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Nutrition and Obesity (O Pickett-Blakely, Section Editor)

Pharmacotherapeutic Options for Weight Regain After Bariatric Surgery

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Abstract

Purpose of review We sought to critically evaluate the recent literature published over the past 3 years on the topic of weight regain after bariatric surgery in children, adolescents, and adults, with an emphasis on clinically relevant information for pharmacologic treatment of weight regain after metabolic and bariatric surgery.
Recent findings There are multiple pharmacotherapeutic agents available to treat obesity in children, adolescents, and adults; these agents have varying efficacy and indications for use and have been studied in a variety of clinical and research scenarios. We present an

overview of these findings.
Summary This review represents a comprehensive compilation of the recently published data on efficacy of anti-obesity pharmacotherapy in the treatment of weight regain after bariatric surgery for children, adolescents, and adults.

Introduction

Obesity is a complex and chronic disease of epidemic proportions in the USA and worldwide. Over 40% of US adults over the age of 20 live with obesity (body mass index (BMI) of 30 kg/m^2 or greater), and 18.5% of US children and adolescents live with obesity (BMI at 95th percentile or higher by age and sex). Additionally, 9% of adults and 6% of youth live with severe obesity, defined as BMI of 40 or greater in adults and 120% or more of the 95th percentile for youth [1, 2]. At the individual level, obesity is a disease driven by myriad complex interactions between environmental, humoral, and genetic factors. It also predisposes patients to many other chronic and fatal comorbidities, such as cardiovascular disease, type 2 diabetes mellitus, obstructive sleep apnea, and several forms of cancer. The rapid global rise in obesity therefore has tremendous ramifications for morbidity, mortality, and economic costs for both individuals and society, and the access to and availability of effective treatment options is paramount [3].

While lifestyle management and pharmacotherapy are common therapeutic options for obesity, bariatric surgery has superior efficacy and demonstrated safety in producing long-term weight control in both pediatric and adult populations [4]. Studies show decreases in body weight ranging from 16 to 23% over the first 10 years post-surgery, in addition to significant reductions in comorbidities [5]. Currently, over 250,000 bariatric surgeries are performed in the USA annually, with nearly two-fold increases in adolescent and ten-fold increases in adult bariatric surgical volume in recent years [6–8].

Indications for bariatric surgery are different in pediatric and adult populations. The American Society for Metabolic and Bariatric Surgery (ASMBS) Pediatric Committee recommends children and adolescents with class II obesity (BMI ≥ 120% of the 95th percentile for age and sex) and a comorbidity, or class III obesity (BMI ≥ 140% of the 95th percentile for age and sex) be considered surgical candidates [9]. Adults are considered candidates if they have (1) severe obesity (BMI≥40) or more than 100 lbs. overweight, (2) BMI≥35 and at least one obesity-related comorbidity, or (3) if they have been unable to achieve healthy, sustained weight loss for a period of time with prior efforts [10]. ASMBS does not specify a minimum time frame needed for sustained prior efforts at weight loss.

Several safe metabolic and bariatric surgical options are available to adult and pediatric patients. For pediatric and adult patients, sleeve gastrectomy is the most common bariatric operation and involves the laparoscopic removal of 80% of the stomach to induce metabolic and restrictive effects [11]. Gastric bypass operations also induce restrictive and metabolic effects through creation of a small stomach pouch followed by anastomosis of the remaining bypassed portion of the stomach and upper small intestine with the middle portion of the small intestine. Roux-en-Y gastric bypass (RYGB) is the second most common surgical procedure performed in the USA and internationally [4, 8, 12]. On average, at 36-month post-procedure, the expected decrease in BMI after sleeve gastrectomy (SG) is approximately 13 kg/m^2, whereas after gastric bypass, it is approximately 14 kg/m^2 and approximately 10 kg/m^2 after gastric banding [4, 13].

Despite these clinically significant postoperative weight reduction outcomes, studies have shown that 20–30% of bariatric surgical patients have significant weight regain (≥15% of initial post-surgical weight loss) within 2–5 years of their surgery [14, 15•, 16••]. Additionally, an estimated 15–35% of patients have inadequate weight loss (<50% of excess weight) by 12-month post-operation [17•]. Weight regain after surgery is multifactorial and is often driven by hormonal and metabolic changes, dietary non-adherence, changes in physical activity and mental health, and anatomic surgical changes [18••]. While various options such as revisional surgeries and endoscopic procedures are available, pharmacotherapy has emerged as a leading non-

invasive and effective option to assist pediatric and adult populations to achieve and sustain recurrent weight loss after bariatric surgery. This review seeks to examine the most recent evidence underpinning the use of pharmacotherapeutic agents in treating weight regain in pediatric and adult bariatric surgical patients.

Methods

A literature search of PubMed and MEDLINE electronic databases was conducted to identify studies examining pharmacotherapeutic options for weight regain after bariatric surgery in pediatric and adult populations. The following keyword search terms were used: "bariatric surgery," "obesity," "weight gain," "weight regain," "pediatric," "adolescence," "adult," "anti-obesity medication," "weight loss medication," and "bariatric pharmacotherapy". Inclusion of studies was limited to publications in English and those with human subjects. The primary outcome of interest among included articles was the use of pharmacotherapy among pediatric and/or adult bariatric surgery patients. Clinical trials, case reports, case series, reviews, systematic reviews, scoping reviews, and meta-analyses were all considered. Studies published prior to 2017 and those not directly relevant to the primary outcome of interest were excluded. Articles were screened by title and abstract review.

An initial search of English language articles published between 2017 and 2021 yielded 1376 results, which were screened for eligibility and inclusion as depicted in Figure 1.

Pharmacotherapeutic options for weight regain after bariatric surgery in children and adolescents

The prevalence of pediatric obesity is increasing at an alarming rate in the USA and throughout the world with no countries experiencing a decreased rate over the past 3 decades [19, 20]. In the USA, prevalence rates are 18.4% among children aged 6–11 years and 20.6% among adolescents aged 12–19 years [21]. Obesity is associated with significant consequences in health and quality of life, and the presence of obesity in youth increases the risk of obesity as an adult [22]. Therefore, effectively treating pediatric obesity is paramount.

The cornerstone of current pediatric and adolescent management focuses on lifestyle interventions including optimizing physical activity and nutrition. Currently, there are only four anti-obesity medications that have been approved by the Food and Drug Administration (FDA) for the treatment of obesity in pediatric patients: orlistat for patients ≥12 years, phentermine for those >16 years, liraglutide for those ≥12 years, and setmelanotide for those ≥6 years [23, 24, 25•]. Several anti-obesity medications (AOM) are approved in adults and are used "off label" to treat pediatric obesity. For pediatric and adolescent patients with severe obesity, metabolic and bariatric surgery (MBS) is a safe and effective treatment option that reduces the risk of persistence of obesity into adulthood and improves or leads to remission of several clinically important comorbidities. Use of MBS in adolescents is supported in clinical practice guidelines by the Endocrine Society and the American Society for Metabolic

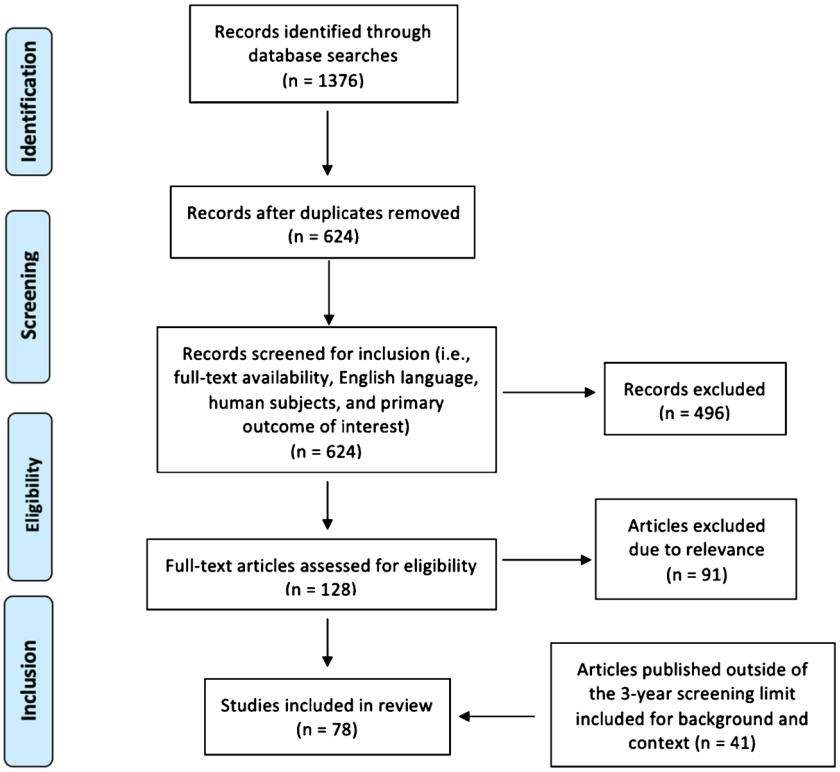

Figure 1. Article screening for eligibility and inclusion

and Bariatric Surgery (ASMBS) [9, 23•]. In December 2019, the American Academy of Pediatrics (AAP) also published its first ever policy statement regarding the expanded use of MBS for adolescent and pediatric patients with severe obesity [26]. The 2018 ASMBS pediatric metabolic and bariatric surgery guidelines recommend MBS for adolescents with class II obesity (120% BMI percentile for age and sex) along with an obesity-related comorbidity or with class III obesity (140% BMI percentile for age and sex), defining pediatric obesity based on the Centers for Disease Control and Prevention age- and sex-matched growth charts [9]. These proposed BMI criteria for MBS in adolescents are similar to those employed in adult guidelines. However, the approach to anti-obesity pharmacotherapy in adolescents does not have the same level of support in clinical practice guidelines. This is evidenced by the Endocrine Society's suggestion that anti-obesity medications should be restricted to clinical trials during childhood and adolescence, and there is no guidance offered regarding the use of pharmacotherapy to treat inadequate weight loss or weight regain following MBS [23•]. A multidisciplinary expert committee published a position statement that recommends applying similar, but modified BMI criteria for the consideration of anti-obesity pharmacotherapy in adolescents with a BMI ≥95th percentile (or BMI ≥30 kg/m^2, whichever is lower) plus the presence of at least one obesity-related comorbidity, or BMI ≥120% of 95th percentile (or BMI ≥35 kg/m^2, whichever is lower) irrespective of co-morbidity, or if criteria for MBS are met [27]. Yet, guidance on the use of AOM for the treatment of weight regain following MBS is lacking.

There are three landmark studies which assess the outcomes of MBS in adolescents: Follow-up of Adolescent Bariatric Surgery (FABS-5+) [28], Adolescent Morbid Obesity Surgery (AMOS) [29], and Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) [30] (Table 1). All of these are prospective observational studies with follow up of 3–5+ years and demonstrated that weight regain relative to lowest weight observed occurs between 1 and 2 years postoperatively; participants tend to regain 13–25% of the maximum observed weight lost, and persistence of obesity at the same or lower classification is common [28–30]. When weight regain does occur in adolescent patients following MBS, there are no clear guidelines, position statements, or studies to provide guidance on the safety and efficacy of anti-obesity pharmacotherapy in this patient population. Stanford et al studied weight regain after bariatric surgery in young adults aged 21 to 30 years; they found that the ideal time to start anti-obesity pharmacotherapy is at the post-surgical nadir weight and patients who underwent RYGB lost a larger percent of weight with medications than SG groups although both groups had weight loss benefits [31••].

With a lack of data guiding post-bariatric surgical weight regain in young populations, clinicians are currently limited to the use of the current FDA-approved and non-approved adult AOM medications (off-label), summarized below (Table 2), to treat weight regain or augment weight loss in adolescents after MBS. As such, there is an urgent need for studies to evaluate the safety and efficacy of anti-obesity medications for the treatment of weight regain following MBS in adolescent patients to provide continued treatment for this increasingly prevalent disease.

A potential barrier to conducting such studies is that there are low utilization rates of MBS in adolescents and young adults at academic healthcare institutions within the USA [32]. Additionally, many pediatric patients who pursue MBS may be adults at the time of having significant weight regain following MBS given that the mean baseline age in FABS-5+, AMOS, and Teen-LABS is 17.1 years (SD 1.7), 16.5 years (SD1.2), and 17 years (SD 1.6), respectively, with lowest mean observed weight occurring at 1–2 years postoperatively [28–30]. The patient's age at the time of weight regain is important because if they are ≥ 18 years of age, adult guidelines may be applied. There are more FDA-approved medications available at older ages, and, although scarce, studies have previously shown the benefits and safety of pharmacotherapy for weight regain following MBS in adult patients. Until further studies are available, pediatric obesity medicine specialists may need to look towards the available adult literature to attempt to make inferences from the data to guide their decisions for treating weight regain following MBS in pediatric patients.

Pharmacotherapeutic options for weight regain after bariatric surgery in adults

Bariatric surgery, as a part of a comprehensive weight management treatment plan, continues to be one of the most effective interventions in the treatment of obesity. Weight regain after bariatric surgery is an undesired outcome and is usually caused in adults by a combination of medical, psychosocial, and behavioral factors. Pharmacotherapy has emerged as a first-line therapy to halt

Table 1. Comparison of long-term outcomes of prospective trials of bariatric surgeries in adolescents

Study, author, year, country	Study type	No. of participants	Mean age in years, (SD)	Type of surgical procedure	Years of follow-up	Mean baseline BMI in kg/m^2 (SD/range)	% change in BMI at 12-month follow up (SD)	Mean BMI kg/m^2 (SD/range) at end of follow up
FABS-5+ study, Inge et al, 2017, USA (28)	Prospective	58	17.1 (1.7)	RYGB	5–12	58.5 (SD 10.5)	–38.5% (6.9)	41.7 (SD 12.02) at follow-up (>5 years)
AMOS study, Olbers et al, 2017, Sweden (29)	Prospective	81	16.5 (1.2)	RYGB	5	45.5 (SD 6.1)	N/A	32.3 (SD 6.3) at 5-year follow-up
Teen-LABS study, Inge et al, 2019, Multicenter study in the USA at five centers (30)	Prospective	242	17 (1.6)	161		underwent RYGB, 67 underwent SG	3	53 (range 51–54)
N/A	38 (range 37–40) at 3-year	follow-up						

Table 2. Medication options for obesity pharmacotherapy in pediatric, adolescent, and adult patients

Medication	Mechanism	FDA indication	Contraindications	Side effects	Efficacy
Orlistat [49, 50]	Pancreatic and gastric lipase inhibitor	≥ 12 years with obesity	Chronic malabsorption syndrome, history of liver disease, history of seizures, pancreatitis, pregnancy, breastfeeding, cholestasis, levothyroxine, on warfarin, on cyclosporine, on antiepileptic drugs	Decreased absorption of fat-soluble vitamins, gastrointestinal side effects (steatorrhea, flatulence with discharge, fecal urgency, incontinence, oily evacuation, increased defecation)	Adolescents: 2.61 kg placebo-subtracted weight loss at 1 year after treatment in a large randomized controlled trial [24]; 3.3% mean BMI reduction at 6 months (not statistically significant compared to placebo) [49] Adults: 4.4 kg and 2.8 kg placebo-subtracted weight loss at 1 and 4 years of treatment respectively [50, 51]
Phentermine [50, 52–54]	Norepinephrine-releasing agent; increases catecholamines and serotonin activity in the central nervous system	≥ 16 years with obesity (for up to 12 weeks); ≥18 years with obesity for long term use in combination with topiramate	Anxiety disorders (agitated states), history of heart disease, uncontrolled hypertension, seizure history, monoamine	Common: Headache, elevated BP/HR, insomnia, dry mouth, constipation, anxiety Cardiovascular: palpitation,	Adolescents: 4.1% mean BMI reduction at 6 months with phentermine plus lifestyle modification therapy

Table 2. (Continued)

Medication	Mechanism	FDA indication	Contraindications	Side effects	Efficacy
			oxidase inhibitor use, pregnancy, breastfeeding, hyperthyroidism, glaucoma, history of drug abuse, sympathomimetic amine use	tachycardia, ischemic events Central nervous system: overstimulation, restlessness, dizziness, euphoria, dysphoria, tremor, headache, psychosis Gastrointestinal: dry mouth, unpleasant taste, diarrhea, constipation Allergic: urticaria Endocrine: impotence, changes in libido	compared to lifestyle therapy alone [52] Adults: 6.06% total body weight loss at 15mg daily and 5.45% at 7.5mg of phentermine daily at 28 weeks plus lifestyle modification therapy compared to 1.7% with lifestyle therapy alone [55]
Glucagon-like-1 receptor (GLP-1) agonists [38, 44, 56]	Incretin mimetic (enhances insulin secretion, delays gastric emptying)	Liraglutide: ≥ 12 years with obesity Semaglutide: T2DM in adult; off-label use for obesity in adults at the time of publication Other GLP1-agonists approved for T2DM in adults, off-label use for T2DM in adolescents and obesity in adults/adolescents (i.e., exenatide, dulaglutide)	Pregnancy, personal history of medullary thyroid cancer, family history of multiple endocrine neoplasia type 2 (MEN2)	Nausea, vomiting, diarrhea, pancreatitis, cholelithiasis	Liraglutide: Adolescents: 4.29% mean BMI reduction at 56 weeks (4.64% mean reduction in BMI at 56 weeks compared to placebo) [56] Adults: 5.6 kg placebo-subtracted weight loss at 56 weeks [38] Semaglutide: Adolescents: Data not yet available Adults: 14.9% body weight reduction compared with 2.4% in placebo [44]
Setmelanotide [57, 58]	Melanocortin 4 (MC4) receptor agonist	≥ 6 years with obesity due to rare genetic conditions (e.g.,			
proopiomelanocortin	None				

Table 2. (Continued)

Medication	Mechanism	FDA indication	Contraindications	Side effects	Efficacy
(POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), leptin receptor (LEPR) deficiencies, MC4R mutation)		Injection site reactions, darkening of the skin, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection; erectile dysfunction; depression, suicidal thoughts	Adolescents: POMC trial: 80% participants in the POMC trial achieved at least 10% weight loss at 1 year [58] LEPR trial: 45% participants achieved at least 10% weight loss at 1 year [58] Adults: MC4R mutation carriers had placebo subtracted group mean difference in weight loss of ~0.6 kg/week compared to placebo (not statistically significant) [57]		
Metformin [27, 59–64]	Upregulates activated protein kinase, inhibits hepatic gluconeogenesis, enhances insulin uptake in peripheral tissues (skeletal muscle, liver); Effective in treating weight gain related to use of antipsychotics induced medications [59–61]	≥ 10 years of age with type 2 diabetes	Chronic renal, cardiac or hepatic impairment	Gastrointestinal symptoms including bloating, diarrhea, and flatus; rarely lactic acidosis	Adolescents: BMI *z*-score reduction of –0.10 and BMI reduction of –0.86 with metformin dose ranging from 1 to 2 g per day [62] Adults: 5.6% mean weight loss (metformin-treated) vs 0.8% weight gain (placebo) [64]
Topiramate [27, 53, 65–69]	Modulation of various neurotransmitters, including the inhibition of voltage-dependent sodium channels,	≥ 2 years for treatment of epilepsy; ≥ 12 years for migraine prophylaxis;	Pregnancy, attempting to conceive, or breastfeeding; angle closure	Paresthesia, cognitive dysfunction (such as memory issues), somnolence, taste changes,	Adolescents: 1.9% BMI reduction vs placebo after initial meal replacement

Table 2. (Continued)

Medication	Mechanism	FDA indication	Contraindications	Side effects	Efficacy
	glutamate receptors and carbonic anhydrase; and potentiation of γ-aminobutyrate (GABA) activity	≥18 years of age in combination with phentermine for obesity	glaucoma; use caution in strict ketogenic diet, history of nephrolithiasis	nephrolithiasis, metabolic acidosis; teratogenic with potential to cause cleft palate and/or lip during first trimester of pregnancy; may decrease the efficacy of oral contraceptives at doses of 200mg and greater [53]	induction phase [66]; 4.9% BMI reduction at 6 months in adolescents with severe obesity [67] Adults: 5.34 kg additional weight loss compared to placebo [69]
Phentermine/topiramate ER [50]	Sympathomimetic amine/antiepileptic (also see above descriptions)	≥18 years for obesity	Pregnancy, glaucoma, hyperthyroidism, recent MOA use, known hypersensitivity to sympathomimetic amines	Paresthesia, dizziness, dysgeusia (altered taste perception), insomnia, constipation, dry mouth	Adolescents: Data not yet available Adults: 8.5% and 9.2% weight reduction at 28 weeks for 7.5/46mg and 15/92mg doses, respectively, vs. 1.7% weight reduction in placebo [50]
Bupropion/naltrexone [53, 70–74] bupropion/naltrexone carries a black box warning regarding increased suicidal risk	Reuptake inhibitor of dopamine and norepinephrine (bupropion) and opioid antagonist (naltrexone) Adolescents: Data not yet available Adults: 9.3% body weight reduction at 56 weeks of 32/360 mg dose compared	≥18 years for obesity; Bupropion: treatment of depression, seasonal affective disorder, and smoking cessation in adults Naltrexone: treatment of alcohol and opioid dependency in adults	Uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, drug or alcohol withdrawal, recent use of MAO inhibitors	Nausea, headaches, vomiting, dizziness, constipation, insomnia, anxiety, irritability;	

Table 2. (Continued)

Medication	Mechanism	FDA indication	Contraindications	Side effects	Efficacy
and ideation in young adults	to 5.1% reduction in placebo group [74]				
Lisdexamfetamine [75–77]	Dopamine agonist, CNS stimulant	≥ 6 years for attention deficit hyperactivity disorder (ADHD); and binge eating disorder (BED) in adults	History of structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems	Irritability, dry mouth, diarrhea, dizziness, BP/HR increase (~2–4 mm Hg/~3–6 bpm); temporary slowing in growth rate (~2 cm less growth in height, 2.7 kg less growth in weight over 3rs) without evidence of growth rebound; may provoke psychiatric disorders (psychosis, hallucinations, delusions) in children and adolescents with no prior mental illness; sudden death reported in children and adolescents with structural cardiac abnormalities; rarely Raynaud phenomenon in adults	Adolescents: dose-dependent weight reduction of up to 4.8 pounds over 4 weeks in adolescents 12–17 years Adults: Dose-dependent weight reduction up 4.9 kg over 11 weeks in adults with BED [77]

weight regain and achieve additional weight loss following bariatric surgery. For patients with challenges meeting lifestyle modification goals, or for those at high risk for complications from revisional surgery, pharmacotherapy is a particularly effective initial interventional choice to support behavioral changes and dietary intervention.

Anti-obesity pharmacotherapy has been recommended for the treatment of obesity in adult patients with BMI ≥ 30 or a BMI ≥ 27 with comorbid conditions. For many patients with weight regain following bariatric surgery, their BMI remains in the obesity category (BMI ≥ 30) [33••]. However, most currently approved medications were not originally tested in patients with prior bariatric surgery. To date, the majority of evidence for the use of weight loss pharmacotherapy in these patients has been reported in retrospective studies. In a multicenter study by Stanford et al., patients were identified following Roux-en-Y gastric bypass or sleeve gastrectomy who received anti-obesity pharmacotherapy postoperatively for weight regain or inadequate weight loss [16••]. In this study, over 50% of patients achieved >5% total body weight loss with medications postoperatively, while 30.3% and 15% of patients lost ≥10% or ≥15% of total body weight, respectively. It was also reported that patients with higher pre-operative BMI achieved greater weight loss after use of weight loss pharmacotherapy. Additional studies have supported these findings [34••].

Medications such as phentermine and topiramate, used individually and in combination as a part of a comprehensive treatment plan post-bariatric surgery, have been studied in adult patients. Phentermine, a centrally acting sympathomimetic drug, stimulates secretion and inhibits reuptake of norepinephrine in the hypothalamus, thus suppressing appetite and promoting weight loss. Topiramate, an anticonvulsant also used for migraine prophylaxis, also suppresses appetite and may have an effect on energy balance [35•]. In the aforementioned multicenter study by Stanford et al., topiramate was the only medication that was associated with a statistically significant response for weight loss of the pharmacotherapy studied, which also included phentermine, metformin, and bupropion. In this study, patients were twice as likely to achieve at least 10% total body weight loss when treated with topiramate [16••]. When the young adults (age 21–30) of this study were examined separately, topiramate and phentermine had a similar level of effectiveness [31••].

Glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide have also been shown to be effective in treating weight regain following bariatric surgery. The primary action of GLP-1 receptor agonists is the glucose-dependent inhibition of glucagon secretion and increase in insulin secretion [36]. They also reduce food intake and promote satiety by their actions on appetite-regulating neuronal activity: inhibiting the activity of neuropeptide Y (NPT)/agouti-related peptide (AgRP) neurons and directly stimulating the proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons. Finally, GLP1 receptor agonists have also shown additional effects of decreasing the rate of gastric emptying and stimulating activity of brown adipose tissue to increase thermogenesis [36, 37]. In non-surgical patients, liraglutide 3.0 mg has been associated with significant weight loss and appetite reduction [38]. This effect has also been shown in studies including post-bariatric surgery patients.

In a study by Suliman et. al, 60% and 23% of patients treated with liraglutide 3.0 mg lost >5% and >10%, respectively, of their total body weight, without a difference in percentage weight loss seen between patients with a

history of bariatric surgery and non-surgical patients [39•]. Gazda et al demonstrated that GLP1 receptor agonists are more effective than non-GLP1 receptor agonist medications at 3, 6, and 9 months of follow up for treating post-bariatric weight regain [40••]. At 9 months after medication initiation, those receiving GLP-1 class medications had lost 6.9% body weight vs. 5.7% body weight reduction in those receiving non-GLP-1 medications, while those on intensive lifestyle modification experienced 1.6% weight gain [40••]. Additional studies have shown significant weight loss of 5.5–7.1% of body weight in post-bariatric surgery patients treated with liraglutide, and the degree of weight loss remained statistically significant 1 year after initiation of liraglutide [41••, 42••]. There are several pharmacotherapeutic agents pending regulatory approval (including 2.4mg dose GLP-1, combination amylin analog/2.4mg GLP1, and combination GIP/GLP1) for which clinical trials have shown even greater weight loss benefits than GLP1 alone [43–45]; we anticipate that these agents will be studied more extensively in post-surgical weight regain populations in the future.

An additional consideration for the use of weight loss pharmacotherapy in patients with weight regain following bariatric surgery is the number of agents used. Postoperative bariatric patients treated with two or more anti-obesity medications have been shown to have significant weight loss [46••]. These findings suggest that for the greatest effect, regimens including two or more agents in combination should be considered. The timing of weight loss pharmacotherapy initiation should also be considered. Stanford et al reported that weight loss medications are particularly useful in adults 60 years of age and older following inadequate weight loss or weight regain after bariatric surgery [47••], while Gutt et al reported that initiation of anti-obesity pharmacotherapy at the time the weight plateau is reached, as opposed to after weight regain, may result in higher total body weight loss [48••].

Conclusion

Anti-obesity pharmacotherapy is severely underutilized for treating primary obesity and only marginally less underutilized in treating recurrent obesity following bariatric surgery [40••]. Due to a lack of evidence-based guidelines for initiation and monitoring of pharmacotherapy in those with weight regain following bariatric surgery, obesity specialists and other clinicians who seek to treat this patient population often face significant challenges and uncertainty. This review represents a compilation of the recently published data on efficacy of anti-obesity pharmacotherapy in the treatment of weight regain after bariatric surgery for children, adolescents, and adults.

The key finding of this review are as follow:

- A number of small, non-randomized, retrospective, and prospective studies provide evidence that multiple pharmacological options, both FDA approved and off-label, are effective in mitigating and managing weight regain after bariatric surgery [78••].
- Randomized controlled trials addressing pharmacotherapeutic management of post-bariatric surgical weight regain are lacking.

- There is much excitement and anticipation among those in the fields of obesity medicine for the pending regulatory approval of additional pharmacotherapeutic anti-obesity agents which will likely provide additional therapeutic options for managing post-bariatric surgical weight regain.
- Despite many promising developments in this clinical area, there is a significant need for future studies to fully characterize and quantify the utility of pharmacotherapeutic treatment options for weight regain after bariatric surgery in children, adolescents, and adults.

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Declarations

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.

Conflict of Interest
Chika Vera Anekwe declares that she has no conflict of interest. Michael G. Knight declares that he has no conflict of interest. Sujatha Seetharaman declares that she has no conflict of interest. Wesley P. Dutton declares that he has no conflict of interest. Shradha M. Chhabria declares that she has no conflict of interest. Fatima Cody Stanford declares that she has no conflict of interest.

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This study asserts that adjuvant pharmacotherapy can help treat weight regain after bariatric surgery however future studies are needed to elucidate the optimal timing for starting such medications as well as the best medications or combinations of medications for managing postoperative weight regain.

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