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Endoscopy (P Siersema, Section Editor)

Endoscopic Bariatric Therapies: Intragastric Balloons, Tissue Apposition, and Aspiration Therapy

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Abstract

Purpose of review Endoscopic bariatric therapies (EBTs) have been identified as a group of procedures that can bridge the treatment gap between bariatric surgical procedures and non-procedural treatments such as pharmacotherapy and lifestyle therapy. We will review the recent progress that has been made in this important area in the past several years.

Recent findings Traditional intragastric balloons (IGB) that are both placed and removed endoscopically have been the fixture of IGB therapy. They have been shown to be safe and effective, when kept in place for 6 months. Newer IGBs, both currently FDA approved and those in clinical trials, have unique features. The Obalon gastric balloon system is gas filled and does not require endoscopy for placement. The Elipse balloon system that is in clinical trials neither requires endoscopy for placement nor removal. The Spatz3 balloon is in clinical trials and can be adjusted endoscopically by adding or subtracting volume to titrate balloon volume to symptoms and weight loss. In addition to IGBs, several other promising therapies have continued to evolve. Endoscopic sleeve gastroplasty (ESG) is a promising gastric restriction technique that has efficacy and durability. POSE is a gastric plication technique that is available in Europe and in clinical trials in the USA. Aspiration therapy is a novel approach to weight loss that requires patient compliance but can be very effective and used long

term.
Summary EBTs are an evolving effective and safe approach for patients who do not qualify for or do not want bariatric surgery. There are multiple EBTs currently FDA approved as well as prospective endoscopic therapies in clinical trials that appear promising.

Introduction

Endoscopic bariatric therapies (EBTs) are procedures performed using flexible endoscopy to facilitate weight loss in the obese population. EBTs have been demonstrated to be more effective in weight loss than lifestyle therapy [1••, 2] and pharmacotherapy [3, 4]. There have been no prospective, randomized controlled trials comparing EBTs with bariatric surgery to date, though weight loss achieved with bariatric surgery is generally accepted as being greater than what has been accomplished endoscopically [5]. Conversely, EBTs are generally associated with fewer complications, which may make them more appealing to those who do not want surgery or are not candidates for surgery. This review will examine currently available EBTs and devices that are Food and Drug Administration (FDA) approved in the USA as well as several that are currently in clinical trials hoping for FDA approval in the coming years.

Space-occupying gastric therapies

The primary space occupying gastric therapy is the intragastric balloon (IGB; Fig. 1; Table 1). Saline-filled intragastric balloons are generally placed and removed endoscopically in those with a body mass index (BMI) of 30–40 kg/m^2 though there is currently a balloon in preapproval clinical trials that requires no endoscopy. It is speculated that IGBs work via a combination of hormonal and physiologic changes including delayed gastric emptying [18].

ReShape

The ReShape Dual Integrated Balloon System (ReShape; ReShape Medical, San Clemente, CA; Fig. 1*A*), FDA approved in 2015, consists of two spheres filled with saline that are joined by a central shaft and are placed endoscopically and removed endoscopically after 6 months [6]. The REDUCE trial in 2015 was a randomized, sham-controlled trial that led to its FDA approval, comparing the balloon system plus diet and exercise vs. sham endoscopy plus diet and exercise [2]. After 24 weeks, in the intention-to-treat (ITT) analysis, the ReShape subjects achieved a mean of 25.1% excess weight loss (EWL) and 6.8% total body weight loss (TBWL) with a responder rate of 48.8% (defined as EWL ≥ 25%) compared to 11.3% EWL and 3.3% TBWL achieved by subjects in the control arm. The serious adverse event (SAE) rate was 7.5%, though 75% of the device-related SAEs were due to accommodative symptoms such as nausea, vomiting, and abdominal pain that generally responded within

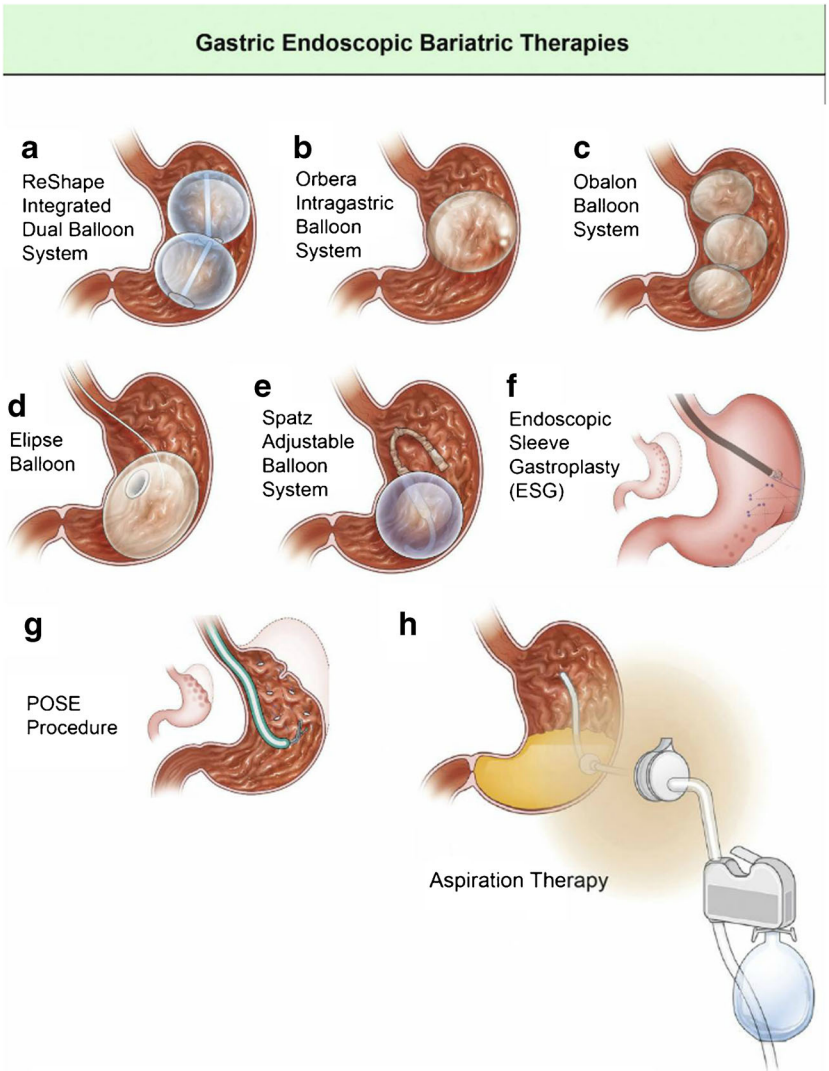

Fig. 1. (A–H) Gastric endoscopic bariatric therapies. Used with permission from Elsevier

1 week of placement. The rate of gastric ulceration was 10.3%, a decrease after the initial balloon design demonstrated a 35% gastric ulceration incidence. A 2018 retrospective study that is more generalizable looked at the safety and efficacy of the Reshape balloon system in a combination of academic centers and private practices, which demonstrated a mean $11.4 \pm 6.7\%$ TBWL and $29.9 \pm 18.2\%$ EWL at 6 months with 55.4% of subjects achieving at least 25% EWL [7]. Like in the REDUCE trial, most common SAEs were nausea, vomiting, and abdominal pain that generally resolved after 1 week. The gastric ulceration rate was 0.9%. As of December 17, 2018, Apollo Endosurgery (Apollo Endosurgery, Austin, TX) purchased ReShape Medical and will focus exclusively on its own Orbera IGB going forward [19]. With this transaction, the ReShape balloon will be phased out, leaving two FDA-approved balloons available at the time of

Table 1. Characteristics, weight loss, and response rates of intragastric balloons with FDA approval or in clinical trials

Intragastric balloon	FDA approved	Gas or fluid-filled	Implantation time	Mean %TBWL at balloon removal	Mean %TBWL (12 mo)	Active group responder rate at balloon removal (% subjects ≥ 5% TBWL or ≥ 25% EWL)
ReShape Integrated Dual Balloon System [2, 6, 7]	Yes	Fluid	6 mo	6.8–11.4%	14.7%	48.8–55.4%
Orbera Intragastric Balloon System [8–10]	Yes	Fluid	6 mo	10.2–11.8	7.6%	79.2–88%
Obalon Balloon System [11••, 12•]	Yes	Gas	6 mo from first balloon	6.6–10.0%	6.9%[a]	62.1–76.7%
Elipse Balloon [13••, 14–16]	No	Fluid	4 mo	10.0–15.1%	5.9%	90.9%
Spatz3 Balloon [17]	No	Fluid	12 mo	16.3%	N/A	88.5%

FDA, US Food and Drug Administration; *TBWL*, total body weight loss; *EWL*, excess weight loss
[a]Value obtained at 48 weeks from the percentage of patients with any weight loss at week 24

this publication in the USA.

Orbera

The Orbera Intragastric Balloon System (Orbera; Apollo Endosurgery, Austin, TX; Fig. 1*B*), FDA approved in 2015, is a single, saline-filled sphere that is placed endoscopically and removed endoscopically after 6 months [8]. The Orbera balloon has been extensively studied internationally as the BIB balloon. A meta-analysis of these studies and the balloons efficacy was published in 2015 [20]. Since the Orbera balloon was demonstrated to be effective and safe in an open-label, randomized control trial in 2015, further trials have demonstrated its safety, efficacy, and utility [21]. In a 2017 multicenter, randomized, open-label clinical trial, subjects achieved a mean of 10.2% TBWL in the Orbera balloon treatment arm vs. 3.3% TBWL in the lifestyle therapy arm at 6 months [9]. At 12 months, the mean TBWL was 7.6% and 3.1% in the treatment and lifestyle arms, respectively. The most commonly reported adverse events (AEs) were nausea, vomiting, and abdominal pain, occurring in 86.9%, 75.6%, and 57.5%, respectively, of all

subjects with an IGB, though no subjects developed ulcers in this study. The SAE rate was 10%, with the most common SAE being intolerance to the device. Due to AEs, device intolerance, or subject request, 18.8% of subjects with the IGB had it removed early. A post-regulatory approval study of the Orbera balloon published in July 2018 demonstrated a mean 11.8 ± 7.5% TBWL at 6 months with 88% and 62% of subjects achieving 5% and 10% TBWL, respectively [10]. Similar to aforementioned 2017 trial, the early removal rate of the IGB was 16.7%, with about 75% of those removals due to excessive symptoms such as nausea, vomiting, abdominal pain, and heartburn, and the other 25% being removed from asymptomatic subjects per request. The Orbera balloon has also been studied as a bridge to bariatric surgery in a UK study to help achieve pre-operative weight loss of 10% in the super obese [22].

Obalon

The Obalon Balloon System (Obalon; Obalon Therapeutics, Carlsbad, CA; Fig. 1C), FDA approved in 2016, consists of a series of three individual IGBs that are swallowed over a period of several months as deflated capsules attached to a catheter [23]. After confirming positioning in the stomach with fluoroscopy, each is inflated with a gaseous mixture. These are removed endoscopically after 6 months. The Obalon pilot study in 2013 demonstrated a mean 5.9% TBWL, though this was just after 12 weeks of balloon implantation [24]. This led to the Six-Month Adjunctive Weight Reduction Therapy (SMART) Trial, a randomized sham-controlled trial evaluating the safety and efficacy of the Obalon, which demonstrated 6.6 ± 5.1% TBWL in the treatment arm ($n = 198$) after 24 weeks vs. 3.4 ± 5.0% TBWL in the control arm ($n = 189$) in the ITT analysis [11••]. Weight loss maintenance in the treatment arm of those who lost any weight by the time of Obalon removal was 88.5% at 48 weeks; this same group of subjects achieved a mean of 7.8 ± 4.4% TBWL at week 24 and 6.9 ± 6.5% TBWL at 48 weeks. The overall responder rate, defined as %TBWL ≥ 5% at 6 months, was 62.1% in the ITT analysis. Like in most IGB trials, nonserious adverse events were reported in almost all subjects (91.1%), but serious adverse events were rare. An industry-sponsored registry was developed for the Obalon balloon to report clinical effectiveness and safety of the device. The prospective registry was retrospectively analyzed, comprising of 1343 subjects who met inclusion criteria [12•]. Of those who completed a minimum of 20 weeks of IGB therapy with all three balloons in place ($n = 787$), a mean 10.0 ± 6.1% TBWL was achieved at time of removal of balloons. A total of 76.7% and 49.7% of subjects lost ≥ 5% and ≥ 10% TBWL, respectively. The AE and SAE rates were 14.2% and 0.15%, respectively, with the most commonly reported AEs being abdominal pain (5.29%), nausea (4.69%), and vomiting (2.31%). There were seven balloon deflations, no bowel obstructions, and one gastric perforation due to a gastric ulcer in a non-compliant subject. Obalon has made recent strides to further improve their product. Through the Obalon Touch Inflation System, FDA approved in September 2018, Obalon hopes to achieve more reliable inflation of their balloons which will now be automated [25]. The FDA also recently approved the Obalon Navigation System in December 2018, eliminating the need for radiography to confirm balloon positioning and instead utilizing magnetic resonance to provide a real-time image of the Obalon on a

computer screen [26]. In addition to eliminating exposure to radiation, this aims to increase the feasibility of placing the balloons as well as decreasing costs associated with using radiography. Due to its relative ease of administration, the Obalon IGB has also been studied in a pediatric and adolescent population with promising results [27].

Elipse

The Elipse Balloon (Elipse; Allurion Technologies, Wellesley, MA; Fig. 1*D*) is a non-FDA-approved IGB that is currently under clinical investigation. The Elipse is unique in that it neither requires endoscopy to place nor to remove. It is a swallowable saline-filled balloon, similar to the Obalon, though it self-deflates and is excreted through the GI tract after about 16 weeks. After the pilot study demonstrated its safety and efficacy in 2016, multiple studies have been performed to further evaluate its safety and efficacy [28]. A 2017 prospective, open-label, multicenter study demonstrated a mean of 10.0% TBWL at 16-week follow-up [13••]. There were no SAEs. Nausea, vomiting, and abdominal pain were experienced by 54%, 64%, and 25% of subjects, respectively. All balloons were safely excreted, with a majority passing in the stool (88%) vs. via emesis (12%). A 2018 prospective, single-arm study from a single center in Italy demonstrated similar results, with subjects achieving a mean 11.6% TBWL after 16 weeks [14]. There were no SAEs including no intestinal obstructions or ulcers. In the largest study to date, a multicenter prospective trial with 135 subjects, mean TBWL at 4 months was 15.1% in the ITT analysis [15]. One subject had a small bowel obstruction and required surgery. Otherwise, the Elipse was well tolerated with 1.5% requiring early removal due to intolerance. All subjects with nausea had a resolution of within 1 week of the balloon ingestion. One prospective, nonrandomized open trial of 12 subjects utilizing the Elipse followed their subjects for 12 months noting a mean of 14.6% TBWL at the time of balloon excretion compared to 5.9% TBWL at 12 months [16]. It is important to note that these subjects only received diet and exercise counseling during the initial 16 weeks of therapy.

Spatz3

The Spatz3 Adjustable Balloon System (Spatz3; Spatz FGIA, Great Neck, NY; Fig. 1*E*) is another balloon currently under clinic investigation that is not currently FDA approved. The Spatz3 is an endoscopically placed, fluid-filled balloon that can be adjusted endoscopically for device intolerance or augmentation of weight loss via an attached inflation tube. An older design that occupied the stomach for 12 months achieved 45.7–48.8% EWL at 52 weeks, but was redesigned due to complications related to the device such as valve malfunction, catheter detachment, and balloon leak [29, 30]. The Spatz3 was studied in a retrospective, multicenter trial published in 2017 that yielded a mean TBWL of 16.3% at the time of balloon removal with 88.5% responding by achieving either a minimum of 10% TBWL or 25% EWL [17]. Of the 165 subjects in the study, 12.7% had their balloon removed prior to 4 months and 70.3% completed at least 8 months of therapy. The response rate differed by BMI, with 91.2% achieving this in those with BMI < 40 kg/m^2 compared to 69.0% in those with BMI > 40 kg/m^2. It is felt that the ability to adjust the

Spatz3 contributed to the high responder rate due to more subjects being able to complete treatment; up adjustments netted an additional mean weight loss of 5.7 kg and down adjustments allowed 80% of those not tolerating the Spatz3 to continue IGB therapy. Five subjects had gastric ulcers and there was one gastric perforation who was non-compliant with ulcer prophylaxis pharmacotherapy.

Current state of IGBs

A systematic review and meta-analysis of 10 studies was performed in 2018 evaluating the various side effects including nausea and vomiting of IGBs, including the Elipse, Obalon, Orbera, and ReShape in their analysis [31]. The study revealed that in comparing the fluid-filled IGBs with the gas-filled IGBs, the latter had lower meta-analytic rates of nausea (55.10 vs. 72.99%) and vomiting (16.2 vs. 76.95%). Furthermore, amongst all the IGBs, the Orbera had the highest meta-analytic rate of nausea (81.97%) and ReShape the highest meta-analytic rate of vomiting (86.42%). It is important to note, however, that the highest rates of nausea and vomiting were reported in FDA-conducted randomized controlled trials (RCTs) which may have impacted these results. Since 2017, the FDA has issued three letters alerting health care providers of additional potential risks with fluid-filled IGBs, specifically balloon over-inflation, acute pancreatitis, and death [32–34]. The most recent letter from the FDA from June 2018 reports a total of 12 deaths that have occurred globally in patients who have liquid-filled IGBs in place, seven of which occurred in the USA. While some of these deaths were associated with a gastric perforation, the FDA has not definitely attributed the deaths to the balloons or their insertion procedure as the underlying causes of death are not entirely clear. Both Apollo Endosurgery and ReShape Medical have since updated their product labeling to address these risks. Of note, in the previously aforementioned post-regulatory approval study of the Orbera balloon that took place across multiple centers with 321 subjects, there were no incidences of balloon hyperinflation, gastric perforation, esophageal perforation, pancreatitis, or death [10]. Additionally, a meta-analysis on the Orbera published by American Society for Gastrointestinal Endoscopy Bariatric Taskforce in 2015 consisting of 68 studies revealed a total of four deaths, either related to gastric perforation or an aspiration event, with a 0.08% incidence rate [20].

While there have been no studies published to date directly comparing the safety and efficacy of the various IGBs, the gas-filled balloons may be better tolerated compared with the fluid-filled balloons and have not been associated with pancreatitis. There have been three spontaneous gastric perforations with the Obalon balloon system that were all managed surgically [35]. These were all related to non-compliance with the daily PPI recommendation, and patients were discovered to have gastric ulcerations all near the incisura.

The Spatz3 has demonstrated the highest amount of weight loss achieved, though it also remained in the stomach the longest and nearly 51% of subjects had their balloon adjusted endoscopically, which will incur increased cost [17]. Given the IGBs are generally not covered by most insurances in the US at this time, the future of procedureless IGBs such as the Elipse or those requiring fewer procedures such as the Obalon is intriguing given their likely lower associated

costs. Intragastric balloons remain vital to the armament of EBTs given their overall high safety profile. Given multiple studies have demonstrated that a portion of weight that is lost during IGB therapy is regained following balloon removal; it is important to also recommend concomitant lifestyle changes and consider combination therapy with pharmacotherapy if there exists no contraindication to help maximize patient success rates with achieving and maintaining weight loss.

Tissue apposition with endoscopic suturing

Two endoscopic procedures can be performed to remodel native gastric anatomy to help achieve weight loss, and a third procedure can be performed to help augment weight loss in those who have regained weight after gastric bypass surgery. These procedures use one of several devices that have FDA 510k approval for tissue apposition, though the procedures themselves are not FDA approved.

Endoscopic sleeve gastroplasty

Endoscopic sleeve gastroplasty (ESG; Fig. 1*F*) is performed using the OverStitch endoscopic suturing system (OverStitch; Apollo Endosurgery, Austin, TX) which is affixed to the end of a double-channel endoscope. The ESG reduces gastric volume, impairs gastric emptying of solids, and possibly alters gut hormones through the creation of a gastric sleeve, made via endoluminally placed, full-thickness sutures through the gastric wall from the fundus to the prepyloric antrum [36–38]. The efficacy of ESG was studied in a prospective, single-center study including 91 subjects with BMI > 30 kg/m^2 who had failed noninvasive weight-loss measures as well as subjects with BMI > 40 kg/m^2 who were not surgical candidates or refused surgery [39]. The procedure success rate was 100% with mean procedure time of 98.3 ± 39.3 min, and after the first 11 ESGs, all subjects were discharged home on the same day. Subjects achieved a mean TBWL of 14.4% at 6 months (n = 73), 17.6% at 12 months (n = 53), and 20.9% TBWL at 24 months (n = 8). At 12-month follow-up, 77% of subjects achieved clinical success defined as TBWL > 15%. There was one SAE (1.1%), which was a peri-gastric leak managed non-operatively via antibiotics and placement of a percutaneous drain. Otherwise, nausea (38.4%) and mild to moderate abdominal pain (27.4%) were the most common AEs lasting less than 48 h following the procedure. In a larger, retrospective multicenter study of 248 consecutive subjects undergoing ESG at three centers, subjects achieved a mean of 15.17% TBWL at 6 months (n = 235) and 18.6% at 24 months (n = 35) [40•]. At 24 months, 84% and 56% of subjects achieved ≥ 10% and 15% TBWL, respectively, in per protocol analyses. In ITT analyses, 53% and 35% of subjects achieved ≥ 10% and 15% TBWL, respectively. It was noted that the odds to achieve ≥ 10% TBWL at 24 months was 0.18 if a subject did not achieve 10% TBWL at 6 months. Mild AEs such as nausea, vomiting, and abdominal pain not requiring medical attention were not recorded and the SAE rate was 2%. There were two peri-gastric fluid collections, one gastric hemorrhage, one pulmonary embolism, and one pneumoperitoneum and pneumothorax requiring chest tube placement; all of these subjects were managed non-

operatively. Another retrospective, multicenter trial of 112 subjects demonstrated similar results with mean TBWL at 6 months of 14.9 ± 6.1% and 81% achieving TBWL ≥ 10% at 6 months with an SAE rate of 2.7% [41]. The largest study to date is a prospective, single-center study from Saudi Arabia with 1000 subjects who underwent ESG [42•]. The mean procedure time was 61 ± 16 min. The mean TBWL attained at 6 months, 12 months, and 18 months was 13.7% ± 6.8% ($n = 369$), 15.0% ± 7.7% ($n = 291$), and 14.8% ± 8.5% ($n = 54$), respectively. Following the procedure, 92.4% of subjects reported nausea or abdominal pain that was treated with pharmacotherapy. There were 215 subjects who visited the emergency department (ED) following the procedure and 24 were admitted, though it is important to note that there was a low-threshold protocol for having patients visit the ED. Due to severe abdominal pain, three subjects had their ESG reversed during the first week after ESG. Seven subjects (0.7%) had post-procedural bleeding, two of whom received blood products. Four subjects developed peri-gastric fluid collections with pleural effusion, which were treated non-operatively with antibiotics and/or percutaneous drainage. Five subjects also developed a fever following ESG which was managed conservatively. Five subjects underwent redo ESG due to weight regain at a mean of 166 days with a mean nadir of 8.4% ± 2.8% TBWL. An additional eight subjects were surgically converted to a sleeve gastrectomy due to TBWL < 5% after 6 months of having their ESG.

Primary obesity surgery endoluminal

Primary obesity surgery endoluminal (POSE; Fig. 1G) is an endoscopic procedure that modifies the gastric anatomy utilizing the Incisionless Operating Platform (IOP; USGI Medical, San Clemente, CA), which consists of a flexible tube, control handle for maneuverability, an endoscope, four working channels, and specialized instruments for grasping tissue and placing anchors [43]. The IOP plicates stomach tissue in the fundus and distal body using suture and the specialized tissue anchors. It has been suggested that mechanisms for weight loss include changes in neuro-hormonal signaling and gastric accommodation [44]. The first published study on POSE from 2013, performed in subjects with BMI 30.0–39.9 kg/m^2 and those with BMI > 40 refusing surgery, yielded 15.5% TBWL at 6 months [45]. The safety and efficacy of the POSE procedure was studied in the ESSENTIAL Study, a multicenter, randomized sham-controlled trial in subjects with BMI 35–39.99 kg/m^2 and BMI 30–34.99 kg/m^2 with at least one obesity-related comorbidity [46••]. There were 34 subjects included in an unblinded lead-in cohort for investigator training but otherwise followed study protocol, after which 332 subjects were randomized in a 2:1 ratio between active or sham procedure with both arms receiving low-intensity lifestyle interventions. Both subjects and evaluators were blinded to treatment assignment. The procedure was completed in 99.5% of subjects with a mean procedure time of 39.7 ± 12.9 min. The mean TBWL achieved at 12 months was a mean of 4.95 ± 7.04% and 1.38 ± 5.58% ($P < 0.0001$) in the active and sham groups, respectively. The responder rate (TBWL ≥ 5%) at 12 months was 41.55% and 22.1% ($P < 0.0001$) in the active and sham groups, respectively, with responders achieving mean TBWL 11.5%. The co-primary endpoints did not meet the super superiority objectives, though differences between active and sham groups were statistically significant. Blinding may have impacted this study as

the lead-in group achieved mean TBWL 7.0 ± 7.4%, 40% more weight loss than the non-lead-in active group. It is also felt that weight loss was less than expected due to the possibility of subjects in the sham control group to enroll in a crossover study if they had not met weight loss goals. The most common AEs were pain (45.2%), nausea (21.3%), and vomiting (19.5%), and the SAE rate was 5.0%. Two of the SAEs were due to post-procedure symptoms, one was an extra-gastric bleed requiring underwent laparoscopy without intervention on a bleeding source, and one was a hepatic abscess requiring drainage and antibiotics. The MILEPOST trial, a European multicenter randomized controlled trial of POSE, saw subjects achieve 13.0 ± 1.4% (standard error) TBWL and 5.3 ± 2.5% (standard error) TBWL in the treatment and control arms, respectively, at 12 months [47]. The weight loss demonstrated in the MILEPOST trial is more consistent with what has been demonstrated previously in observational data from Lopez-Nava et al. [48].

Aspiration therapy

The AspireAssist System (AspireAssist; Aspire Bariatrics, King of Prussia, PA; Fig. 1*H*) is an EBT that was FDA approved in 2016 for subjects with BMI 35–55 kg/m^2 that removes approximately 30% of an ingested meal through a modified percutaneous gastrostomy tube (PEG) called an A-tube [49]. Similar to PEG tube placement, the A-tube is placed endoscopically through the abdominal wall using the standard pull technique. One to two weeks following A-tube placement when the tract is partially healed, the external portion of the A-tube is trimmed so it is nearly flush to the skin surface and the skin port is connected to the end of the A-tube to initiate aspiration. The A-tube connector contains a mechanical counter device that requires the patient to have the device reset by their physician to continue aspirating after approximately 1 month, thus ensuring office follow-up. The US pilot study in 2013 by Sullivan et al. first demonstrated its safety and efficacy, with subjects undergoing aspiration therapy achieving 18.6 ± 2.3% TBWL at 52 weeks vs. 5.9 ± 5.0% TBWL in the lifestyle therapy alone group with no SAEs. The 2017 US pivotal trial (PATHWAY), the largest study to date, was a 1-year US multicenter, randomized, controlled trial compared outcomes between subjects who received the AspireAssist plus lifestyle counseling ($n = 111$, mean BMI 42.2 ± 5.1 kg/m^2) vs. lifestyle counseling alone ($n = 60$, mean BMI 40.9 ± 5.1 kg/m^2) [1••]. The A-tube was successfully placed in 97% of attempts with a mean procedure time of 16 ± 7 min. At 52 weeks, in the treatment, the subjects in the aspiration therapy group lost more weight than in the lifestyle counseling only group in both the modified intention-to-treat analysis (12.1 ± 9.6% vs. 3.5 ± 6.0% TBWL, respectively) and in the completer analysis (14.2 ± 9.8% vs. 4.9 ± 7.0% TBWL respectively). There were five SAEs (3.6%) in four subjects: severe abdominal pain requiring hospitalization, mild, perioperative peritonitis treated with intravenous antibiotics and 2-day hospital stay, a gastric ulceration 53 weeks after A-tube placement resulting in A-tube removal, and product malfunction requiring A-tube exchange. The most common adverse events that occurred include peristomal granulation tissue (40.5%), postoperative abdominal pain (37.8%), nausea and vomiting (17.1%),

peristomal irritation (17.1%), intermittent abdominal discomfort (16.2%), and possible or definite peristomal bacterial infection (13.5%). The A-tube was removed before the 52-week mark in 26.1%. A 2018 multicenter post-market European registry study with 201 enrolled subjects evaluated aspiration therapy with up to 4-year follow-up [50]. At 1 year, mean TBWL was 18.2 ± 9.4% in the 155 subjects that completed 1 year of treatment. Mean TBWL achieved at 2, 3, and 4 years were 19.8 ± 11.3% ($n = 82$), 21.3 ± 9.6% ($n = 24$), and 19.2 ± 13.1% ($n = 12$), respectively. The only SAEs that occurred were buried bumpers ($n = 7$) and peritonitis ($n = 1$) requiring 2 days of intravenous antibiotics. These data demonstrate not only the safety and efficacy of aspiration therapy but also the durability.

While aspiration therapy results in decreased absorption of calories, this is not believed to be the only mechanism of weight loss. Using a weight-loss predictor calculator and bomb calorimetry of gastric aspiration as part of the US pilot trial, aspiration of 30% of ingested calories only accounts for 80% of the TBWL achieved by subjects if they are perfectly compliant and aspirate after all meals [51]. However, subjects frequently aspirated beyond the recommended time frame following a meal and less than three times per day in the pilot study, and subjects in the PATHWAY study aspirated between 2.2 and 2.5 times per day, suggesting that there are additional mechanisms contributing to at least 20% of weight loss achieved [1••]. This may include changes in eating behavior resulting in decrease caloric consumption, as patients need to chew significantly longer and increase water consumption to ensure successful aspiration. Despite aspiration of a portion of caloric intake, subjects do not experience increased hunger and there has been no evidence of subjects developing eating disorders, adverse eating behaviors such as overeating, or overusing the device [1••, 51].

Conclusion

Obesity is a growing pandemic associated with significant morbidity and mortality. More than two-thirds of adults in the USA are overweight and more than one-third of adults in the USA have obesity [52]. These rates are projected to rise; a trend that is being seen in both developed and developing countries [53]. The economic impact of obesity is enormous: an estimated $147–200 billion, or 21% of US health care expenditures, are spent annually on medical problems attributable to obesity [54]. While bariatric surgery remains the most effective and durable treatment option, it is estimated that less than 1% of patients with morbid obesity who qualify for bariatric surgery will undergo this intervention [55]. This may be due to high surgical costs, patient fear and preference, access to care, or morbidity and mortality associated with surgical interventions deeming patients, not surgical candidates.

Various EBTs that have been developed, including those involving IGBs, endoscopic suturing, and aspiration therapy have been FDA approved for marketing and use in the USA. They have been demonstrated to be safe and effective in numerous trials, though further research is needed to demonstrate

long-term durability and the effect on comorbidities over time. While EBTs have not yet been demonstrated to be as effective as surgical approaches, they provide patients and healthcare providers alternatives that appear safer with likely lower associated cost to help bridge the gap for the many patients who do not or will not undergo bariatric surgery.

Compliance with Ethical Standards

Conflict of Interest

Steven Edmundowicz serves on the medical advisory board for Olympus, is a paid consultant for Elsevier, Medtronic, and Allurion, and receives research support from Medtronic, Spironetics, and Elira. Joshua Turkeltaub declares no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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This is the first, randomized, controlled trial evaluating aspiration therapy.

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