

How to address weight regain after bariatric surgery in an individualized way

Ricardo V Cohen¹ · Tarissa BZ Petry¹

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Abstract

Bariatric surgery is the most effective obesity treatment. As a chronic and progressive disease, weight loss response to surgery will vary individually. Thus, insufficient weight loss or regain can happen after surgery, but they lack a standard definition. There are different mechanisms underlying weight regain and/or insufficient weight loss, such as genetics, maladaptive eating behaviors, and the inadequate choice of index operations, among others. Patients with weight regain or insufficient weight loss should be submitted to an individualized and comprehensive evaluation by a multidisciplinary team. This may help identify the causes and direct the appropriate treatment individually. Options for patients with insufficient weight loss and/or weight regain following bariatric surgery include repair of postoperative complications, conversion into another operation, endoscopic therapies with inconsistent outcomes, and dietary/behavioral counseling. Revision and conversion surgeries have higher complication rates than primary operations. Although there is no standard pharmacological regimen for that indication, the new agents seem efficient and safe to promote the loss of the regained weight and even be adjunctive to selected patients before they reach the plateau. This review aims to summarize the knowledge of the best approach for patients with weight regain/insufficient weight loss and suggests an algorithm to customize the approach and therapeutic options after bariatric surgery.

Keywords Bariatric surgery \cdot Revisional surgery \cdot Roux-en-Y gastric bypass \cdot Sleeve gastrectomy \cdot Weight regain \cdot Insufficient weight loss \cdot Antiobesity medication

Abbreviations

MBS	Metabolic/bariatric surgery
WL	Weight loss
IWL	Insufficient weight loss
TBWL	Total body weight loss
WR	Weight regain
BMI	Body mass index
GI	Gastrointestinal
GLP1RA	Glucagon-like receptor 1 analog
SG	Sleeve gastrectomy
BPD-DS	Biliopancreatic diversion with duodenal
	switch
SADI-S	Single anastomosis duodenal ileostomy and
	sleeve gastrectomy version
OAGB	One-anastomosis gastric bypass

Ricardo V Cohen ricardo.cohen@haoc.com.br

¹ Center for the Treatment of Obesity and Diabetes, Hospital Alemao Oswaldo Cruz, São Paulo, Brazil

RYGB	Roux-en -Y gastric bypass
AOM	Anti-obesity medication
FU	Follow-up

Obesity is a chronic and progressive disease. Currently, metabolic/bariatric surgery (MBS) is a safe and the most effective option to treat it [1]. However, as a disease with an underlying biological component, there may be non-responders to surgery. Moreover, on an individual level, weight loss (WL) is highly variable [2]. Improvements in weight-related comorbidities following MBS, such as type 2 diabetes mellitus, are related to the amount of weight loss achieved [3]. In all randomized controlled trials that compared MBS with medical treatment, those with more significant weight loss had better glucocentric outcomes [4].

Thus, weight regain (WR) or insufficient weight loss (IWL) may be an issue after surgery, and as it can be a complex issue, an individualized approach is important to address the root causes of the problem.

1 Challenges in definitions

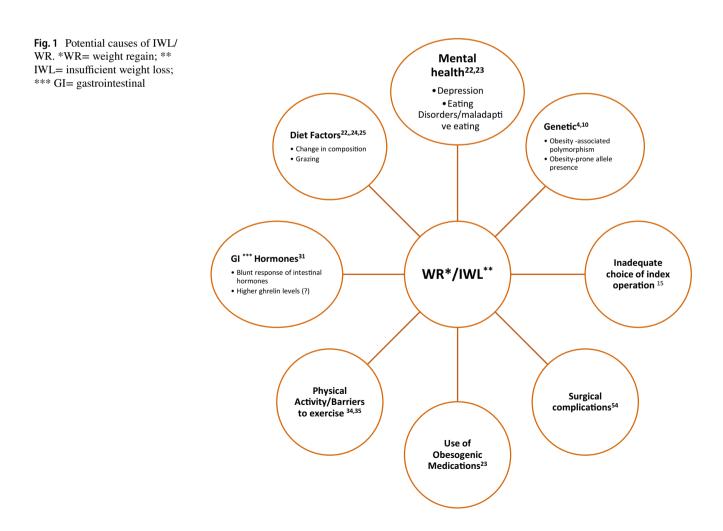
Successful weight loss after surgery is defined based on the amount and durability associated with controlling comorbidities. However, there is some confusion in the literature regarding the definition of insufficient weight loss and weight regain, as most reports do not differentiate those 2 conditions [5]. IWL has no universal definition. Using total body weight loss (TBWL) is superior to employing excess weight loss as it less influences preoperative body mass index (BMI) [6]. Thus, IWL may be defined as less than 20% of TBWL as it is usually linked to the recurrence of associated conditions [7]. WR may be defined as progressive weight gain after reaching the successful nadir weight loss (>20% TBWL). Some argue that weight regain should only be defined if there is a concomitant recurrence of comorbidities [8], [9]. The lack of standardization in the definitions means that data on the prevalence of IWL and WR is unknown. There is a need for standardizing the reporting of both insufficient weight loss and weight regain.

2 Mechanisms

WR and IWL can occur for various reasons, including diet, exercise, hormonal changes, medications, psychological factors, inadequate choice of operative technique, and surgical complications. Identifying the underlying causes can help to develop a tailored treatment plan. Figure 1 summarizes the potential causes for WR and IWL.

3 Management strategies

A customized approach to addressing WR/IWL after bariatric surgery requires input from a multidisciplinary team, including endocrinologists, bariatric surgeons, dietitians, mental health professionals, and other healthcare providers as needed. Before developing a management plan, it is important to identify the cause of WR/IWL. This can be done through a comprehensive medical evaluation that includes a review of the patient's diet, exercise habits, and other relevant factors contributing to weight regain. It may



also involve diagnostic tests to evaluate the patient's metabolic status and gastrointestinal anatomy.

(a) Identification of non-responders

Obesity, like all chronic diseases, has different individual biological responses. The high degree of variability in weight loss following bariatric surgery may be due to a genetic predisposition to resist weight loss. Different gene allele carriers predispose to individual responses to surgery [10]. Consequently, with the evolution of genetic markers linked to obesity and weight outcomes, clinicians can identify poor responders eligible for different therapeutic options, such as adjunct medical and surgical approaches. As with the new glucagon-like receptor 1 analog (GLP1RA), where early weight loss response with treatment predicts better outcomes [11], the same is valid with MBS. Manning et al. [2] showed that most patients who lose less than 1 lb (- 500g) a week during 3 to 6 months after MBS are unlikely to achieve a maximal TBWL of more than 20 %. Patients with WR may be identified as those who reached nadir weight loss of over 20% in the first 24 months after surgery. Although they are not classified as non-responders, patients with BMI over 50 kg/m² may predict IWL and/or WR [12, 13]. While robust information is still scarce, spotting predictive factors may lead the multidisciplinary team to adopt stricter diet and exercise programs and start pharmacological interventions shortly after surgery [14].

(b) Choice of the index operation

Guiding patients toward the most appropriate bariatric and metabolic procedure is crucial for improving outcomes [15]. Assessment of the value of each procedure is complex, requiring evaluation based on factors beyond weight loss alone, namely the metabolic effects, as these are most likely to contribute to improvements in long-term outcomes. Given the heterogeneity of the population affected by obesity and its varying impact on individual patients, we may never identify a 'gold standard,' a single operation that is best for all patients [16]. The number of operations recognized by the International Federation of Surgery of Obesity and Metabolic Disorders is slowly increasing. It includes sleeve gastrectomy (SG), adjustable gastric banding, biliopancreatic diversion with duodenal switch (BPD-DS) and its single anastomosis version (SADI-S), one-anastomosis gastric bypass (OAGB), and Rouxen -Y gastric bypass (RYGB) [17]. Although BPD-DS may have fewer patients with short to midterm WR or IWL, their nutritional complications are not worth the risk. SADI-S and OAGB are still underperformed in numbers worldwide compared with SG and RYGB.

SADI-S is relatively new, and so far, no long-term evidence shows better WL and metabolic outcomes with acceptable nutritional risks compared with RYGB or SG. The only randomized controlled trial comparing RYGB and OAGB did not show the superiority of the latter technique [18]. Thus, it is still not possible to appropriately balance the incidence of WR/IWL after OAGB and SADI-S.

The most performed MBS worldwide are SG and RYGB. As the definitions of WR and IWL are not standard, numbers vary. For example, in metanalysis of long-term studies [19] (over 7 years of follow-up) after SG, patients regained a mean of 27.8% (range 14–37%) of their lost weight. The Longitudinal Assessment of Bariatric Surgery (LABS) study [12] reported a 3.9% WR 3–7 years after RYGB. Although WR/IWL was not addressed, the Sleevepass study [20], a randomized controlled trial that compared SG with RYGB with 10 years of follow-up, showed that the RYGB had better WL than SG, an indirect way to measure WR after each procedure.

RYGB and SG are safe and efficacious operations. SG has higher numbers of WR/IWL when compared with RYGB, and it is often associated with gastroesophageal reflux leading to a significant number of revisional surgery. A customized proper patient selection for the procedure is mandatory to achieve the best possible long-term outcomes after MBS.

(c) **Dietary interventions**

Dietary interventions after MBS are relatively unexplored regarding promoting additional weight loss or preventing WR in the long term. There is no information on the effect of any dietary strategy to mitigate IWL. Available randomized controlled studies, although all short-term, reported improvements in WL after nutritional and lifestyle education programs or using *a* structured dietary intervention that used portion-controlled foods compared to the usual care [21, 22]

Studies related to dietary adherence suggested that poor observance of the dietary guidelines -represented by higher carbohydrate intake, alcohol intake, and lower dietary quality were key contributors to WR/IWL long-term after MBS [23]. Higher carbohydrate consumption appears to be linked to WR/ IWL. Although the source of carbohydrates was not clearly defined in all studies, some have demonstrated that increased consumption of liquid calories and sugar intake from non-nutritive sources were attributable to weight regain. Thus, increases in patients' non-nutritive, free- and added-sugar intake potentially explain some WR/IWL following MBS [24, 25]. So far, there is no consensus on the relation between postoperative weight regain and levels of alcohol intake [26]. There is an urgent need for solid scientific knowledge on the best dietary strategies to optimize WL, decrease the incidence of IWL, and avoid, stop, and help reverse WR.

(d) Behavioral interventions

Postoperative behavioral management may facilitate long-term weight control in the bariatric surgery population. A systematic review and metanalysis [27] reported that behavioral management positively affected weight loss following surgery. In 13 studies, patients receiving behavioral management had more weight loss than those receiving usual care or no treatment. A metanalysis of five randomized controlled trials suggests greater weight loss in patients with behavioral lifestyle interventions compared with control groups [27]. It seems that optimizing those interventions can decrease the number of IWL after MBS, but the small and heterogeneous samples of studies limit conclusions.

Grazing and binging were the most commonly identified eating behaviors associated with WR. Although maladaptive eating habits do not negatively affect one's weight outcomes at one year post-operation, people who continue binge have a higher risk of regaining weight by the second year following surgery [25]. Furthermore, Himes et al. [28] suggest that controlling maladaptive eating behaviors can encourage weight loss following WR. Therefore, targeted therapy toward maladaptive eating behaviors provided early in the patient's recovery process may help prevent weight regain and/or insufficient weight loss.

Behavioral interventions to help control WR are scarce as well. Bradley et al. [29] in a small pilot study, recruited 11 patients that regained 10% of their nadir weight and were submitted to *a novel* 10-week acceptance-based behavioral intervention to stop postoperative WR. They achieved a retention of 72%, and WR was stopped and even reversed significantly, improving eating-related and acceptance-related variables.

Literature confirms that loss of control on overeating or appearance of grazing after surgery is associated with less excess weight loss, greater WR, and decreased perceived quality of life. It is known that patients who engage in grazing behaviors 2 or fewer times per week after surgery have lesser weight loss and larger WR than those who have not had such a problem [29, 30].

Physical activity and outcomes of MBS are relatively unexplored. Several systematic reviews [31–34] show an association between physical inactivity and WR. However, it is observed that despite having similar moderate to vigorous physical activity habits when compared with the general population, people who have had bariatric surgery are less active in daily tasks, in both responders and non-responders to surgery [35]. Thus, no one could spot a direct causation link between the impact of physical activity on postoperative bariatric surgery outcomes. Little information is available on physical activity, and weight regain as most articles cite the association of low energy expenditure associated with weight regain [36, 37], most retrospective or with short follow-up.

As with dietary interventions, more data is needed to address the role of behavioral management and WL outcomes. Both approaches are mainly complementary to medical and even surgical interventions for patients with IWL or WR after MBS.

(e) **Pharmacotherapy**

The Endocrine Society's clinical practice guidelines on managing the post-bariatric surgery patient recommend that pharmacotherapy be included in the multidisciplinary treatment of WR [38]. However, most studies evaluating anti-obesity medication (AOM) have excluded participants with previous MBS.

Istfan et al. [39] present a retrospective study on using phentermine and topiramate, individually or combined, to mitigate WR after RYGB. Despite the lack of a unified protocol for the timing of using AOM, the three statistical models employed converged to show that phentermine and topiramate, used individually or in combination, can significantly reduce WR after RYGB.

In another multicenter retrospective study [40] in patients who previously underwent RYGB or SG, there were several high responders, with 30.3% of patients losing \geq 10% of their total weight. Topiramate was the only medication that demonstrated a statistically significant response for weight loss, with patients being twice as likely to lose at least 10% of their weight when placed on this medication. Interestingly, RYGB patients responded better than SG to adjuvant pharmacotherapy.

Schwartz et al. [41] retrospectively reviewed 65 patients who experienced postoperative WR or weight plateau and were treated with phentermine or phentermine-topiramate. Patients receiving phentermine weighed significantly less than those on phentermine-topiramate throughout this 90-day study.

The introduction of GLP1RA changed the landscape of treating obesity and even WR or IWL after surgery. The largest such series to date by Wharton et al. [42], although not specifying the timing of the drug's introduction (weight plateau or WR), showed that after 12 months on liraglutide 3-mg/d injections and lifestyle counseling, 75% of patients lost >5%, and 25% lost >10% of total body weight. The GRAVITAS trial [43] examined the effects of liraglutide 1.8 mg/d versus placebo in patients with persistent or recurrent type 2 diabetes at least 1 year after RYGB or SG. The primary endpoint was glycemic control, which was significantly better with liraglutide. However, the secondary weight loss outcome was also better in that group. At each of the four study visits over 26 weeks, participants taking liraglutide lost progressively more weight than placebo.

Another small RCT [44] addressed the effect of the early addition of liraglutide to SG prospectively compared with placebo on weight loss and other obesity-related comorbidities from 6 weeks until 6 months after surgery. All patients had a BMI >30 kg/m², with or without obesity-related comorbidities. The %TBWL at 6 months was 28.2 ± 5.7 and 23.2 ± 6.2 (p = 0.116) in the liraglutide and placebo groups, respectively. Liraglutide added early after SG significantly augments weight loss from SG in people with obesity, with few adverse events.

The use of semaglutide in IWL/WR has very little information in the literature. A retrospective study by Lautenbach et al. [45] used an arbitrary definition for IWL and WR. WR was defined as continuous WR after an initial successful weight loss (defined as EWL > 50%), and IWL was defined as achieving a nadir weight with EWL < 50% after surgery

Patients reached a mean weight loss of 10.3%, with 85% achieving a weight loss of \geq 5% after 6 months. GLP1-RA therapy was reported with semaglutide, 0.5 mg, weekly subcutaneous injection.

Analogous to the results of the semaglutide Phase III trial STEP-1 (the Semaglutide Treatment Effect in People with Obesity) [46], post-bariatric patients that showed more than a 2% reduction in body weight within only the first 4 weeks of treatment initiation with semaglutide (early responders), continued to lose weight throughout the 6-month follow-up period.

Jensen et al. [47] defined WR as any weight gain following the weight nadir at least 12 months after bariatric surgery. As it was a retrospective chart study, the indication to initiate GLP1RA therapy was at the treating physician's discretion, considering the overall weight status, cardiovascular risk profile, and patient preferences. The median percentage of total body weight loss following 6 months of GLP1RA therapy was 8.8%. More than three in four patients lost over 5% of their baseline weight, and more than one in three lost more than 10%. The median patient had lost 67.4% of the weight regained after the bariatric procedure. The authors did not report serious adverse events.

There is no data on the use of AOMs before the plateau. This aligns with the lack of standard definitions of IWL and the ideal timing to start adjuvant pharmacotherapy. Ideally, AOMs should be tailored to the patient's needs as an adjunct to dietary modifications and behavioral changes to optimize weight loss and help the resolution of obesity-associated comorbidities [48].

(f) Revisional surgery and endoscopic interventions

Revisional procedures are a growing subset of bariatric operations, representing around 7% to 15% of the total number [49]. The American Society for Metabolic and Bariatric Surgery Revision Task Force in 2014 [50] standardized the nomenclature for various types of revisional bariatric surgery. They were classified as "corrective" of index bariatric operations to achieve their original desired function. A "conversion" is exchanging one procedure to another type, and "reversal" is intended to restore normal or near-normal anatomy. Although rare, gastro-gastric fistulas may be a cause of IWL/WR, and its correction may improve weight loss [51]. Although safe, revisional operations carry a higher chance of complications than any primary MBS [52].

Potential indications for revisional MBS include IWL/WR and/or recurrence of weight-related comorbidities or complications related to the initial operation. Weight regain is the reported indication for more than half of revisional procedures [53].

If revisional surgery is indicated after a comprehensive multidisciplinary evaluation, upper gastrointestinal endoscopy and radiologic studies, including contrast studies and, eventually, a computed tomography, need to be performed. Besides that, a proper nutritional evaluation and micro and macronutrients supplementation may be needed. The most common MBS worldwide are the SG and RYGB. For that reason, we will cover the revisional alternatives for those procedures.

4 Revisional surgery and endoscopic options after SG and RYGB

WR or IWL are more common after SG when compared to RYGB and other operations [54]. Some evidence suggests that the development of gastroesophageal reflux disease (GERD) after SG may be associated with weight regain [55].

One possible explanation for this association is that GERD symptoms can lead to changes in eating habits, such as consuming smaller and more frequent meals or avoiding certain foods that trigger symptoms. These changes in eating habits may not be sustainable in the long term, leading to weight regain. Multiple surgical alternatives to revise a SG were proposed, such as resleeving and sleeve plication for weight regain and/or GERD. However, most have no solid long-term reported outcomes [56].

Although still without robust evidence regarding longterm outcomes, there is more data on converting SG into RYGB (Table 1). There is insufficient data on converting SG to single anastomosis duodenal ileostomy (SADI-S) and one-anastomosis gastric bypass (OAGB) [57, 58].

Revisional surgery after SG						
First Author	Year	Additional weight loss after revision	Total no. of patients	Follow-up (months)		
Conversion of SG	to RYGB					
Van Rutte [63]	2012	BMI $43 \rightarrow 39$	32	12		
Gautier [64]	2013	BMI $47 \rightarrow 36$	18	16		
Carmeli [65]	2015	BMI $40 \rightarrow 30$	10	16		
Pok [66]	2016	BMI $35 \rightarrow 25$	18	12		
Poghosyan [67]	2016	BMI $45 \rightarrow 41$	34	36		
Iannelli [68]	2016	BMI $39 \rightarrow 31$ EWL 49%	40	19		
Casillas [69]	2016	EWL 24%	48	24		
Conversion of SG	to DS					
Dapri [70]	2011	BMI 47 \rightarrow 35 EWL 55%	31	29		
Carmeli [65]	2015	BMI $43 \rightarrow 30$	9	31		

Table 1 Outcomes after revisional surgery after SG and RYGB

Revisional surgery after RYGB

First Author	Year	Type of revision	Additional weight loss after revision	Total no. of patients	Follow-up (months)
Revision of pouch	and/or stoma after RYGB				
Gobble [71]	2008	Band over pouch	BMI $43 \rightarrow 37$ EWL 21%	11	13
Bessler [72]	2010	Band over pouch	EWL 47%	22	60
Iannelli [73]	2013	Resizing pouch	BMI $35 \rightarrow 30$	20	21
Moon [57]	2014	Revision of pouch/ stoma and placement of patch around the pouch	BMI $40 \rightarrow 34$ EWL 19%	46	9
McKenna [74]	2014	Revision of stoma	BMI $42 \rightarrow 36$ EWL 36%	20	18
Nguyen [75]	2015	Revision of pouch/stoma	EWL 38%	44	26
Daigle [76]	2016	Revision of pouch/ stoma(n=2) Band over (n=2)	EWL 82% EWL 32%	4	52
Revision of RYG	B to distal bypass				
Rawlins [77]	2011	100 cm distal common channel	BMI $48 \rightarrow 32$	29	12

Conversions of RYGB into other operations are anecdotal and not well studied [57]. Nevertheless, RYGB is the most commonly used revisional procedure performed after primary bariatric surgery of any type [59]. Different options are performed after WR/IWL after RYGB, such as pouch trimming, anastomosis redo, and increased limb lengths. As shown in Table 1, the outcomes are heterogeneous. With the new pharmacotherapy, "conversion" revisional surgery, mainly after IWL/WR after RYGB, has a trend to decrease its number. Moreover, patients with BMI over 50 kg/m² or those early identified as non-responders may benefit from the adjunct drug therapy to prevent IWL before the plateau [60].

Several different endoscopic options have been proposed. Among them suturing devices to decrease an enlarged gastrojejunal anastomosis after RYGB or endoscopic plication of a SG [61]. Results are modest and with short-term follow-up [62].

5 Treating WR and IWL after MBS in the era of precision medicine

After ruling out surgically correctable complications such as gastro-gastric fistula, a comprehensive, multidisciplinary, and individual approach are fundamental for the appropriate care of IWL/WR after MBS

Treating either WR or IWL demands different tactics. Despite the current lack of robust data, patients with lessthan-ideal weight loss during the first 6 months are classified as non-responders, and stricter dietary and behavioral

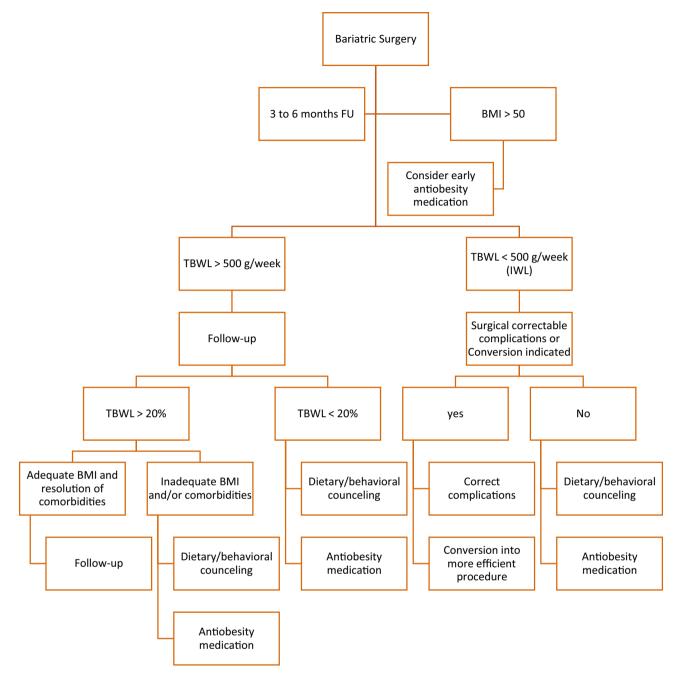


Fig. 2 Proposed strategy for Insufficient weight loss/weight regain after metabolic/bariatric surgery. FU: Follow-up; BMI: Body Mass Index; TBWL: Total Body Weight Loss

counseling, and after proper evaluation, adjuvant pharmacotherapy, including topiramate, phentermine-topiramate, and GLP1RA should be immediately started. It is important to highlight that some pharmacological agents may not be accessible in different countries worldwide, and medication management should be customized according to local availability. Similarly, patients with a BMI>50 kg/m² have a severe form of obesity. This group attains poorer weight loss with AOMs or MBS alone. The best strategy is to associate the proper operation with the best available medication, namely GLP1RA before they plateau their weight. If, during evaluation, an inadequate choice of index operation is recognized, or there is a concomitant complication associated with WR (as GERD, WR &SG), a conversion into another operation is warranted.

The recent GLP1RA studies on weight loss showed that early responders, e.g., those who lost weight early after medication's introduction are the individuals who will have significant weight loss during follow-up. The same is valid to patients submitted to MBS. Figure 2 suggests an algorithm for an individualized strategy for IWL/WR

With the development of newer pharmacological agents that are safe and carry significant weight loss, the landscape of the management of IWL/WR after MBS will change. Revisional surgery is riskier, and outcomes are uncertain. Endoscopic interventions still have no convincing data. There is a compelling need for studies to provide level 1 evidence that better defines the role of pharmacological approaches to IWL/WR after bariatric surgery.

Author contribution RVC and TBZP conceived the idea, searched and analyzed the literature, wrote the manuscript and approved all content

Declarations

Ethical approval Not needed.

Informed consent Not needed.

Conflict of interest The authors have no conflicts of interest to declare.

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