of analysis and the reporting of long-term outcomes. In a number of studies, withdrawal rates were high, and in some cases, reasons for withdrawal were not reported. No study compared the safety and efficacy of IGS to other weight loss strategies, such as bariatric surgery. Two studies were supported by the device manufacturer, while the remaining three studies did not disclose conflict of interest.

Recommendation

Based on the limitations of the evidence presented in this report, it is not possible to draw firm conclusions as to the safety and efficacy of IGS as a treatment for obesity or glycemic control. Further studies (particularly well-constructed, high quality RCTs) are required, with long-term outcomes reported for both safety and efficacy. It is recommended that the safety and efficacy of IGS be compared to existing treatments for obesity and poor glycemic control. At this stage, it appears to be too early to introduce this technology into general practice for the indications mentioned.

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Appendix A NHMRC Evidence Hierarchy

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention ¹	Diagnostic accuracy ²	Prognosis	Aetiology ³	Screening Intervention
I ⁴	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among consecutive persons with a defined clinical presentation ⁶	A prospective cohort study ⁷	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among non-consecutive persons with a defined clinical presentation ⁶	All or none ⁸	All or none ⁸	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomized, experimental trial⁹ ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomized, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single-arm studies¹⁰ ▪ Interrupted time series without a parallel control group 	Diagnostic case-control study ⁶	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single-arm studies
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ¹¹	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Resource: (Merlin et al 2009)

Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000).

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005; Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilized.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6 Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases, the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies, a selected sample of patients already known to have the disease is compared with a separate group of normal/healthy people known to be free of the disease. In this situation, patients with borderline or mild expressions of the disease and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7 At study inception, the cohort is either non-diseased or all at the same stage of the disease. A randomized controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

8 All or none of the people with the risk factor(s) experience the outcome, and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus, and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C to determine A vs. C with statistical adjustment for B).

10 Comparing single-arm studies, that is, case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C to determine A vs. C but where there is no statistical adjustment for B).

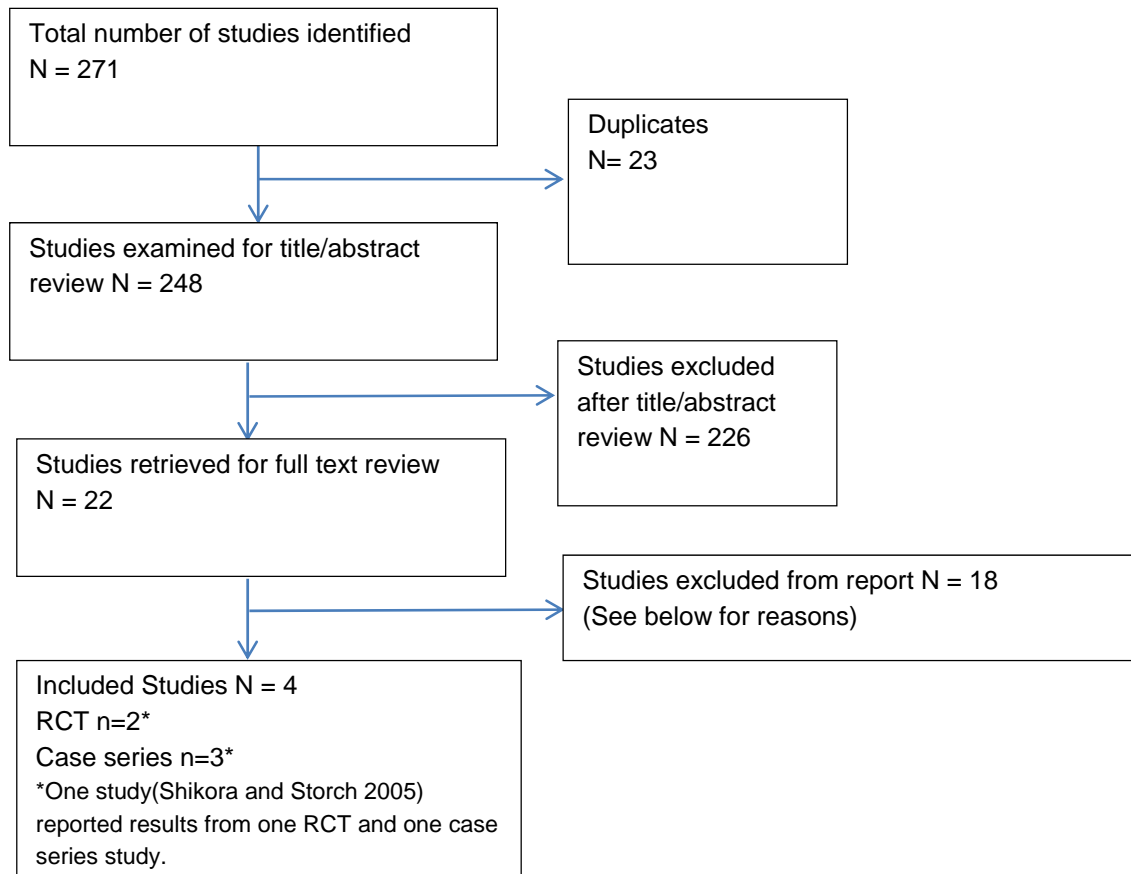
11 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question, for example, level II intervention evidence, level IV diagnostic evidence, or level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: Bandolier editorial (1999), Lijmer et al. (1999), NHMRC (1999) and Phillips et al (2001).

Appendix B Excluded studies



Adapted from (Liberati et al 2009)

List of studies excluded with reason

Non-English language

Wolff, S, Pross, M, Knippig, C, Malfertheiner, P & Lippert, H 2002, 'Gastric pacing Eine neue methode in der adipositaschirurgie' (Gastric pacing. A new method in obesity surgery), *Chirurg*, vol. 73, no. 7, pp. 700–3.

Low patient numbers (<20 patients)

Bohdjalian, A, Prager, G, Aviv, R, Policker, S, Schindler, K, Kretschmer, S, Riener, R, Zacherl, J & Ludvik, B 2006, 'One-year experience with Tantalus: a new surgical approach to treat morbid obesity', *Obes Surg*, vol. 16, no. 5, pp. 627–34.

Cigaina, V & Hirschberg, AL 2003, 'Gastric pacing for morbid obesity: plasma levels of gastrointestinal peptides and leptin', *Obes Res*, vol. 11, no. 12, pp. 1456–62.

Miller, KA 2002, 'Implantable electrical gastric stimulation to treat morbid obesity in the human: operative technique', *Obes Surg*, vol. 12, Suppl. 1, pp. 17S–20S.

Sanmiguel, CP, Conklin, JL, Cunneen, SA, Barnett, P, Phillips, EH, Kipnes, M, Pilcher, J & Soffer, EE 2009, 'Gastric electrical stimulation with the TANTALUS System in obese type 2 diabetes patients: effect on weight and glycemic control', *J Diabetes Sci Technol*, vol. 3, no. 4, pp. 964–70.

Sanmiguel, CP, Haddad, W, Aviv, R, Cunneen SA, Phillips, EH, Kapella, W, & Soffer, EE 2007, 'The TANTALUS system for obesity: effect on gastric emptying of solids and ghrelin plasma levels', *Obesity surgery*, vol. 17, no. 11, pp. 1503–9

Overlapping population with an included study

Favretti, F, De Luca, M, Segato, G, Busetto, L, Ceoloni, A, Magon, A & Enzi, G 2004, 'Treatment of morbid obesity with the Transcend Implantable Gastric Stimulator (IGS): a prospective survey', *Obes Surg*, vol. 14, no. 5, pp. 666–70.

Korner, J, Nandi, A, Wright, SM, Waitman, J, McMahon, DJ, Bessler, M & Aronne, LJ 2011, 'Implantable gastric stimulator does not prevent the increase in plasma ghrelin levels that occurs with weight loss', *Obesity*, vol. 19, no. 10, pp. 1935–9.

Policker, S, Haddad, W & Yaniv, I 2009, 'Treatment of type 2 diabetes using meal-triggered gastric electrical stimulation', *Isr Med Assoc J*, vol. 11, no. 4, pp. 206–8.

Inappropriate PICO

Champion, JK, Hunt, T & DeLisle, N 2002, 'Role of routine intraoperative endoscopy in laparoscopic bariatric surgery', *Surg Endosc*, vol. 16, no. 12, pp. 1663–5.

Cigaina, V 2004, 'Long-term follow-up of gastric stimulation for obesity: the Mestre 8-year experience', *Obes Surg*, vol. 14, Suppl. 1, pp. S14–22.

Liu, J, Hou, X, Song, G, Cha, H, Yang, B & Chen, JD 2006, 'Gastric electrical stimulation using endoscopically placed mucosal electrodes reduces food intake in humans', *Am J Gastroenterol*, vol. 101, no. 4, pp. 798–803.

Cigaina, V, & Hirschberg, AL 2007, 'Plasma ghrelin and gastric pacing in morbidly obese patients', *Metabolism*, vol. 56, no. 8, pp. 1017–21.

Preliminary report

Champion, JK, Williams, M, Champion, S, Gianos, J & Carrasquilla, C 2006, 'Implantable gastric stimulation to achieve weight loss in patients with a low body mass index: early clinical trial results', *Surg Endosc*, vol. 20, no. 3, pp. 444–7.

Cigaina, V 2002, 'Gastric pacing as therapy for morbid obesity: preliminary results', *Obes Surg*, vol. 12, Suppl. 1, pp. 12S–16S.

D'Argent, J 2002, 'Gastric electrical stimulation as therapy of morbid obesity: preliminary results from the French study', *Obes Surg*, vol. 12, Suppl. 1, pp. 21S–25S.

Study could not be obtained

Buchwald, H 2004, 'Gastric stimulation: a new paradigm for management of morbid obesity', *Obes Surg*, vol. 14, Suppl. 1, p. S2.

Shikora, SA 2004, "'What are the yanks doing?' the U.S. experience with implantable gastric stimulation (IGS) for the treatment of obesity - update on the ongoing clinical trials', *Obesity surgery*, vol. 14, Suppl. 1, pp. S40–8.

Appendix C Databases searched for clinical practice guidelines

Resources	Website
National Guideline Clearinghouse	www.guideline.gov
National Institute for Health and Clinical Excellence (NICE) Guidelines	www.nice.org.uk
BMJ Best Practice	www.bestpractice.bmj.com
NHS Evidence in Health and Social Care search engine	www.evidence.nhs.uk
Guidelines International Network	www.g-i-n.net
New Zealand Guidelines Group	http://www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group
Scottish Intercollegiate Guidelines Network	www.sign.ac.uk