Endoscopic bariatric therapies for obesity: a review

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Summary

- Obesity is reaching pandemic proportions globally, with overweight or obesity affecting at least two-thirds of Australian adults.
- Bariatric surgery is an effective weight loss strategy but is constrained by high resource requirements and low patient acceptance.
- Multiple endoscopic bariatric therapies have matured, with well established and favourable safety and efficacy profiles in multiple randomised controlled trials (RCTs), and are best used within a multidisciplinary setting as an adjuvant to lifestyle intervention.
- Three types of intragastric balloon are currently in use in Australia offering average total weight loss ranging from 10% to 18%, with others available internationally.
- Endoscopic sleeve gastroplasty produces average total weight loss of 15–20% with low rates of severe complications, with RCT data anticipated in December 2021.
- Bariatric and metabolic endoscopy is rapidly evolving, with many novel, promising therapies currently under investigation.

Overweight and obesity represent a slow moving global pandemic that has been growing in magnitude and severity over at least the past four decades. According to a World Health Organization report published in 2014, 600 million adults worldwide have obesity, and its prevalence has doubled since 1980.[1] Contrary to popular belief, this is no longer an affliction of Western cultures, indeed some of the highest incidences of overweight and obesity in the world are found in low income countries in Africa and South East Asia.[2] In the Australian setting, the prevalence of obesity has been rapidly rising across age groups and in 2014 almost two-thirds of Australians were found to be overweight or obese.[3] Furthermore, those same data suggest the problem continues to accelerate, with one in four children afflicted and rates of obesity among adolescents being twice that of the prevalence in the 1970s.[3] Clearly, the ramifications of this growing problem are significant, not only on health care resources and social safety nets but also in terms of the potential economic impacts relating to the increased morbidity, disability and mortality associated with overweight and obesity.[1] The management of obesity has conventionally included lifestyle modification, pharmacotherapy and bariatric surgery.

Lifestyle intervention comprises exercise, diet therapy and behaviour modification for both weight loss and weight maintenance. Various studies have proven that a comprehensive program of high intensity lifestyle therapy may induce loss of up to 10% of the initial weight in the first 4–6 months, but with high rates of recidivism.[4,5] Less weight loss is seen with moderate intensity lifestyle therapy.[6]

Long term weight control is facilitated by continuous patient–therapist contact, whether provided in person or by telephone or email.[7]

Pharmacological agents have been used as adjuncts to lifestyle therapy since the early 1990s. In general terms, the most effective pharmacotherapeutic agents in trial settings will achieve an average total weight loss of 9–10%, but weight recidivism is seen universally on drug withdrawal.[8]

Modern guidelines for the management of morbid obesity now recognise bariatric surgery as a highly effective therapy in weight loss and improvement in obesity-related comorbidities. This surgery is included in many guidelines, with recent revisions now recommending conventional bariatric surgery as the therapy of choice in patients failing lifestyle intervention with a body mass index over 35 kg/m^2 or of at least 30 kg/m^2 where an obesity-related comorbidity is present.[9-11] At present, the two most commonly performed procedures in Australia are laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB), with both demonstrating an excess weight loss of over 50% at one-year follow-up.[12,13] Large prospective studies have reported long term effectiveness and improvements in mortality, but emerging real-world data suggest that recidivism requiring revisional bariatric surgery is far higher than initially described, approaching 50% in some reports by the fifth postoperative year.[9,12] Moreover, both laparoscopic sleeve gastrectomy and RYGB are marked by high rates of long term micronutrient deficiency (more pronounced with RYGB) and require lifelong monitoring and replacement.[13] Studies also reveal generally low patient acceptance, with typically less than 2% of eligible patients electing to proceed with bariatric surgery annually.[14,15] These considerable limitations leave a large proportion of patients with obesity untreated or undertreated.

Over the past 10 years, many endoscopic bariatric devices and procedures have become available overseas and within Australia. For this narrative review, we searched PubMed for original and review articles from 2000 to 2020 as well as specialist society guidelines to formulate a contemporary overview of endoscopic bariatric therapy as applied to obesity treatment. We focus on procedures and devices that are or were available in Australia, bearing in mind that numerous new devices are available overseas or in development, which may have the potential to create a substantial impact on the obesity epidemic in the near future.

Endoscopic bariatric therapy

At large, endoscopic-based therapies represent minimally invasive techniques to alter gastrointestinal physiology, often in a reversible fashion, to modulate appetite and satiety, leading to caloric restriction and weight loss.[16,17] The primary drivers behind the development of these therapies are to allow lower cost, lower risk interventions that permit scalability to more fully meet the requirements of the obesity epidemic. They are associated with greater weight loss than either lifestyle intervention or pharmacotherapy alone but with a lower risk profile than bariatric surgery. Moreover, anecdotally, endoscopic

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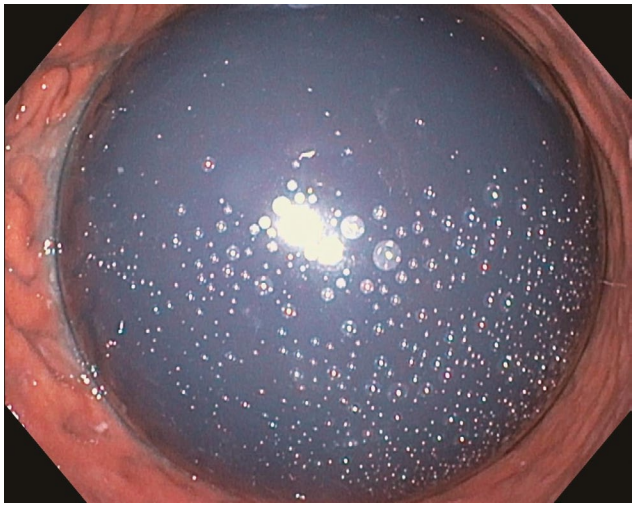
1 Spatz3 (Spatz Medical) intragastric balloon (in vivo)



bariatric therapies are commonly more acceptable to patients, presumably related to their lesser invasive and often reversible nature, lower risk profile and shorter recovery times. In 2011, the American Society for Gastrointestinal Endoscopy, in collaboration with the American Society for Metabolic and Bariatric Surgery set prospective guidelines establishing the requisite characteristics of endoscopic bariatric therapies to be assessed as clinically useful therapies.[18] Excess weight loss of 25% and a rate of major complications of less than 5% were set as efficacy and safety thresholds.[18] In general terms, endoscopic bariatric therapies offer average total weight loss of between 10% and 20% and results are generally augmented by providing multidisciplinary lifestyle intervention.[19] As such, endoscopic bariatric therapies should be considered adjuncts to lifestyle intervention rather than as a replacement for them.

Intragastric balloons

The most well established endoscopic bariatric therapy is the intragastric balloon — a non-surgical approach to weight loss. It is a space-occupying device that is placed in the stomach, leading to an early feeling of satiety and delaying gastric emptying.[20-22] The earliest gastric balloon was developed in 1985;[21] nowadays, there are several types of intragastric balloons available worldwide, differing in materials used, techniques of placement and removal, and the number of balloons concurrently placed. At present, the best known are Orbera (Apollo Endosurgery), ReShape (ReShape Medical), Obalon (Obalon Therapeutics), Ellipse (Allurion Technologies) and Spatz3 (Spatz Medical); however, Spatz3, Orbera and Ellipse are the only devices currently approved for use in Australia.

In the 1990s, the first of the large-volume intragastric balloons, known as the BioEnterics Gastric Balloon (Inamed) and currently known as Orbera, was developed and registered for use in Europe, and was first registered for use in Australia in 2004.[21] These silicon balloons (Box 1) are inserted endoscopically and filled with saline and methylene blue solution, which permits the identification of balloon rupture or leak by way of urinary discolouration (blue or green urine). These devices are inflated to a typical volume of 600–650 mL (range, 500–700 mL) and remain within the stomach for a period of up to 6 months. The average 12-month total weight loss is about 12–15% in most studies, and a randomised controlled trial (RCT) demonstrated significantly better weight loss against a sham at 12 and 6 months after device removal.[23,24] Owing to its large insertion volume, intolerance is an issue with Orbera, with up to 10% of balloons being removed early owing to severe gastrointestinal side effects, including nausea, vomiting and abdominal cramping and pain, although this has been somewhat ameliorated in recent years with improved antiemetics.[25,26]

The Ellipse intragastric balloon is a novel fixed-volume, fluid-filled device with a comparable efficacy and safety profile to the Orbera device, with the notable difference that this device is ingested and inflated without the need for endoscopy.[27,28] The Ellipse device predictably deflates after 16 weeks via a valve and passes spontaneously through the gastrointestinal tract.

Spatz3 (Box 1), on the other hand, may be implanted for up to 12 months. Furthermore, its volume may be adjusted as needed to increase efficacy or improve tolerability.[22] This permits a lower inflation volume and as such, the Spatz3 has a lower rate of intolerance and results in an average total weight loss in real-world studies of 17–18%.[20,22] However, this device is associated with a higher rate of gastric ulceration compared with Orbera (2–5% v < 1% respectively),[29] although these ulcers are typically superficial and of little clinical consequence.[20,30] The RCT pivotal study for this device has recently concluded and is being considered for registration in the United States by the Food and Drug Administration (FDA).

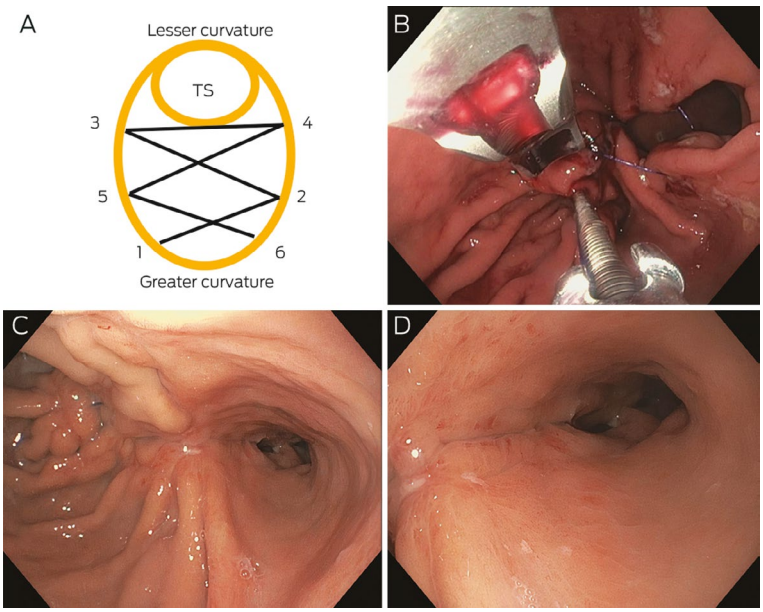
A meta-analysis of RCTs showed a significant improvement in most metabolic parameters (fasting glucose, glycated haemoglobin [HbA_{1c}] level, blood pressure, waist circumference) following intragastric balloon compared with controls.[31] Fluid-filled intragastric balloons (Orbera and Spatz3) are marked by an adaptation period of 3–5 days, during which time patients may experience abdominal cramping, nausea, vomiting, reflux or regurgitation, and bloating. Regimented pharmacotherapy is generally required to minimise symptoms and improve tolerability.[30,32] After the adaptation period, symptoms should abate completely, and recurrence of these symptoms typically indicate dietary indiscretions such as rapid or overconsumption or consumption of foods incompatible with the device, including red meat and raw vegetables. Device-related complications occur infrequently and include spontaneous hyperinflation, gastric outlet obstruction, gastric ulceration and perforation.[33,34] Although the risk of perforation is low, proton pump inhibitors for the duration of the intragastric balloon therapy and *Helicobacter pylori* eradication are important for ulcer prevention following intragastric balloon deployment.[29,35] To further reduce the risk of gastric ulceration, non-steroidal anti-inflammatory drugs should be avoided and alcohol consumption minimised.[29] The rates of other major complications associated with Orbera and Spatz3 are low (Box 2).

2 Adverse events associated with Orbera (Apollo Endosurgery) and Spatz3 (Spatz Medical) intragastric balloons*

Complications	Orbera	Spatz3
Hyperinflation	1.0%	0.9%
Spontaneous deflation	0.6%	1.1%
Migration	0.1%	0.2%
Ulcer	1.0%	5.0%
Bleeding	0.1%	0.4%
Perforations	0.04%	0.1%

* Results derived from Neto et al.[29] ◆

3 (A) Suture pattern of the endoscopic sleeve gastroplasty (ESG) procedure with the tubular stomach (TS); (B) ESG procedure with the OverStitch (Apollo Endosurgery) suturing device; (C) 3 weeks after ESG; (D) 6 weeks after ESG



Endoscopic sleeve gastroplasty

The endoscopic sleeve gastroplasty is a novel, transoral procedure to reduce gastric capacity and delay gastric emptying by way of full thickness suturing along the greater curvature of the stomach (Box 3, A).[36,37] This procedure has been facilitated by the development of a cap-based endoscopic suturing device: the OverStitch (Apollo Endosurgery) (Box 3, B). The endoscopic sleeve gastroplasty is performed under general anaesthesia and is frequently a day procedure, with full patient recovery after 3 days following intervention (Box 3, C–D). The procedure was initially published in 2013 and has been reproduced and modified several times by key centres around the world.[37-42] Technical aspects of the procedure as well as aftercare continue to evolve to optimise safety and efficacy. Data from multiple centres indicate a weight loss of about 15% at 6 months and 20% at 18 months.[23,37,38,43] Moreover, early data suggest that this procedure results in significant improvements in markers of metabolic syndrome (HbA_{1c} level, systolic blood pressure, waist circumference, alanine aminotransferase, and serum triglycerides).[44] Major complications are experienced by about 1% of patients, which include perigastric inflammatory collections, major bleeding and deep vein thrombosis.[23] Most complications can be managed conservatively and rarely require surgical intervention. According to the device manufacturer, it is estimated that at least 12 000–15 000 procedures have been performed worldwide, and to date, there has been a single complication resulting in death due to deep vein thrombosis with pulmonary embolism.[45] An RCT of endoscopic sleeve gastroplasty (the MERIT Trial; ClinicalTrials.gov identifier NCT03406975) has recently concluded and the results are anticipated in December 2021. Further long term and controlled studies assessing technical improvements, patient selection, and long term metabolic effects are needed. Alternative devices that permit endoscopic suturing and bariatric gastroplasty are emerging, including the Incisionless Operating Platform (USGI Medical) used to perform the primary obesity surgery endoluminal (POSE) procedure[46] and the Endomina (Endo Tools Therapeutics) device.[47]

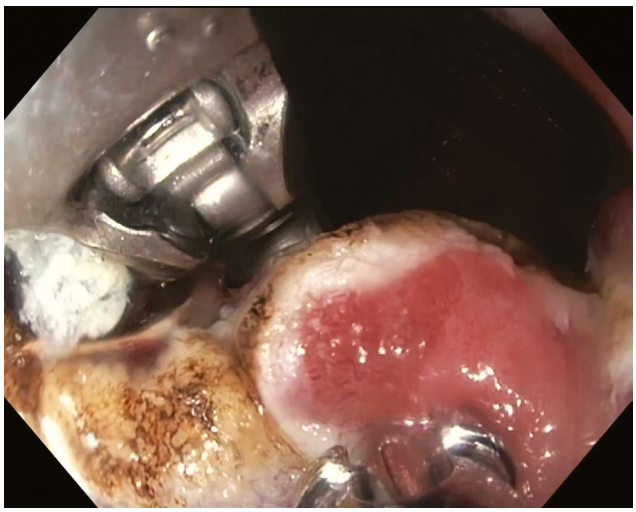
Revision intervention for weight regain after bariatric surgery

As previously described, weight regain is not uncommon following RYGB.[9,12] This is often associated with a dilated gastrojejunal anastomosis. Surgical correction is technically challenging, typically requires an even longer procedure and hospital stay than RYGB, and is associated with significant morbidity and limited efficacy. Several endoscopic procedures have been developed to tackle this problem, including endoscopic transoral outlet reduction (Box 4) and restorative obesity surgery endoluminal (ROSE). The former is accomplished using the OverStitch device to resize the gastrojejunal anastomosis following treatment with argon plasma coagulation, whereas the latter uses the Incisionless Operating Platform to place plications at the gastrojejunal anastomosis and distal gastric pouch following argon plasma coagulation. A prospective multicentre study of 116 patients achieved technical success in 97% of patients and an average weight loss of 18% after 6 months as well as no significant adverse events.[48] A multicentre international meta-analysis reported an average weight loss of 8 kg after 18 months following transoral outlet reduction.[49]

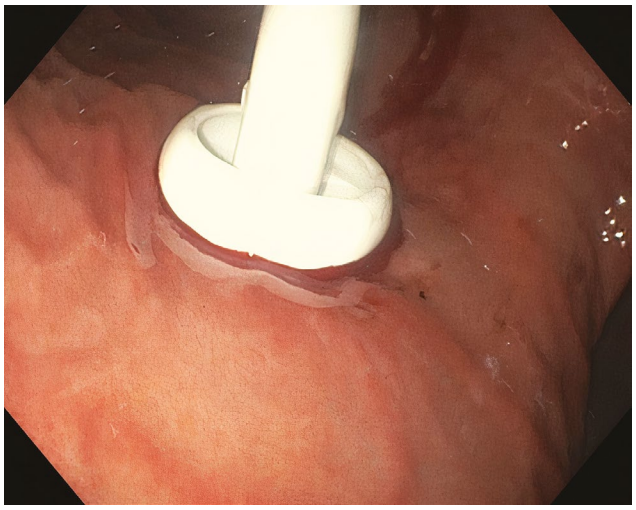
Aspire Assist

The Aspire Assist device (Aspire Bariatrics) allows for controlled postprandial aspiration of gastric contents, amounting to up to 30% of ingested calories, three times per day to reduce caloric intake and, thus, achieve weight loss (Box 5). This technique represents a modification of the application of percutaneous endoscopic gastrostomy tubes, which have a well established periprocedural safety profile. The device is inserted endoscopically and may be used for several years. On conclusion of the therapy, the device can be removed, making the intervention completely reversible.[47] Studies reveal a 12-month

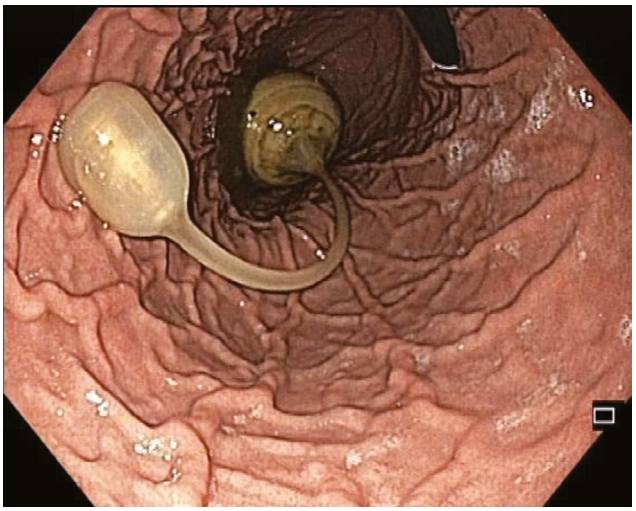
4 Transoral outlet reduction with the OverStitch (Apollo Endosurgery) device



5 Aspire Assist device (Aspire Bariatrics)



7 TransPyloric Shuttle (BAROnova) in vivo



weight loss of about 14–20% with the Aspire Assist device, with additional weight loss observed for longer periods of regular use.[36,47,50] Interestingly, observed weight loss is in excess of aspirated calories, indicating a significant behavioural effect.[51] The application of this form of therapy is likely to be reserved for patients with clinically severe morbid obesity (body mass index > 35 kg/m^2) and/or for those with excessive anaesthetic risk. The Aspire Assist device is available in Australia.

Endoscopic bariatric therapies under assessment

EndoBarrier: a duodenal-jejunal bypass liner

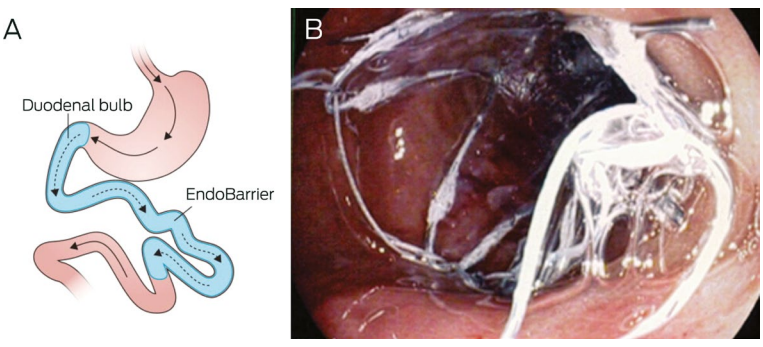
The duodenal-jejunal bypass liner, or EndoBarrier (GI Dynamics), is a 60 cm Teflon-coated plastic sleeve designed to be anchored within the duodenal bulb and prevents both mucosal contact with chyme as well as admixture of chyme with biliopancreatic juices to putatively induce malabsorption[52-54] (Box 6, A). The use of the EndoBarrier device (Box 6, B) leads to a modest weight loss of about 12% but causes disproportionate and significant improvements in glycaemic control and HbA_{1c} level.[54,55] However, the anchoring mechanism included a number of short metal barbs that contributed to infrequent complications, notably gastrointestinal bleeding, perforation and, in particular, hepatic abscess formation (2%).[17,52] This device was withdrawn from the Australian market in 2016. However, in September 2019, a new randomised, multicentre, pivotal study evaluating the device for efficacy and safety in type 2 diabetes and obesity started in the United States.[56] In particular, the risk of hepatic abscess was thought to be related to high dose proton pump inhibitor-facilitated biofilms forming over the liner and gaining access to the portal circulation by way of the barb–mucosa interface. As a result, proton pump inhibitors are now given at standard dose and prophylactic antibiotics are administered at the time of implant and again at explant in order to reduce the risk of bacterial seeding during device manipulation. The EndoBarrier device is not yet available in Australia.

TransPyloric Shuttle

The TransPyloric Shuttle (BAROnova) is a novel silicon device that straddles the pylorus to induce delayed gastric emptying (Box 7). The first ENDObesity study of 20 patients with a mean body mass index of 36 kg/m^2 was conducted in Australia in 2014.[57] The follow-up, randomised, double-blinded clinical trial ENDObesity II compared the percentage of total body weight loss in patients treated with the TransPyloric Shuttle device versus a sham endoscopic procedure. The mean percentage of total body weight loss at 12 months for the TransPyloric Shuttle group was 9.5% compared with 2.8% in the control group ($P < 0.0001$). In addition, the TransPyloric Shuttle group showed a statistically significant reduction in insulin resistance, blood pressure, and lipids.[56] As a result, the device received FDA approval in April 2019 but has not entered the market yet. The TransPyloric Shuttle remains in the stomach for up to 12 months.

Numerous additional endoscopic therapies are under assessment. The incisionless anastomosis system (GI Windows) has recently begun phase 2 studies. With this approach, one of a pair of magnets is released in the proximal jejunum and another in the distal ileum. These devices self-assemble into an octagonal configuration and approximate to induce an entero-enteral anastomosis by compression and ischaemia — essentially, a bidirectional small bowel bypass — to

6 (A) EndoBarrier (GI Dynamics) duodenal-jejunal bypass liner (a 60 cm teflon-coated plastic sleeve, anchored within the duodenal bulb and inducing malabsorption); (B) EndoBarrier in vivo



8 Summary of the different techniques

	IGB[20,24,59]	ESG[43,60-62]	Aspire Assist*[47,50,63]	LSG/ RYGB[43,64,65]
BMI	≥ 27	≥ 30 (< 30†)	≥ 35	≥ 35–50 (> 30†)
Complication rates	2.50%	1–2%	1–3%	4–9%
TWL (at one year)	12–18%	15–20%	14–20%	23–28%

BMI = body mass index; ESG = endoscopic sleeve gastroplasty; IGB = intragastric balloon; LSG = laparoscopic sleeve gastrectomy; RYGB = Roux-en-Y gastric bypass; TWL = total weight loss. * Aspire Bariatrics. † Plus other obesity related health conditions. ◆

induce malabsorption and weight loss and have been shown to have impressive glycaemic effects in a phase 1 study.[56]

Mucosal ablation techniques of the small bowel (Revita DMR [duodenal mucosal resurfacing], Fractyl Health) and stomach (gastric mucosal devitalisation) also show early promise as metabolic and weight loss therapies respectively.[58] These techniques are in early stages of assessment.

Conclusions

The long-evolving field of bariatric endoscopy appears to have matured to a critical point in its development. These myriad of techniques (Box 8) appear safe and effective and greatly expand the therapeutic arsenal available to patients with excess weight, providing the next major breakthrough in the management of obesity. While it is unlikely that all the endoscopic bariatric therapies under assessment will mature to clinical application, it is likely that many will, especially when considering that less than 2% of qualified patients undergo bariatric surgery annually. This represents a potential paradigm shift to minimally invasive and potentially individualised therapy for weight loss, which only stands to improve patient access and resource utilisation in a manner akin to the revolution of endovascular stenting in the management of coronary artery disease. Future research must be directed to further establishing the optimal application of the therapies (eg, patient selection) and establishing long term data. Furthermore, the combination of endoscopic therapies in series or parallel and with and without adjunctive pharmacotherapy must be examined to optimise weight loss efficacy and durability.

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