Communication from the ASGE Technology Committee

STATUS EVALUATION REPORT

Endoscopic bariatric therapies

The ASGE Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methodology is used, performing a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases, data from randomized, controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. This Technology Status Evaluation Report is drafted by 1 comember of the ASGE Technology Committee and the Bariatric Endoscopy Task Force (B.K.A.D.). It was reviewed and edited by the entire ASGE Bariatric Endoscopy Task Force and the Chair of the ASGE Technology Committee and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided.

For this review, the MEDLINE database was searched through December 2014 for relevant articles by using the key words "bariatric," "endoscopic," "intragastric balloon," "bypass sleeve," "gastroplasty," and "aspiration therapy."

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BACKGROUND

More than one-third of U.S. adults are obese.[1] The increasing prevalence of obesity in the United States has been accompanied by an increasing prevalence in its associated comorbid conditions including hypertension, diabetes, dyslipidemia, coronary heart disease, stroke, sleep apnea, osteoarthritis, gallbladder disease, GERD, nonalcoholic fatty liver disease (NAFLD), and cancer. Obesity is associated with an increased risk of all-cause and cardiovascular mortality and accounts for about 2.5 million preventable deaths annually.[2] The economic consequences of obesity are enormous, and projected increases may threaten the integrity of our health care system. Recent analyses estimate that 147 to 210 billion dollars are spent annually to treat obesity-attributable medical problems in the United States, accounting for about 21% of health care expenditures.[3,4]

Current approaches to therapeutic weight loss include lifestyle modification, pharmacotherapy, and bariatric surgery. Intensive lifestyle modification is associated with only modest weight loss.[5-7] The available pharmacological approaches for the treatment of obesity increase weight loss by 3% to 9% compared with lifestyle therapy alone, but are associated with unfavorable side effects.[8] Weight loss achieved by lifestyle modification or pharmacological approaches is rarely maintained as both interventions are subject to significant weight recidivism.[9] Bariatric surgery remains the most effective and durable treatment option for obese patients. Available procedures include laparoscopic and open Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, adjustable gastric band, vertical banded gastroplasty, duodenal switch, and biliopancreatic diversion. Despite its proven efficacy, it is estimated that less than 1% of obese subjects who qualify for bariatric surgery will undergo this intervention.[10] The explanation for this is likely multifactorial, including high surgical costs, patient preference, access to care, and the morbidity and mortality associated with surgical interventions. Although mortality rates associated with bariatric surgery have decreased significantly and are now comparable to those of cholecystectomy or appendectomy in bariatric centers with high surgical volumes, early and late rates of adverse events associated with bariatric surgery remain problematically high at 17%.[11]

There is consequently a need for less-invasive weight loss interventions to bridge the current gap in our management approach to obesity and also to improve access. Our understanding of the mechanisms by which bariatric surgery works has evolved from the initially narrow view that weight loss was largely related to mechanical restriction and malabsorption. It is now evident that anatomic surgical manipulations of the GI tract also result

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in physiological alterations in gut neuroendocrine signaling, GI motility, autonomic nervous system signaling, bile acid production and absorption, and gut microbiota, all of which contribute to weight loss and to improvement in diabetes.[12,13] Emerging endoscopic technologies can reproduce some of the anatomic alterations created during bariatric surgery and are proving to be effective treatments for obesity in selected patients. They additionally offer the potential advantages of reduced invasiveness, reversibility, repeatability, and cost-effectiveness. These advantages may allow endoscopic procedures to be applied to a larger segment of the population with moderate obesity.

This review focuses on endoscopic bariatric therapies (EBTs) that are in clinical practice or in advanced stages of development and regulatory approval. Of note, however, at the time of this review, none of the EBTs discussed are as yet approved for use in the United States for bariatric indications. In discussing EBTs, it is helpful to separate them into gastric and small-bowel endoscopic interventions.

TECHNOLOGY UNDER REVIEW

Gastric interventions

Gastric restriction is an important component of surgical weight loss procedures (Table 1). This is accomplished through the creation of a small gastric pouch in RYGB surgery, through placement of an adjustable gastric band, or through the creation of a sleeve in sleeve gastrectomy surgery. In addition to inducing early satiety, it is thought that reducing the gastric reservoir capacity increases the stimulation of gastric mechanical and chemical receptors, alters gastric emptying, and modulates the level of gastric orexigenic hormones, which further contribute to weight loss.[14-16] Several EBTs attempt to mimic these mechanisms by decreasing effective gastric capacity. These technologies include space-occupying devices and those that alter gastric anatomy. Space-occupying devices most commonly take the form of temporarily placed prostheses such as balloons. EBTs that alter gastric anatomy use endoscopic suturing or plication devices.

Intragastric balloons. Endoscopically placed intragastric balloons (IGBs) for the treatment of obesity were first introduced to the U.S. market in 1985 with the Garren-Edwards Gastric Bubble (GEGB). The GEGB was associated with multiple adverse events including gastric mucosal damage and small-bowel obstruction related to spontaneous balloon deflation with migration into the small bowel. This necessitated endoscopic or, more commonly, surgical retrieval of the migrated balloons. In addition, the GEGB failed to demonstrate efficacy in a prospective, double-blind, sham-controlled, randomized trial of 59 obese patients with a 9-month follow-up period.[17] These issues resulted in its withdrawal from the U.S. market. In the early 1990s, the BioEnterics Intragastric Balloon (BIB) (Allergan, Irvine, Calif), currently known as the Orbera Intragastric Balloon (Apollo Endosurgery, Austin, Tex), was developed. The Orbera is an elastic spherical balloon made of silicone, filled with 450 to 700 mL of saline solution. The deflated balloon comes preloaded on a catheter, which is blindly advanced transorally into the stomach. An endoscope is then advanced alongside it to ensure accurate placement of the balloon in the fundus. Under direct visualization, the balloon is then inflated by injecting saline solution mixed with methylene blue through the external portion of the catheter. If inadvertent balloon rupture occurs, the methylene blue is systemically absorbed, causing a change in urine color, which serves as an alert that the balloon has deflated. The Orbera balloon is currently used in many countries outside the United States and is typically implanted for 6 months and then retrieved endoscopically.

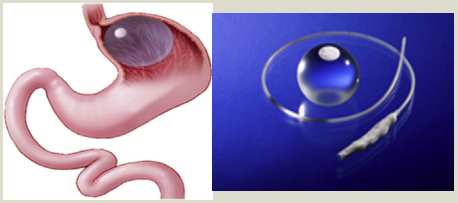
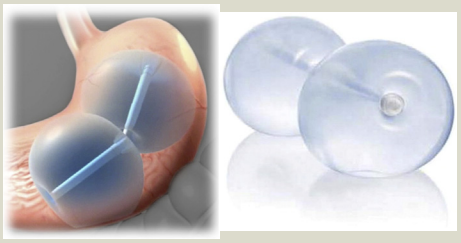
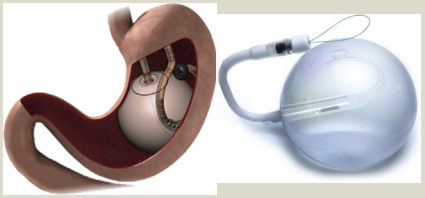
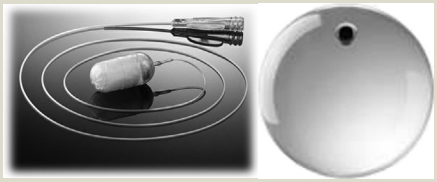
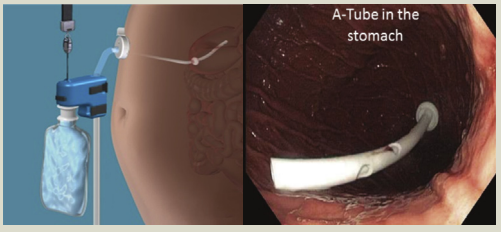
Newer IGBs with different migration-hindering and deployment/retrieval mechanisms and some that allow for endoscopic balloon volume adjustments are now available. The ReShape Duo (ReShape Medical, San Clemente, Calif) is an endoscopically inserted and retrieved, saline-solution filled, dual intragastric balloon system with 2 balloons attached to each other by a flexible tube. Each balloon has independent channels so that unintentional leaks or deflation in 1 balloon does not affect the other balloon. The ReShape Duo is filled with 900 mL of saline solution with methylene blue by a power pump delivering 450 mL to each balloon. The manufacturer recommends that the balloon be removed endoscopically after 6 months.

Other IGBs with unique design features have been developed. The Spatz Adjustable Balloon System (Spatz Medical, Great Neck, NY) is an endoscopically placed IGB that is filled with saline solution. It has an extractable inflation tube that allows for volume adjustment while the IGB remains in the stomach. The balloon volume may be decreased to improve patient tolerance or increased to enhance efficacy. Outside the United States, the Spatz balloon is approved for 12-month implantation.

The Obalon Gastric Balloon (Obalon Therapeutics Inc, Carlsbad, Calif) is packaged within a large gelatin capsule. The balloon contains a self-sealing valve connected to a thin catheter. The capsule with the balloon is ingested, while the catheter extends from the stomach through the esophagus and the mouth. Fluoroscopy is used to verify that the capsule has entered the stomach. The gelatin dissolves, freeing the balloon. The catheter is then used to inflate the balloon by using a gas-filled canister. After balloon inflation, the catheter is detached and removed. Up to 3 balloons can be swallowed during the same or sequential sessions, and balloons are removed endoscopically after 12 to 26 weeks.

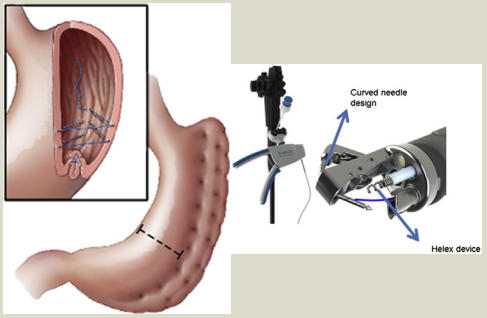
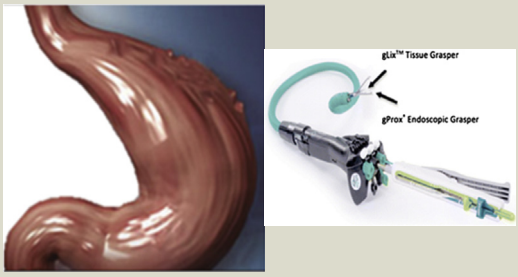
The Elipse balloon (Allurion Technologies, Wellesley, Mass) is enclosed inside a capsule and is attached to a thin, flexible catheter long enough to remain outside the

TABLE 1. Gastric Interventions

Intragastric Balloons (IGB)		
Orbera Apollo Endosurgery		Elastic spherical balloon made from silicone and filled with about 500-700 ml of saline. It is inserted and retrieved endoscopically.
ReShape Duo ReShape Medical		Saline solution-filled, dual intragastric balloon system with 2 balloons attached to each other by a flexible tube. Each balloon has independent channels so that unintentional leaks or deflation in 1 balloon do not to impact the other balloon.
Spatz Adjustable Balloon System Spatz Medical		Saline filled intragastric balloon with an extractable inflation tube for volume adjustment, while the IGB remains in the stomach.
Obalon Gastric Balloon Obalon Therapeutics		Gas-filled balloon with a maximal volume of 250ml. It is compressed, folded, and fitted in a large gelatin capsule. Once the capsule is ingested, the catheter extends from the stomach to outside the body through the esophagus and the mouth. After balloon inflation, the catheter is detached and removed. One or more balloon can be swallowed during the same session.
Other space occupying EBTs		
TransPyloric Shuttle BAROnova, Inc.		Endoluminally delivered solid silicone funnel-type device that delays gastric emptying by intermittent sealing of pylorus with peristalsis.
Full Sense Device BFKW LLC		Modified fully-covered gastroesophageal stent with a cylindrical esophageal component and a gastric disk that are connected by struts, which ensure that the gastric disk applies pressure on the gastric cardia to induce satiety.
Aspiration Therapy		
A-tube and Aspire Assist Device Aspire Bariatrics		Specially designed percutaneous gastrostomy tube, known as the A-Tube. The tube is made of silicone and is inserted in a fashion similar to that of a percutaneous endoscopic gastrostomy tube. Two weeks after insertion, the external portion of the tube is shortened, and a connecter valve is attached. The connector valve is flush with the skin and is connected to the Aspire Assist device to allow aspiration of 30% of the ingested meal 20 minutes after ingesting it.

(*continued on the next page*)

TABLE 1. Continued

Gastroplasty Techniques		
Endoscopic Sleeve Gastroplasty (ESG) with Overstitch Endoscopic Suturing Device Apollo Endosurgery		ESG is created by a series of endoluminally placed free-hand, full-thickness, closely spaced sutures through the gastric wall from the pre-pyloric antrum to the gastroesophageal junction by using an endoscopic suturing device (Overstitch). This procedure reduces the entire stomach along the greater curvature, to form an endoscopically created sleeve.
Primary Obesity Surgery Endolumenal (POSE) USGI Medical		Large, overtube-style platform that has 4 working channels that can accommodate a slim endoscope and 3 specialized instruments to place transmural tissue anchor plications in the gastric fundus (to reduce accommodation) and in parts of the distal gastric body.

patient's mouth once the capsule is swallowed. Once in the stomach, the capsule dissolves rapidly, and the balloon is filled with 550 mL of fluid. When filling is complete, the detachable catheter is removed. The Elipse balloon is designed to remain within the stomach for a predetermined period of several months, at which point a valve opens, allowing balloon to empty. The empty balloon is small and designed to be spontaneously excreted from the GI tract, thereby altogether eliminating the need for endoscopy.

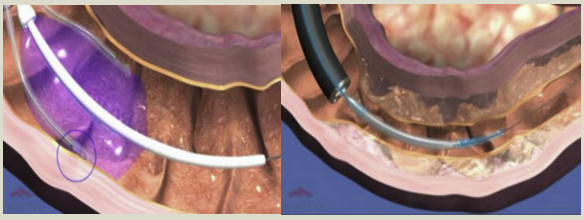
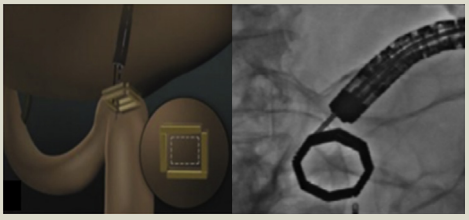
Other space-occupying EBTs. Other space-occupying EBTs use nonballoon devices to fill the GI tract. The TransPyloric Shuttle (BAROnova Inc. Goleta, Calif) comprises a larger spherical silicone bulb connected to a smaller cylindrical silicone bulb by a flexible tether. The delivery system for the device is advanced through an overtube into the stomach, where the device is deployed and self-assembles. In its assembled state, the size of the larger bulb prevents migration from the stomach, whereas the smaller bulb advances into the duodenum with peristalsis, allowing the device to assume transpyloric positioning. The base of the larger bulb is compliant, allowing it to engage the pylorus, thereby creating an intermittent seal intended to delay gastric emptying and induce early and prolonged satiety.

The Full Sense Device (Baker, Foote, Kemmeter, Walburn [BFKW] LLC, Grand Rapids, Mich) is a modified fully covered gastroesophageal stent with a cylindrical esophageal component and a gastric disk connected by struts. It is deployed and removed endoscopically. Once deployed, the gastric disk applies pressure to the gastric cardia, inducing satiety.

Aspiration therapy. Aspiration therapy (AT) is a novel treatment approach for obesity that allows obese patients to dispose of a portion of their ingested meal via a specially designed percutaneous gastrostomy tube, known as the A-Tube. The tube is made of silicone and is inserted in a similar fashion to that of standard percutaneous endoscopic gastrostomy tubes. Two weeks after insertion, the external portion of the tube is shortened and a skin port incorporating a valve is attached flush with the skin. An Aspire Assist device (Aspire Bariatrics, King of Prussia, Penn) is connected to the skin port to perform aspiration. An attached water reservoir flushes boluses of tap water into the stomach to facilitate subsequent aspiration cycles. Aspiration is performed via a siphon effect, ideally 20 minutes after consumption of the meal and typically a third of the meal is removed and discarded. The process takes only about 5 to 10 minutes to complete.[18]

Gastroplasty techniques. Endoscopic sleeve gastroplasty (ESG) is a transoral endoscopic gastric volume reduction technique that reduces gastric capacity by creating an endoscopic sleeve in a fashion similar, but not identical, to sleeve gastrectomy. This is accomplished by a series of endoluminally placed full-thickness sutures through the gastric wall, extending from the prepyloric antrum to the gastroesophageal junction. This technique reduces the entire stomach along the greater curvature, creating a sleeve. ESG is created by using a U.S. Food and Drug Administration (FDA)–approved and

TABLE 2. Small Bowel Interventions

Gastrointestinal Bypass Sleeves		
Endobarrier GI Dynamics		Duodenaljejunal bypass sleeve made of a Teflon liner and deployed in the duodenal bulb extending 65 cm into the small bowel, creating a mechanical barrier that allows food to bypass the duodenum and proximal jejunum without mixing with pancreaticobiliary secretions until later in the gastrointestinal tract.
Gastroduodenojejunal Bypass Sleeve ValenTx		120cm sleeve secured at the gastroesophageal junction, thus excluding the stomach, duodenum and proximal jejunum.
Other Small Bowel Interventions		
Duodenal Mucosal Resurfacing Fractyl Laboratories		Specialized radiofrequency ablation technology to ablate the superficial duodenal mucosa after lifting it with a submucosal saline injection
Self-assembling Magnets for Endoscopy GI Windows		Self-assembling magnets for endoscopy is a technology that can create incisionless magnetic compression anastomoses such as gastrojejunostomies, gastroileostomies, and duodenoileostomies

commercially available endoscopic suturing device (Overstitch; Apollo Endosurgery, Austin, Tex) that requires a double-channel therapeutic gastroscope to operate. Full-thickness suture placement is aided by the use of a tissue helix device that captures the targeted suture placement site on the gastric wall and retracts it into the suturing arm of the device.

Primary Obesity Surgery Endoluminal (POSE) uses a peroral incisionless operating platform (USGI Medical, San Clemente, Calif) to place transmural tissue anchor plications that reduce accommodation of the gastric fundus. Three additional plications are placed in the distal gastric body to delay gastric emptying. The procedure is performed by using a large, overtube-style platform that has 4 working channels that accommodate a slim endoscope and 3 specialized instruments: the g-Prox EZ Endoscopic Grasper (USGI Medical, San Clemente, Calif), a flexible shaft with a jawed gripper for creating and approximating full-thickness (serosa-to-serosa) tissue folds; the g-Lix Tissue Grasper (USGI Medical), a flexible probe with a distal helical tip designed to assist the g-Prox in capturing target tissue for a full-thickness mini-plication; and the g-Cath EZ Suture Anchor Delivery Catheter (USGI Medical), a catheter system with a needle at its distal tip that, after advancement through the lumen of the gProx, penetrates the mobilized target tissue and installs

a pair of preloaded paired tissue anchors joined by suture material holding the plication until there is serosal fusion.

Small-bowel interventions

The proximal small intestine is extremely efficient in nutrient absorption, and it plays a major role in glucose homeostasis and in the pathogenesis of diet-induced diabetes. Within the mucosa of the small intestine, enteroendocrine cells sense luminal nutrients and release gut peptides that are thought to mediate satiety and enhance insulin secretion (incretins); however, this process is not well understood. Thus, bypass of the proximal small intestine may contribute to weight loss and diabetes improvement (Table 2).[12,19,20]

GI bypass sleeves. The Endobarrier (GI Dynamics, Lexington, Mass) is a duodenojejunal bypass sleeve comprising an impermeable sleeve of Teflon, anchored in the duodenal bulb by a nitinol crown with barbs. The entire sleeve and anchoring crown are restrained within a delivery capsule that is advanced to the duodenal bulb over a stiff wire under endoscopic and fluoroscopic guidance. Once the capsule is in the duodenal bulb, the sleeve is advanced to the proximal jejunum and then the anchoring crown is deployed within the duodenal bulb. The sleeve extends 65 cm into the small bowel, creating a mechanical barrier that allows food to bypass the duodenum and proximal jejunum without mixing with pancreaticobiliary secretions until later in the GI tract, thus potentially manipulating the enteroinsulin system. The sleeve is removed endoscopically in 12 months by grasping a polypropylene drawstring with a custom device that collapses the anchoring crown into a foreign-body retrieval hood, thereby avoiding trauma to the stomach or esophagus during withdrawal.

The gastroduodenojejunal bypass sleeve (ValenTx, Inc, Hopkins, Minn) is a 120-cm long fluoropolymer sleeve that is secured at the gastroesophageal junction by using a combination of endoscopic and laparoscopic techniques. The deployed device functionally mimics the anatomic changes after RYGB surgery, as the longer sleeve excludes the stomach, duodenum, and proximal jejunum. A fully endoscopically deployable version of this device is in development.

Other small-bowel EBTs. *Duodenal mucosal resurfacing.* In the Revita duodenal mucosal resurfacing procedure (Fractyl Laboratories, Cambridge, Mass), thermal ablation of the superficial duodenal mucosa is performed by using radiofrequency. Mucosal remodeling may hypothetically reset duodenal enteroendocrine cells that have become diseased, thus restoring signaling that can improve diabetes control potentially through an incretin effect. This procedure will likely be useful in the management of type 2 diabetes in normal weight and obese individuals.

Self-assembling magnets for endoscopy (GI Windows, Boston, Mass) is a technology that can create incisionless magnetic compression anastomoses such as gastrojejunostomies, gastroileostomies, and duodenoileostomies. The proposed mechanism of action of this procedure is that nutrient and bile delivery to the distal small bowel will induce an ileal break phenomenon, resulting in decreased food intake and improved diabetes control.[21]

EFFICACY AND COMPARATIVE EFFECTIVENESS STUDIES

Primary obesity therapy

The goals of EBT are to induce weight loss and improve medical comorbidities, with an acceptable safety profile. Weight loss after a surgical or pharmacologic intervention is often determined as either changes in the percentage of total body weight lost (%TBWL) or the percentage of excess weight loss (%EWL) to define efficacy. The subject's ideal body weight is typically determined using the Metropolitan Life Insurance height and weight tables for men and women for a medium frame person. A joint task force convened by the American Society for Gastrointestinal Endoscopy (ASGE) and the American Society for Metabolic and Bariatric Surgery defined acceptable thresholds of safety and efficacy for EBTs in a Preservation and Incorporation of Valuable Endoscopic Innovations document.[22,23] The efficacy threshold for an EBT intended as a "primary" obesity intervention was set at 25% EWL measured at 12 months, with a statistically significant mean %EWL difference between a "primary" EBT and a control group of at least 15%. The threshold for incidence of serious adverse events associated with a particular EBT was set at 5% or less. Although achieving these minimum thresholds will be subsequently assessed for each available EBT in systemic reviews and meta-analyses, we introduce these thresholds as a framework for the discussion to follow.

Intragastric balloons. The %TBWL at 6 months after Orbera balloon implantation (time of removal) ranged between 9.3% and 21% with a median value of 12%.[24-42] Ten prospective trials including 1161 patients with obesity reported the 12-month (6 months after removal) %EWL with the Orbera balloon.[30,36,39,41,43-49] The %EWL ranged from 11% to 51% at 12 months. Two studies reported long-term data after Orbera balloon implantation.[50,51] At 36 months after implantation, approximately 6% TBWL is maintained. Four small randomized, controlled trials (RCTs) compared the Orbera with either a sham or a control group.[48,52-54] The mean difference in %EWL over the sham or control group ranged from -7% to 33% and was statistically significant in 3 studies. Three prospective studies evaluated the efficacy of sequential use of the Orbera balloon compared with single use.[55-57] The mean decrease in body mass index (BMI) after 2 sequential treatments with the Orbera balloon was 4 BMI points

($P = .047$) more than that seen with single treatment at 12 months after insertion.

A randomized study indicated that the Orbera balloon was more effective than pharmacotherapy in accomplishing weight reduction. In this study, 50 patients with obesity were randomized to either lifestyle modifications combined with the Orbera balloon for 6 months (n = 30) or to lifestyle modifications combined with sibutramine (pharmacotherapy group) (n = 20) for 6 months.[58] After Orbera balloon removal, patients were randomly assigned to lifestyle (Orbera/lifestyle) or lifestyle plus pharmacotherapy (Orbera/pharmacotherapy) for an additional 6 months. Patients in the Orbera/pharmacotherapy arm had more significant weight loss, suggesting a potential synergistic effect.

A pivotal U.S. multicenter study evaluating the safety and effectiveness of the Orbera balloon in the weight management of obesity randomized 272 patients with obesity to the Orbera balloon as an adjunct to a behavioral modification program or to a behavioral modification program alone. The study is completed and currently under review by the FDA.

In a European study, 21 obese patients were randomized to the ReShape Duo double-balloon system and 9 to lifestyle modification. The mean %EWL at 6 months in the balloon group (time of balloon removal) was 31.8% compared with 18.3% in the lifestyle modification group. At 12 months (6 months after device removal), the balloon group maintained 64% of their weight loss.[59] The REDUCE pivotal trial is a U.S. multicenter, randomized, sham-controlled trial of 326 obese patients randomized to the ReShape Duo balloon plus diet and exercise (n=187) or to sham endoscopy plus diet and exercise (n=139). Patients randomized to the ReShape Duo balloon had a significantly greater %EWL at 6 months compared to the sham group (25.1% vs 11.3%, $P = .004$) on intent-to-treat (ITT) analysis.[60]

Other intragastric balloons have more limited data. Two small observational noncontrolled studies evaluated weight loss outcomes after deployment of the Spatz adjustable balloon in 94 obese patients. Percent EWL at 12 months (time of balloon removal) was 46%.[61,62] A case-control study found no difference in weight loss outcomes at 12 months when comparing 80 patients who had sequential placement of 2 Orbera balloons (6 months each) to 40 patients who had the adjustable Spatz balloon placed for 12 months.[41]

Aspiration therapy. In a pilot study, 18 subjects were randomized in a 2:1 ratio to 1 year of aspiration therapy (AT) plus lifestyle intervention (BMI = 42.0 ± 4.7 kg/m^2) or lifestyle intervention alone (LIA) (BMI = 43.4 ± 5.3 kg/m^2).[18] Patients in the AT group were permitted to continue therapy for an additional year (2 years total). Seven of 11 patients randomized to AT opted to continue therapy for 2 years. Ten of 11 AT and 4 of 7 LIA subjects completed the initial 1 year. Among subjects completing 1 year of therapy, AT and LIA subjects lost 18.3 ± 7.6% (49.0 ± 24.4% EWL) and 5.9 ± 10.0% (14.9 ± 24.6% EWL) body weight, respectively. The 7 subjects who completed 2 years of AT maintained 20.1 ± 9.3% body weight loss (54.6 ± 31.7% EWL) at 2 years. A single-arm prospective trial in Sweden demonstrated a similar rate of weight loss after 26 weeks of aspiration therapy, with 14.8 ± 6.3% body weight loss (40.8 ± 19.8% EWL) at 26 weeks in 22 patients who completed the trial.[63]

A pivotal multicenter, randomized, controlled, open-label, 52-week trial to support FDA approval of this device is currently underway in the United States. Given the potential mechanism of action of this device, and the possible continued steady weight loss with long-term use, this device might be suitable for the treatment of individuals with super-obesity. Pilot European studies demonstrating the utility of aspiration therapy in super-obese patients with BMIs greater than 55 kg/m^2 are under way.

Gastroplasty techniques. Two studies evaluating the ESG procedure on 20 and 10 obese patients respectively reported a %EWL between 30% to 40% at 6 months.[64,65] Results are not yet available from the PROMISE (Endoscopic Suturing for Primary Obesity Treatment) trial, which is a recently completed multicenter, prospective, single-arm study that evaluated the safety, durability, and 12 months outcomes with this technique.

A single-center, open-label, prospective trial enrolling 45 obese patients mostly with class I and II obesity demonstrated the feasibility and safety of the POSE procedure.[66] A mean of 8.2 suture anchors were placed in the fundus and 3 in the distal body. Subjects lost around 49% EWL at 6 months. The ESSENTIAL trial is a U.S. multicenter, randomized, sham-controlled pivotal trial of the POSE procedure that has enrolled 332 patients and will follow them for 12 months to evaluate safety and efficacy endpoints.

Duodenojejunal bypass sleeve (Endobarrier). Seven studies reported the %EWL after Endobarrier implantation.[67-73] The %EWL ranged between 12% and 22% at 12 weeks, 24% and 32% at 24 weeks, and 30% and 47% at 52 weeks. Four RCTs compared 12 to 24 weeks treatment with the Endobarrier (90 subjects) with a sham or control arm (84 subjects).[67-69,73] The %EWL with the Endobarrier over sham ranged between 9% to 17% at 12 weeks, and 15.6% at 24 weeks.

The ENDO Trial is a randomized, double-blind, sham controlled, multicenter pivotal U.S. trial that is currently underway and expected to enroll around 500 obese subjects with uncontrolled diabetes. Unlike the previous RCTs, this trial is designed to assess improvements in diabetes as well as weight over a treatment period of up to 12 months.

Improvement in obesity-related comorbidities

Obesity is associated with multiple co-morbid conditions that compound its health-care burden and are

therefore important targets for medical and surgical obesity therapy. In a recent meta-analysis, 9 studies evaluated improvement in obesity-related co-morbidities 2 years after bariatric surgery.[74] Remission rates of type 2 diabetes mellitus (dm^2), hypertension, and hyperlipidemia were 66.7%, 38.2%, and 60.4% for RYGB and 28.6%, 17.4%, and 22.7% for gastric band, respectively.

Intragastric balloons. Crea et al[46] investigated the effects of Orbera balloon implantation on the metabolic syndrome, dm^2, hypertension, and hyperlipidemia at 6 months (time of balloon retrieval) and 18 months (12 months after balloon retrieval) in 143 obese patients with a mean BMI of 36.2kg/m^2. The proportion of study subjects with the metabolic syndrome decreased from 34.8% at the outset of the study to 14.5% and 11.6% at 6 and 18 months, respectively. Similarly, decreases were noted in the incidence of type 2 diabetes mellitus (32.6% at outset, 20.9% at 6 months, 21.3% at 18 months), hypertriglyceridemia (37.7% at outset, 14.5% at 6 months, 17.4% at 18 months), hypercholesterolemia (33.4% at outset, 16.7% at 6 months, 18.9% at 18 months) and hypertension (44.9% at outset, 30.4% at 6 months, 34.8% at 18 months) in the study subjects. The HbA1c blood concentration decreased from a pre–balloon implantation value of 7.5% (SD 2.1) to 5.7% (SD 1.9) at 6 months, and 5.5% (SD 0.9) at 18 months. A multi-center European study evaluated the impact of the Orbera balloon on weight related comorbidities in 261 overweight patients (BMI 27-30 kg/m^2).[51] Decreases were noted in the proportion of patients with hypertension (29%-16%), dm2 (15%-10%), hypercholesterolaemia (32%-21%), and osteoarthropathy (25%-13%) at 3 years. Mui et al[36] evaluated improvements in obesity-related comorbidities and quality of life in 119 consecutive patients with obesity after 6 months of Orbera balloon implantation. The proportion of patients with the metabolic syndrome decreased from 42.9% to 15.1% ($P < .0005$). Fasting glucose, cholesterol, triglyceride, C-reactive protein, and blood pressure also improved compared to base-line values ($P < .005$). In the 28 patients with dm^2, the HbA1c level significantly decreased from 7.4% to 5.8% ($P < .0005$) at 6 months. The quality of life of patients was significantly improved as well ($P < .05$). Two other studies demonstrated improvements in insulin resistance after Orbera implantation.[75,76]

Obesity is a major risk factor for obstructive sleep apnea (OSA) with about 50% to 60% of patients with obesity having that condition.[77] Resent research has shown that OSA is not just a mere epiphenomenon of obesity, but rather has a pathophysiologic role in the development of metabolic syndrome and increases cardiac risk in obese patients.[78] Visceral fat accumulation and large neck circumference are predictive risk factors for OSA.[79] A study of 17 morbidly obese males with severe OSA evaluated the effects of weight loss with Orbera balloon on OSA by measuring apnea-hypopnea index with cardiorespiratory sleep studies and measuring neck circumferences before and 6 months after implantation of the Orbera balloon. Six months after Orbera implantation, neck circumference decreased from 51.1 cm (SD 3.7) to 47.9 cm (SD 4.3) ($P < .001$). Weight loss induced by the Orbera balloon was also associated with nearly complete resolution of OSA as evidenced by a decrease in apnea-hypopnea index from 52.1 events/hour (SD 14.9) to 14.0 events/hour (SD 12.4) ($P < .001$).[25]

NAFLD is thought to afflict about 70% of patients with obesity.[80] Of those, about 5% will progress to cirrhosis and end-stage liver disease.[81] Nonalcoholic steatohepatitis is projected to be the leading cause of liver transplantation in the United States by 2020.[82] A small study randomized 18 obese or overweight patients with histologically proven nonalcoholic steatohepatitis (NASH) to lifestyle modification plus Orbera balloon placement or to lifestyle modification plus a sham procedure. Weight and liver histology were assessed before and 6 months after balloon insertion or the sham procedure. The Orbera balloon placement group had a significantly higher reduction in mean BMI (1.52 vs 0.8; $P = .0008$) and a superior improvement in nonalcoholic fatty liver disease activity scores at the end of treatment (2 [SD 0.75] vs 4 [SD 2.25]; $P = .03$).[83] Another study evaluated liver fat content with US, chemical-shift MRI, and body composition with bioimpedance analysis in 31 patients with obesity before and 6 months after Orbera balloon (n=13), laparoscopic gastric banding (n = 5), and hypocaloric diet (n= 13). After 6 months, weight loss in patients receiving the Orbera balloon or gastric band was higher than in diet-treated patients with a significantly higher decrease in liver fat, body fat composition, and liver biochemical tests.[84] Two other single-arm studies showed improvement in liver steatosis by ultrasound and liver biochemical tests with the Orbera balloon.[75,85]

There is a strong association between obesity and infertility in obese women.[86] The endocrinopathy associated with obesity is characterized by excess estrogen, low progesterone, hyperinsulinemia, and an abnormal follicle-stimulating hormone/luteinizing hormone ratio; this hormonal profile can result in anovulation.[87] Obesity can also damage endometrial receptivity to embryo implantation and growth, resulting in miscarriage.[88] Effective weight loss has been shown to reverse the altered reproductive hormone profile associated with morbid obesity, thereby restoring fertility and decreasing the risk of obstetric adverse events during pregnancy.[89] A retrospective study of 110 obese infertile women, evaluated the effectiveness of weight loss with the Orbera balloon (n=24) and surgical techniques including the adjustable gastric band (n=43), sleeve gastrectomy (n=34), and gastric bypass (n=9) in restoring fertility. All procedures were effective in reversing infertility with no significant difference between them. Only weight loss with reduction of BMI by >5 kg/m^2 was the predictor of pregnancy (odds

ratio 20.2, $P = .001$).[90] A further retrospective study performed by the same investigators on 27 obese women with infertility indicated a success rate of 55% in reversing infertility and carrying a full term pregnancy with no obstetric adverse events, after Orbera balloon implantation.[91]

Duodenojejunal bypass sleeve (Endobarrier)

The Endobarrier has demonstrated a significant impact on diabetic control after implantation. Several studies have demonstrated decreases in HbA1c blood concentrations after Endobarrier implantation, of 0.3% to 1.1% at 12 weeks,[67,69] 1.3% to 2.4% at 24 weeks,[72,73,92] and 1.1% to 2.3% at 52 weeks.[70,71,93,94] Three of these studies were RCTs and indicated a significant improvement in HbA1c ranging from 0.9 to 1.7 over that seen in the control group.[69,73,92]

A study of 17 patients with obesity and DM2 investigated the effects of Endobarrier implantation on plasma parameters of NAFLD before, 12 weeks after, and 24 weeks after implantation. Plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (γ-GT), albumin, caspase-cleaved cytokeratin-18 (CK-18), and liver fatty acid-binding protein (L-FABP) were measured and followed. Twelve weeks after implantation, all NAFLD-related parameters significantly decreased from baseline (all $P < .05$). After 24 weeks (time of Endobarrier removal), levels of ALT and γ-GT had further decreased, whereas levels of AST, caspase-cleaved CK-18, and L-FABP had stabilized. Six months after Endobarrier removal levels of ALT (37 ± 3 IU/L), γ-GT (42 ± 5 IU/L), and caspase-cleaved CK-18 (124.5 ± 12.5U/L) were still reduced ($P < .05$), whereas AST and L-FABP had returned to near baseline levels.[95] This study indicates that the Endobarrier may have a positive effect on NAFLD, although no histological endpoints were evaluated in this study.

Bridge therapy

Acute weight loss before definitive bariatric surgery has been proposed to lower the incidence of intraoperative and/or postoperative surgical adverse events, especially in super obese individuals and to predict postoperative success by selecting motivated and compliant patients.[96] A preoperative absolute weight loss of 10% translates into improvements in cardiovascular and thromboembolic risk, reduction in proinflammatory status, and improvement in respiratory mechanics. Furthermore, it leads to a decrease in the visceral fat volume, decreased thickening of the omentum and abdominal wall, and reduction in liver volume, thus improving the technical complexity of bariatric surgery and decreasing operative times.[97-99]

The use of the Orbera balloon before surgery has been studied in super obese patients. In 2 small prospective studies, together including 41 super-obese patients, the Orbera balloon resulted in 10% or higher of total body weight in more than 90% of patients before laparoscopic RYGB.[100,101] Two matched case-control studies of 43 and 23 super obese patients treated with the Orbera balloon followed by laparoscopic adjustable gastric band (LAGB) or laparoscopic RYGB, respectively, matched by sex, age and BMI to 43 and 37 super-obese controls treated with LAGB or RYGB alone, indicated a decreased operative time, shorter hospital stay, fewer conversions to open procedures, and fewer intraoperative adverse events in the preoperative balloon group.[102,103] In a further study, 26 high-risk super-obese patients with a mean body mass index of 65 kg/m^2 and severe comorbidities treated initially with 24 weeks placement of the Orbera balloon, were able to achieve a mean weight loss of 28.5 ± 19.6 kg with significant improvements in comorbidities, allowing 20 of them to subsequently undergo a bariatric surgical procedure. Of note, in this study, one death occurred due to aspiration complicated by cardiac arrest a day after balloon insertion.[104]

Not all studies have shown benefit from preoperative weight loss with IGB before a primary bariatric surgical procedure. A study of 23 super-obese patients who self-selected either the Orbera balloon or a structured weight loss program before surgery, indicated that there was no additional benefit from the Orbera balloon compared with the structured weight loss program.[105]

SAFETY

Intragastric balloons

The rates of adverse events after implantation of the Orbera balloon are pooled from a manual review of 67 studies (8500 implantations) and are summarized in Figure 1. Pain and nausea are frequent side-effects after Orbera balloon implantation, occurring in up to 33.7% of subjects. Medications such as proton pump inhibitors, antispasmodic drugs including anticholinergics, and antiemetics are usually prescribed prophylactically before, during, and after balloon placement to prevent or minimize these expected common side effects. Early removal rate of the Orbera balloon was required in 7.5% subjects. Serious side-effects with Orbera balloon are rare with an incidence of migration and gastric perforation of 1.4% and 0.1%, respectively. Most of the reported perforations with the Orbera were in patients who had undergone previous gastric surgeries.

Similarly, in the pivotal REDUCE US trial that evaluated the safety and efficacy of the ReShape Duo IGB in 264 patients, pain and nausea were common symptoms and were successfully managed medically. Early retrieval for intolerance was necessary in 9% of patients. Spontaneous balloon deflation occurred in 6% of subjects without balloon migration. Gastric ulcers and erosions were frequent adverse events, initially observed in 35% of the study subjects. However, a subsequent device design modification led to decreases in both ulcer frequency (reduced to 10%) and

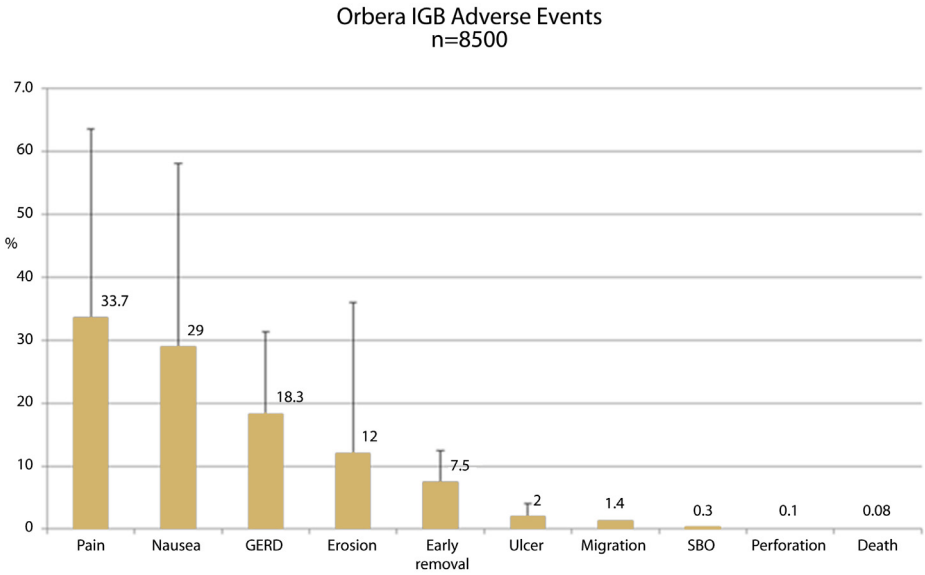


Figure 1. Prevalence of adverse events after Orbera balloon implantation. *IGB*, intragastric balloon; *SBO*, small-bowel obstruction.

in ulcer size (1.6cm to 0.8cm). Most of the reported ulcers were not clinically significant, except for one ulcer-related upper GI hemorrhage requiring blood transfusion. There were no deaths, balloon migrations, intestinal obstruction, or gastric perforations reported in the REDUCE trial. Three serious adverse events were observed with ReShape Duo retrieval, including an esophageal mucosal tear requiring hemoclips application, contained cervical esophagus perforation managed conservatively with antibiotics, and one post-retrieval aspiration pneumonitis.[60]

Other balloons have more limited safety data. Earlier generations of the Spatz Adjustable Balloon System had a noncollapsible loop with an internal metal chain that maintained a 7-cm balloon diameter within the gastric lumen to prevent or delay a deflated balloon from migrating. This design has been implicated in a higher incidence of migration complicated by balloon impaction, necessitating surgical removal.[41,61,62,106] The Spatz 3 balloon has been modified with removal of the metal chain and stiff catheter, thereby mitigating these unwanted effects.

Duodenojejunal bypass sleeve (Endobarrier)

The safety profile of the Endobarrier appears favorable based on experience with 271 implantations detailed in the literature (Fig. 2). However, the incidence of early removal is high at 18%, and 3 patients experienced serious adverse events including esophageal perforation secondary to trauma from an uncovered barb at withdrawal, cholangitis, and liver abscess. The currently ongoing multicenter RCT will better define the safety profile of the Endobarrier.

Other devices

A discussion of the safety of other EBTs discussed in the review is premature given the limited available data.

FINANCIAL CONSIDERATIONS

With the exception of the Overstitch, none of the cited EBTs are clinically available in the United States; therefore, a discussion of their costs is not possible at this time. The cost of the Overstitch device is US$799. Each Prolene suture costs US$48, and the helix device costs US$180. These prices may vary depending on the volume of use per institution.

AREAS OF FUTURE RESEARCH

The number and diversity of emerging devices to achieve EBT will dictate a broad and rigorous research agenda to help understand their optimal role in patient care and their adoption into clinical practice. The priorities will include the following:

1. Investigating the durability of weight loss induced by EBTs and their impact on obesity-related comorbidities.
2. Determining all of the physiological consequences of EBTs and the clinical predictors of response to better define their role in the spectrum of care offered to patients with obesity.
3. Comparative-effectiveness studies comparing different EBTs deployed individually, sequentially, simultaneously, and/or in combination with pharmacotherapies.
4. Investigating the cost-effectiveness of EBTs including the direct cost of the device and associated health

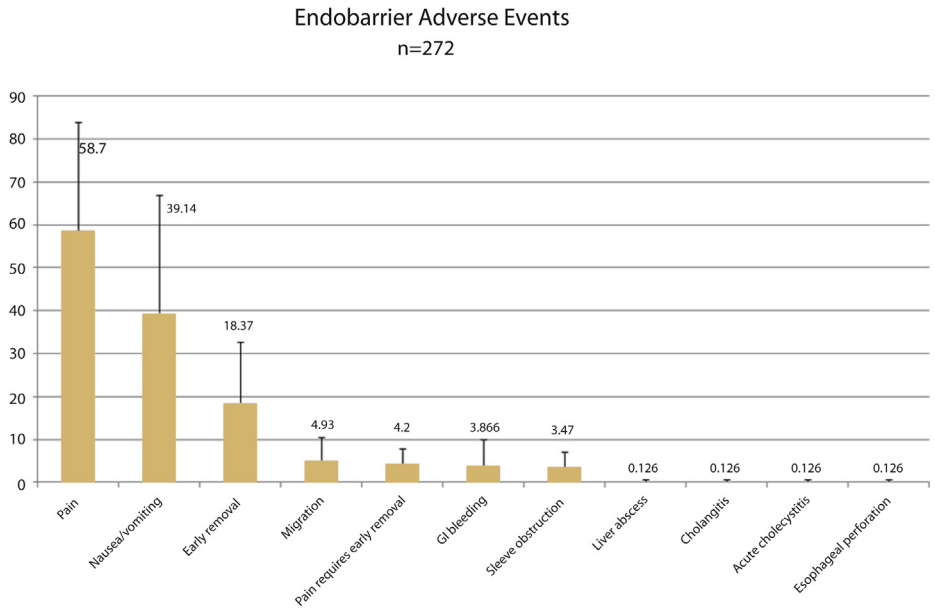


Figure 2. Prevalence of adverse events after Endobarrier implantation.

care use required to help define safety and efficacy thresholds where a particular EBT provides an incremental cost benefit over medical and pharmacological therapies for obesity.

5. Establishing standards of practice for the use of EBT, including pre- and postprocedural care and longer term follow-up care.
6. Development of training and credentialing programs and the establishment of quality metrics to help develop quality assurance programs for EBT.

SUMMARY

EBTs hold the promise of providing the next major breakthrough in the management of obesity. At a time when less than 1% of qualified patients actually undergo bariatric surgery, the development of a variety of new endoscopic therapies that replicate the physiological benefits of bariatric surgery in a safe, cost-effective, and minimally invasive fashion may potentially offer the best path to making a meaningful impact on the obesity epidemic. Currently investigated devices have established promising outcomes in short-term weight loss and in control of the metabolic and other medical adverse events of obesity. Pending regulatory approval in the United States, further studies will help define their optimal role in the comprehensive management of obesity.

DISCLOSURES

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Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; AT, aspiration therapy; BIB, BioEnterics Intragastric Balloon; BMI, body mass index; EBT, endoscopic bariatric therapy; ESG, endoscopic sleeve gastroplasty; FDA, U.S. Food and Drug Administration; %EWL, percentage of excess weight loss; GEGB, Garren-Edwards Gastric Bubble; IGB, intragastric balloon; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; POSE, Primary Obesity Surgery Endoluminal; RCT, randomized, controlled trial; RYGB, Roux-en-Y gastric bypass; %TBWL, percentage of total body weight lost.

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