

ASMBS guidelines/statements

Literature review on antiobesity medication use for metabolic and bariatric surgery patients from the American Society for Metabolic and Bariatric Surgery Clinical Issues Committee

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Abstract

The following literature search is in response to inquiries made to the American Society for Metabolic and Bariatric Surgery (ASMBS) regarding antiobesity medication (AOM) use in patients who are having or have already had metabolic and bariatric surgery (MBS). These recommendations are based on current clinical knowledge, expert opinion, and published peer-reviewed scientific evidence available at this time. This paper is not intended to establish a local, regional, or national standard of care. The paper will be revised in the future as additional evidence becomes available. (Surg Obes Relat Dis 2022;18:1109–1119.) © 2022 American Society for Metabolic and Bariatric Surgery. Published by Elsevier Inc. All rights reserved.

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A literature search was conducted using Ovid Medline and PubMed in July 2021. The U.S. Food and Drug Administration (FDA) website also was searched because we were

interested in the initial trials for AOMs. The final search terms used were “Bariatric Surgery” OR “Gastric Bypass” OR “Sleeve Gastrectomy” OR “Intragastric Balloon” OR “Biliopancreatic Diversion or Duodenal Switch” OR “Endoscopic Stomal Revision” AND “*Anti-Obesity Agents” OR “Phentermine” OR “Qsymia” OR “Naltrexone” OR “Contrave” OR “Liraglutide” OR “Saxenda” OR “Semaglutide” OR “Orlistat.” The search was limited to papers available in the English language, those with human participants, and those published from 2000 to the present. Case reports, commentaries, and editorials were excluded from the final summary of the literature.

There are currently 9 FDA-approved AOMs on the market in the United States: semaglutide 2.4 mg, orlistat, phentermine, diethylpropion, phendimetrazine, benzphetamine, bupropion SR/naltrexone SR, phentermine/topiramate ER, and liraglutide 3.0 mg. These medications have been used and studied in patients with obesity and obesity-related co-morbidities. The aim of this paper is to describe current research about patients who are planning for or have already undergone MBS and may benefit from AOM use. Results of data for AOM use in non-MBS patients, both adult and pediatrics, have been reported elsewhere [1–5].

Review of the physiologic basis for obesity

Research has shown that patients with the disease of obesity have a complicated homeostatic mechanism that controls body weight. The balances between hunger and satiety and weight gain and weight loss are not directly proportional to the input and output of calories or creation of a calorie deficit alone. Studies on exogenous leptin administration highlight this point. Outside the setting of a very rare congenital leptin deficiency, exogenous leptin administration to patients did not result in expected levels of weight loss. It was later determined that patients with obesity likely have a systemic leptin resistance and actually may have high levels at baseline [6].

Animal models have demonstrated that anorexigenic signaling from cocaine and amphetamine regulated transcript (CART) neurons interact with the central nervous system (CNS) in the hypothalamus. Signaling is carried out via hormone secretion, including thyrotropin-releasing hormone, melanin-concentrating hormone, and neuropeptide Y (NPY) [7]. Proopiomelanocortin (POMC) neurons play a similar role in energy homeostasis and exert effects directly on CNS targets [8]. Stimulation of POMC and CART neurons increases energy expenditure and decreases food intake.

Gastrointestinal hormones also have been found to play an important role in energy homeostasis. Endogenous insulin and peptide YY have been shown to have an anorexigenic effect, whereas systemic ghrelin causes a strong orexigenic state [9]. Gastrointestinal stimulation by food ingestion, which may vary based on meal size or frequency,

results in factors such as cholecystokinin secretion that act to promote fullness and satiety [10].

Intracellular energy levels are proposed to play a role in energy homeostasis. Studies have shown that low intracellular levels of long-chain fatty acyl-CoA and increased adenosine monophosphate to adenosine triphosphate levels cause signaling resulting in a downstream orexigenic state via the mammalian target of rapamycin protein signaling pathway [11].

Additional pathways involving reward signals that are generated from food tastes and textures may be under separate homeostatic control. This is highlighted by increased reward perception in the setting of starvation in animal models [12]. This pathway may function in parallel with the neurohormonal pathways discussed earlier. It can independently increase food-seeking behavior despite inhibition or negative feedback to other pathways.

Adipose tissue has separately been found to produce factors that influence energy homeostasis. Neurons that express NPY and agouti-related protein are inhibited by leptin, insulin, and peptide YY. Ghrelin, in contrast, has been found to be strongly stimulatory for hunger. When weight decreases, these neurons may be activated. Activation of nearby POMC leading to downstream release of α -melanocyte-stimulating hormone (α -MSH) has an anorexigenic effect on energy balance [13–15].

MBS has been found to have an impact on CNS pathways involved in energy homeostasis. A small study looking at functional brain imaging in patients who underwent gastric bypass procedures (GBPs) showed that mesolimbic pathways involved in reward were much less active postoperatively to food cues with high calorie density [16]. Another small study showed functional imaging changes in patients who lost weight after MBS in the hypothalamic region of the brain. Postoperatively, patients who underwent MBS had brain imaging patterns similar to those seen in patients without obesity [17]. Furthermore, there are data on Power of Food Scale questionnaire results from 366 patients who were divided nearly equally into patients with and without obesity and patients who underwent MBS. After MBS, patients were found to have significantly lower motivation for food consumption than patients with obesity who did not undergo MBS. Scores in the patients who had MBS were similar to those of individuals who did not have obesity [18].

Animal models have more specifically investigated neurohormonal alterations after MBS. Rat studies have demonstrated decreased NPY and increased α -MSH activity after GBPs, which may be one mechanism through which it helps with weight loss [19]. Other research has shown a homeostatic increase in NPY expression after biliopancreatic diversion in rats that can be viewed as a resistance mechanism to weight loss [20]. Weight regain in mice after GBPs showed an association with failure to maintain plasma

peptide YY levels [21]. These represent areas where AOMs can have the potential to increase weight loss and durability after MBS.

AOMs targeting different points in this complex neuro-hormonal pathway may work synergistically and additively in combination with MBS. Treating patients with obesity via a multimodal approach has the potential to increase and possibly enhance the efficacy and durability of MBS.

Summary of the most commonly prescribed FDA-approved AOMs

This section discusses the most commonly prescribed AOMs: orlistat, phentermine, phentermine-topiramate, naltrexone-bupropion, liraglutide, and semaglutide (Table 1). The FDA has approved the use of AOMs for any patient under the following conditions: (1) obesity (defined as body mass index [BMI] ≥ 30 kg/m²) or (2) pre-obesity (or overweight) (defined by BMI ≥ 27 kg/m²) with at least 1 obesity-related co-morbidity.

AOMs are considered to be effective when patients are able to lose >3%–5% total body weight after 12 weeks of therapy or when patients are able to achieve weight stabilization if that is a clinical therapeutic goal. If the minimum weight loss goal has not been achieved by that time, modification or discontinuation of therapy is recommended. AOMs should be used in conjunction with intensive lifestyle changes that incorporate caloric modification, physical activity, and healthy nutrition. All AOMs are pregnancy risk factor category X drugs and should not be prescribed to a patient who is pregnant, breastfeeding, or trying to conceive. Consideration should be given to pregnancy testing in female patients of childbearing age before starting an AOM [1,22,23].

Orlistat

Orlistat is a lipase inhibitor that was first approved by the FDA as an AOM in 1999. It was marketed as Xenical at 120 mg and approved for over-the-counter (OTC) use as Alli at 60 mg in 2007. When taken with a meal, it blocks fat absorption by 30%, thus decreasing overall total caloric intake. There is no evidence of systemic absorption, and it does not appear to act on the homeostasis of energy balance directly. The most common adverse reactions are gastrointestinal, such as oily stool, fecal urgency, flatulence with discharge, and stool leakage. These side effects significantly limit patient adherence to this medication. Prescribers should be aware that orlistat will also decrease the absorption of fat-soluble medications; thus, fat-soluble vitamin supplementation will be needed for patients who are taking orlistat for a prolonged period [23]. This AOM should be avoided in patients with gallbladder disease because it can increase the risk of cholelithiasis.

Phentermine

Phentermine is a sympathomimetic amine and a controlled substance. It was approved by the FDA in 1959 for weight loss use for 90 days, but this original labeling has not been updated since then. It was subsequently approved for longer-term use for treatment of patients with obesity when combined with topiramate in the brand-name medication of Qsymia. The exact mechanism of action for appetite suppression is not known, but it is suspected to be related to an increase in norepinephrine [23,24]. The effects of phentermine are mediated by direct activity at the hypothalamus, where it promotes an anorexigenic state. While phentermine is considered to have lower abuse potential than amphetamine, because it lacks dopaminergic properties, it should be avoided in patients with a history of drug abuse [22]. Phentermine (15–37.5 mg) is taken daily in the morning to minimize stimulant-like side effects on sleep. However, at an 8 mg dose, it can be taken up to 3 times a day. Some of the most common side effects are increased blood pressure, palpitations, increased heart rate, headaches, insomnia, anxiety, dry mouth, and irritability. Phentermine is contraindicated in patients with known serious cardiovascular diseases, uncontrolled hypertension, hyperthyroidism, and glaucoma and within 14 days of monoamine oxidase inhibitor use [23].

Phentermine-topiramate

Phentermine and topiramate (antiepileptic) in combination, marketed as Qsymia, was approved to manage obesity by the FDA in 2012 for long-term use (can be given for >3 months). Topiramate's exact mechanism of action for weight loss is unknown. It likely occurs via neurotransmitter and cell signaling modulation. Unlike phentermine monotherapy, phentermine-topiramate requires titration to start as well as a taper to stop because of the topiramate component. The initial dose is 3.75–23 mg daily in the morning for 14 days and should be doubled (7.5–46 mg) afterward. After 12 weeks, if weight loss is less than 3% and the patient is without renal or hepatic impairment, another trial can be started with 14 days of 11.24–69 mg followed by 12 weeks of 15–92 mg daily. Patients should be tapered off over 3–5 days because abrupt discontinuation can potentially trigger seizures even in patients without a known seizure history. Common adverse reactions are increased heart rate, paresthesia, dizziness, altered taste, insomnia, constipation, and dry mouth. Worsening of mood disorders including anxiety, depression, and suicidal ideation is possible, and collaborating with a psychiatric clinician is recommended prior to initiation in patients with these conditions. Patients also may report memory problems or difficulty concentrating. Patients should be warned of vision changes, such as blurred vision or sudden loss of sight due to acute angle-closure glaucoma that has been reported in patients on this

Table 1
Summary of the most commonly prescribed FDA-approved antiobesity medications*

Category	Orlistat	Phentermine	Phentermine-topiramate	Naltrexone-bupropion	Liraglutide	Semaglutide
Class	Lipase inhibitor	Sympathomimetic amine	Sympathomimetic amine-antiepileptic	Antidepressant-opioid receptor antagonist	Glucagon-like peptide 1 analogue	Glucagon-like peptide 1 analogue
Administration	PO	PO	PO	PO	SQ	SQ
Renal adjustment	No	Maximum daily dose (MDD) of 15 mg. Avoid in dialysis or ESRD	MDD of 7.5–46 mg. Avoid use with severe impairment.	MDD of 1 tablet bid. Avoid use in ESRD.	Use with caution. Postmarketing report of acute kidney injury.	Use with caution. Postmarketing report of acute kidney injury.
Hepatic adjustment	No	No	MDD of 7.5–46 mg. Avoid use with severe impairment.	MDD of 1 tablet bid.	Use with caution.	Use with caution.
Contraindications	Chronic malabsorption syndrome, cholestasis	Cardiovascular disease, hyperthyroidism, glaucoma, agitated states, history of drug abuse, within 14 d of MAOI	Glaucoma, hyperthyroidism, or within 14 d of MAOI	Uncontrolled hypertension, seizure disorders, eating disorders (anorexia nervosa or bulimia), chronic opioid therapy, within 14 d of MAOI, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 3
Drug interactions	Cyclosporine, fat-soluble vitamins, levothyroxine, warfarin	MAOI, alcohol, adrenergic neuron blockers	Oral contraceptives, CNS depressants (i.e., alcohol), non-potassium-sparing diuretics	CYP2D6 metabolizer (i.e., antidepressants, antipsychotics, beta-blockers, and type 1C antiarrhythmics), CYP2B6 inhibitors, CYP2B6 inducers, drugs that lower seizure threshold, dopaminergic drugs	May slow down absorption of oral medications	May slow down absorption of oral medications

FDA = U.S. Food and Drug Administration; PO = oral; SQ = subcutaneous; MDD = maximum daily dose; ESRD = end-stage renal disease; MAOI = monoamine oxidase inhibitor; MTC = medullary thyroid cancer; MEN2 = multiple endocrine neoplasia type 2.

* All AOMs are contraindicated during pregnancy and lactation.

medication. This medication should be used with caution in patients who are at high risk for kidney stones, metabolic acidosis, and hypokalemia. Patients should be monitored periodically for electrolytes and creatinine levels. Glucose should be monitored in patients receiving antidiabetic medications because weight loss may cause hypoglycemia. Patients who are on oral contraceptives should be warned of their possible decreased effectiveness while on phentermine-topiramate [23,24]. Furthermore, women of childbearing age should be counseled to use effective contraception because topiramate is teratogenic.

Naltrexone-bupropion

Naltrexone-bupropion is a combination of an opioid-receptor antagonist and antidepressant. It was approved for treatment of patients with obesity in 2014 under the trademark Contrave. Weight loss is thought to be mediated through food intake and satiety feedback inhibition. Bupropion is thought to increase secretion of α -MSH, which has an anorexigenic effect. Combining with naltrexone may help decrease the effects of the opioid products of POMC, which may have a negative-feedback loop on α -MSH activity [25]. It is also thought that bupropion has influence over the reward pathway involved in energy homeostasis. The appetite-suppression effect of bupropion-naltrexone tends to decrease after 1 year of therapy [24]. Bupropion has a black box label warning for suicidal ideation and can lower the seizure threshold. The initial dose for bupropion-naltrexone in combination is 8–90 mg daily in the morning, and the dose is increased weekly over a 1-month period to the intended therapeutic dose of 16–180 mg twice daily. The most common side effects are nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, increase in blood pressure, increase in heart rate, and diarrhea. Patients should be monitored for changes in mood and suicidal ideation. Bupropion-naltrexone is contraindicated in patients with a history of seizures or in those at high risk for seizure, drug addiction history, high risk for angle-closure glaucoma, eating disorders (anorexia nervosa or bulimia), and uncontrolled hypertension. Patients should be educated on how therapy is adjusted while they are being treated with opioids. Bupropion-naltrexone can render a toxicology urine screen test falsely positive for amphetamines [22,23,26].

Liraglutide

Liraglutide is a glucagon-like peptide 1 (GLP-1) analogue that is used for the treatment of type 2 diabetes. GLP-1 receptor agonists induce weight loss primarily by reducing appetite and calorie intake via effects on the hypothalamus and hindbrain. In the initial weeks of GLP-1 receptor agonist therapy, delayed gastric emptying also plays a role in regulating appetite. It was approved for treatment of patients with GLP-1 in 2014 under the trademark

Saxenda. It is injected subcutaneously daily with an initial dose of .6 mg, increasing weekly by .6 mg to the maximum daily dose of 3 mg. The most common side effects are nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase. It is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 syndrome. This was based on the finding of increased incidence of C-cell-type thyroid tumors during the animal trial phase in rats. Liraglutide should be discontinued in patients suspected of pancreatitis, and its use should be avoided in patients with a history of or high risk for pancreatitis. Concurrent use with insulin or sulfonylureas can cause hypoglycemia. In the SCALE trial, in which participants were taking 3 mg daily for a 1-year period, a small increase in heart rate was noted; because of this, patients' vital signs should be monitored [22,23,26].

Semaglutide

Semaglutide, like liraglutide, is a GLP-1 analogue. It was approved by the FDA in June 2021 for treatment of patients with obesity under the trademark Wegovy. The mechanism of action for weight loss is likely similar to that of liraglutide, and it has the same black box warning for medullary thyroid carcinoma or multiple endocrine neoplasia type 2 syndrome as well as similar side effects. The main difference is that while liraglutide is given as a daily injection with weekly titration, semaglutide is a weekly injection with monthly titration, and it has superior weight loss efficacy. Available doses are .25, .5, 1, 1.7, and 2.4 mg. An additional 4 weeks of a 1.7 mg trial can be used for patients who do not tolerate the 2.4 mg dose. Deescalation of therapy should be considered if patients are unable to tolerate the 2.4 mg dosage. If less than 5% weight loss is achieved after 3 months of therapy, medication discontinuation should be considered. The most common side effects of semaglutide are nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia, increase heart rate, and flatulence. Patients also may report gastroenteritis or gastroesophageal reflux disease. Semaglutide should be used with caution in patients with a history of diabetic retinopathy. For patients who are interested in pregnancy, it is recommended to discontinue semaglutide at least 2 months before trying to conceive because of its long half-life [27].

AOM use in MBS in the preoperative setting

In the latest release of its Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program standards, the American College of Surgeons endorsed the accreditation of comprehensive centers with obesity medicine qualifications, thus recognizing and emphasizing the value of multimodal and multidisciplinary management of patients with obesity [28]. The use of AOMs in the preoperative

setting can follow the general guidelines described in this paper with a goal of weight loss prior to undergoing MBS, although few studies have assessed such use.

Two rationales support the use of AOMs in the preoperative setting: reduction of perioperative risk and increased proportion of those achieving weight loss goals and comorbidity resolution after surgery. Two large studies have demonstrated benefits of preoperative weight loss (PWL) with reduction in perioperative mortality and morbidity. Sun et al. [28] studied 480,075 patients in the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program database and observed that patients with a preoperative total body weight loss of 0%–5.0%, 5.0%–9.9%, and >10.0% had 24%, 31%, and 42%, respectively, lower risk of 30-day mortality [29]. Another similar study of 548,597 patients showed a similar protective benefit with a >10% PWL leading to 30% decreased odds of leak (odds ratio [OR] = .68%; 95% confidence interval [CI]: .56–.84; $P < .0001$) and a 40% decrease in odds of mortality versus those with no PWL (OR = .60; 95% CI: .39–.92; $P = .02$) [30]. It should be noted that no high-quality data exist to support insurance-mandated preoperative weight loss. This practice is scientifically unfounded and discriminatory toward patients with obesity. The practice leads to attrition or delay in access to lifesaving treatment via MBS [31].

Achieving 5%–10% total body weight loss is extremely challenging for patients with the disease of obesity. A goal of weight loss prior to surgery should not be used as a sole criterion to proceed or delay MBS because the benefits significantly outweigh the risks of the procedure. Hutcheon et al. [31] studied the impact of a 4-week preoperative very low-calorie diet prior to bariatric surgery. While it proved to be beneficial for weight loss, only 63% of patients on a very-low-calorie diet were able to achieve 8% total weight loss or greater. AOMs theoretically could be used to increase rates of preoperative weight loss [32].

Another benefit of preoperative AOM use may be in the setting of patients with very high BMIs. In a small cohort of patients with an average BMI of 59.5 kg/m², Alexandrou et al. [32] showed that only 29% reached a BMI <35 kg/m² after sleeve gastrectomy (SG), and only 51% achieved a BMI <40 kg/m² without co-morbidities or <35 kg/m² with co-morbidities after SG followed by Roux-en-Y gastric bypass (RYGB) [33]. Adding AOMs to this cohort of patients may improve outcomes beyond what is possible with MBS alone. Future studies looking at AOM use versus second-stage operations would be of great value.

The use of AOMs in the preoperative setting can follow the general guidelines described in this paper, although few studies have assessed such use. One note should be made regarding phentermine: given that its approval by the FDA is only for short-term use, its use as longer-term monotherapy needs to be monitored by a physician and documented as off-label use when not used in combination with topiramate. Phentermine lends itself well to the

preoperative setting, where rapid weight loss is favored in order to limit attrition and not discourage the most severely affected patients from being offered lifesaving surgical therapy. It also can be combined with several other medications for layering of therapy. In addition, phentermine needs to be discontinued prior to surgery in order to minimize interaction with anesthesia during the procedure. The timing for discontinuation of phentermine prior to anesthesia currently varies greatly throughout the country and depends on the anesthesiology team. Older anesthetics interacted more strongly with phentermine, whereas the newer ones are not as much of an issue. A national consensus on this topic would have value to many patients because stopping the medication before surgery when the patient is following a low-calorie diet to shrink the liver can be challenging when appetite is increased. While GLP-1 agonists are more effective for weight loss, these medications are often financially out of reach for many patients, even those with insurance because of the lack of AOM coverage under the diagnosis of obesity. Phentermine is significantly more affordable, even without insurance coverage.

Orlistat has been studied in a small cohort of patients prior to MBS (19 patients and 19 control individuals) and failed to show any benefit in preoperative or early postoperative weight loss [34]. The only prospective study looking at preoperative AOM use was in patients with high BMIs (>50 kg/m²). Comparing 13 patients who were prospectively enrolled to receive phentermine-topiramate plus SG with 40 historical control patients who underwent SG during the same time frame without adjunctive phentermine-topiramate, patients in the SG + phentermine-topiramate group were given 7.5/46 mg up to 15/92 mg for 3 months before and 2 years after surgery along with close supervision. The percent excess weight loss was not significantly different between the 2 groups in this study at 24 months. BMI change was significantly different starting at 6 months postoperatively between the 2 groups, with greater improvement seen in the SG + AOM group. This difference remained significant to the end point of the study at 24 months [35]. It is not clear from this study if increased BMI change in the MBS + AOM group was from preoperative AOM use or continued use postoperatively. Larger studies are needed in this area.

AOM use in MBS in the postoperative setting and for weight recurrence

Much more has been published on the use of AOMs in the postoperative setting. This includes research on patients who have experienced weight recurrence after surgery. The etiology for weight recurrence after MBS can include metabolic, anatomic, nutritional, psychosocial, and environmental factors [36]. AOMs along with lifestyle interventions provides a useful therapeutic approach for patients experiencing weight recurrence.

A Cochrane review of 22 trials found bariatric surgery compared with any nonsurgical intervention was more effective in promoting weight loss and resulted in an improvement in associated co-morbid conditions irrespective of the type of surgery [37]. Despite the demonstrated efficacy of MBS as a stand-alone treatment for obesity and related diseases, some studies suggest that AOMs may serve as an adjunct to surgery and increase the durability of the metabolic effects in some patients [38].

Most of the studies describing the use of AOMs as an adjunct for weight loss after MBS were conducted after the patients either plateaued or experienced weight recurrence [39–44]. Side effects reported were overall consistent with those previously reported in nonsurgical populations. Very few publications have targeted AOMs in the early post-bariatric surgery phase when weight loss is occurring prior to plateau. Ideally, AOMs should be tailored to the patient's needs, acting as an adjunct to dietary modifications and behavioral changes with the goal to optimize weight loss and help the resolution of obesity-associated co-morbidities. More studies are needed in this area to help identify which patients may be partial or nonresponders to MBS that may benefit from AOM use in the early postoperative setting.

A retrospective study from Ard et al. [34], previously discussed in this paper for its preoperative use of AOMs, also provided data on longer-term outcomes in AOM use after MBS. It reviewed a total of 15 patients who underwent SG with a 3-month course of phentermine-topiramate preoperatively that was extended for 2 years after MBS. The authors compared the results of SG + AOM with those of a matched cohort of SG patients without AOM use. Preoperative BMI was 61.2 kg/m² in the AOM group and 57.0 kg/m² in the control group. The patients with adjunct pharmacotherapy had an 11.2% greater weight loss at 12 months after surgery, and mean BMI of the +AOM group was 33.8 kg/m² compared with 42 kg/m² in the –AOM group. All patients had 6 extra postoperative dietician visits than was done historically in the program, and the +AOM group had up to 9 additional contacts for medication management. Overall, there were 9 additional encounters postoperatively per patient at 2-year follow-up. Patients in the +AOM group maintained improved results through the 2-year end point of the study relative to the –AOM group [35].

In a more recent paper, Thakur et al. [44] compared 2 cohorts of patients undergoing SG in a small prospective, double-blind, randomized, placebo-control, single-center study in which one group received liraglutide (6 patients) and the control group received a placebo (11 patients) postoperatively [45]. Pharmacotherapy was initiated at the 6-week mark after SG and was maintained to 24 weeks. Liraglutide was started at .6 mg/d and gradually increased to reach the maximum dose tolerated at 3 mg/d. Both cohorts were matched by BMI (42.6 ± 6.3 versus 41.6 ± 5.1 kg/m²) and by the number of similar obesity-related co-morbidities. This study was characterized by pre- and postoperative

dietary regimen uniformity in both cohorts and good adherence to study medication and rigorous follow-ups. The percentage of excess body weight loss was significantly higher in the group receiving liraglutide (58.7% ± 14.3% and 44.5% ± 8.6%; *P* = .043). When added after MBS, liraglutide promoted 14% additional percent total body weight loss compared with placebo. All the patients in the AOM group experienced complete resolution of diabetes and prediabetes compared with only 50% in the control group. The authors did not report any significant differences when it came to the resolution of other obesity-related co-morbidities.

Stanford et al. [39] evaluated the use of FDA-approved and -nonapproved medications in 390 patients who had undergone RYGB or SG and had at least 12 months of postoperative follow-up. The average number of medications for the study patients was 2. Patients were more likely to be prescribed AOMs after weight recurrence (78.5%) than at their plateau (21.5%). Patients who had AOMs prescribed at their plateau demonstrated a higher cumulative total weight loss (32.3%) compared with those who were prescribed an AOM after weight recurrence (26.8%), although the results did not reach statistical significance. Fifty-four percent of patients had >5% total body weight loss with AOMs after surgery, 30.3% had >10% total body weight loss, and 15.4% had >15% total body weight loss. In this study, topiramate was the only medication that demonstrated statistically significant weight loss results. It should be noted that this study was conducted prior to the more widespread use of GLP-1 agonists. Additionally, patients on topiramate were twice as likely to lose at least 10% of their postoperative weight. Regardless of postoperative BMI, RYGB patients were significantly more likely to have had >5% postoperative total weight loss with the aid of AOMs (OR = –2.86; *P* = .001). Women were more likely to lose >5% (OR = 1.81; *P* = .031) compared with men. The authors noted that patients with higher preoperative BMIs were more likely to lose postoperative weight with AOMs [40].

Another retrospective review of the use of AOMs in the post-bariatric surgery population was conducted by Nor Hanipa et al. [38]. Enrolled patients either had inadequate weight loss or weight recurrence following MBS. Two-hundred and nine patients were enrolled in the study, which included 126 RYGB, 52 SG, 21 laparoscopic adjustable gastric bands, 4 gastric plications, and 6 revisional bariatric procedures. Median interval time between surgery and the start of AOMs was 38 months. AOMs used included phentermine (*n* = 156; 74.6%), phentermine-topiramate (*n* = 25; 12%), lorcaserin (withdrawn from market; *n* = 18; 8.6%), and naltrexone-bupropion (*n* = 10; 4.8%). The overall percent total weight losses (%TWLs) at 3 and 12 months were 3.2% and 2.2%. The %TWL >5% after initiation of AOM at 1 year was 37%. The %TWL >10% at 1 year after initiation of AOM was 19%. The %TWL for patients with a BMI >36 kg/m² compared with those with a BMI <36 kg/m² was 3.5% ± 7.9% and .9% ± 7.0% (*P* = .27). However,

in contrast to Stanford et al. [39], no correlation between preoperative BMI and response to AOMs was noted in this study [39].

A retrospective cohort study examined the use of postoperative topiramate, phentermine, and/or metformin in 37 adults 21–30 years of age following RYGB (28) and SG (9). These medications were given at weight plateau or for weight recurrence. The researchers noted additional losses of $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ of their postoperative total body weight in 54.1%, 34.3%, and 22.9% of patients treated with AOMs. The authors also concluded that patients started on AOMs at weight plateau lost a greater amount of weight to their new plateau than patients started after weight recurrence. Furthermore, this study noted that patients who underwent RYGB had significantly higher %TWLs on AOMs compared with those who underwent SG (-8.1% versus -3.3%) [46].

A retrospective review evaluating phentermine versus phentermine-topiramate in the RYGB ($n = 51$) and laparoscopic adjustable gastric band ($n = 14$) populations demonstrated that phentermine (52 patients) and phentermine-topiramate (13 patients) patients lost 6.35 kg (12.8% excess weight loss [EWL]) and 3.81 kg (12.9% EWL) at 90 days on AOMs. The patients on phentermine alone consistently lost more weight than patients on phentermine-topiramate in combination [47].

In a study on postoperative liraglutide use, Wharton et al. [42] evaluated 117 patients following MBS and noted a significant weight loss (-6.3 ± 7.7 kg) 7 months after beginning the intervention regardless of the type of bariatric surgery performed. After 1 year, patients on liraglutide continued to demonstrate significant weight loss. Nausea was the most prevalent side effect at 29.1%. By taking liraglutide 3.0 mg subcutaneously once a day, patients saw statistically significant weight loss within the first month and were able to lose, on average, 13.89 lb within 8 months and maintained or continued to lose weight by 1 year, all irrespective of the procedure performed [43].

Liraglutide 3.0 mg added after SG also provided upward of 14% additional weight loss and diabetes resolution in 62.5% of patients in a study by Thaker et al. [45] Compared with phentermine, liraglutide may be favored because of its positive effect on diabetes and decreased number of drug interactions. Semaglutide may be another promising pharmacologic agent to treat weight recurrence [27]. No current studies have investigated semaglutide use in post-MBS patients.

In another retrospective study evaluating weight loss outcomes in postoperative bariatric surgical patients presenting for weight recurrence ($n = 48$), patients lost an average of -4.4 kg in 6 months with AOMs coupled with intensive lifestyle and behavioral modification. Weight loss after weight recurrence was greater for bariatric patients treated with >2 AOMs (-5.7%) but was less than in nonsurgical patients enrolled in the specialized obesity program (-9.5% ; 2 AOMs), which warrants further research [44]. Medications

to treat weight recurrence included metformin, phentermine, combination phentermine-topiramate, combination bupropion-naltrexone, lorcaserin, zonisamide, topiramate, and GLP-1 agonists. In this particular study, there were no differences between the types of bariatric surgery performed, though variability was large and the sample size was small.

Gadza et al. [47] did a retrospective analysis of 207 individuals treated for post-MBS weight recurrence comparing weight loss outcomes among an intensive lifestyle modification (ILM) group, a non-GLP-1 receptor agonist-based weight loss pharmacotherapy (WLP) group, and a GLP-1 receptor agonist-based WLP group (the latter 2 groups in conjunction with ILM) [48].

At 9 months, the percent total body weight loss was significantly different between groups (-1.6% versus 5.6% versus 6.9% ; $P = .007$) for ILM, non-GLP-1 receptor agonist-based WLP, and GLP-1 receptor agonist-based WLP groups, respectively). Regardless of surgery type, GLP-1 receptor agonist-based WLP therapies were found to be more effective for treating post-MBS weight recurrence than non-GLP-1 receptor agonist-based WLP or ILM [49].

In a small cohort of patients with an average BMI of 59.5 kg/m^2 , Alexandrou et al. [32] showed that only 29% reached a BMI <35 kg/m^2 after SG, and only 51% achieved a BMI <40 kg/m^2 without co-morbidities or <35 kg/m^2 with co-morbidities after SG followed by RYGB [33]. Adding AOMs to this cohort of patients may improve outcomes beyond what is possible with MBS alone. Future studies looking at AOM use versus second-stage operations would be of great value.

It is important to note that the type of procedure performed may affect the response of MBS patients receiving adjuvant pharmacotherapy for weight recurrence. While both RYGB and SG patients are very responsive to AOMs, RYGB patients appear to be even more responsive to non-GLP-1 receptor agonist-based pharmacotherapy compared with SG patients [39,43,50]. Response to adjuvant AOM therapy after MBS was similar in younger versus older adults [43].

AOMs are an option for patients following MBS. According to limited available data, upward of 33% of patients can achieve $>5\%$ total body weight loss [39]. Data also suggest benefits to beginning AOMs once weight loss begins to plateau for maximum effectiveness. AOMs may be effective adjuvant treatment prior to weight plateau in selected patients, but further data are needed. AOMs are effective for weight recurrence, and this may be particularly true for patients who have gained weight after RYGB versus SG. Considering that the majority of studies are retrospective with small sample sizes, larger prospective studies comparing different AOMs, the time of AOM initiation after MBS, and factors predictive of success are needed [43]. Results have validated that

AOM use post-MBS is well tolerated with only mild to moderate side effects in most cases.

AOM use with endoscopic gastroplasty and intragastric balloons

Badurdeen et al. [51], in a nonrandomized multicenter setting, studied the combination of endoscopic gastroplasty (EG) for patients with a BMI >27 kg/m² in conjunction with initiation of liraglutide at 5 months postoperatively for a total of 7 months. The study encompassed 52 patients divided into 2 one-to-one matched groups. The percent total weight loss in the EG patients treated with liraglutide was superior to that of the control group at 4 and 7 months after initiation of the medication (22.28 ± 3.26 kg versus 19.23 ± 3.33 kg; $P = .02$ and 25.02 ± 3.80 kg versus 20.95 ± 3.21 kg; $P < .001$, respectively). The authors also noticed that at 1 year after EG, the visceral fat percentage decreased significantly in patients treated with liraglutide ($7.85\% \pm 1.26\%$ versus $10.54\% \pm 1.88\%$, respectively; $P < .001$) [51].

Mosli et al. [50] analyzed 44 patients given a 6-month course of liraglutide starting 30 days after intragastric balloon (IGB) insertion compared with 64 patients with IGB alone. At baseline, the groups' mean BMIs were statistically the same. After IGB removal, the mean %TWL was 8.3 kg greater in the IGB + liraglutide group than in the IGB alone group, and the improvement was significantly greater 6 months after balloon removal in the group receiving liraglutide. However, the authors concluded that the benefit might not be substantial: after adjusting for covariates, patients treated with IGB alone demonstrated a higher %TWL at the time of balloon removal (coefficient = 7.71; 95% CI: 4.78–10.63) and a higher odds of treatment success 6 months after balloon removal (OR = 5.74; 95% CI: 1.79–188.42) [52].

A recent retrospective study from Brazil looked at liraglutide use following IGBs left in place for 12 months in 53 matched patient groups. At the time of IGB removal, patients were treated with routine follow-up or follow-up + liraglutide for 9 months. There was significantly less weight recurrence in the IGB + liraglutide group ($-1.15 \pm .94$ kg versus $-.66 \pm .99$ kg; $P = .01$). Body fat composition measured by bioimpedance also was significantly lower in the IGB + liraglutide group versus IGB alone [53].

In a multicenter retrospective study of 102 patients including 23 patients treated with IGB + AOM and 79 patients treated with IGB + lifestyle modifications, weight loss was similar while the IGB was in place, but patients receiving IGB + AOM did have greater weight loss ($12.6\% \pm 1.2\%$ versus $9.7\% \pm .7\%$; $P = .04$) and diminished weight recurrence after balloon removal compared with those receiving just IGB and lifestyle changes [54].

AOMs are showing promising results in combination with EG and IGBs. Because of the short-term nature of IGB therapy, this may be an area where standardized AOM use can extend weight loss benefits.

AOM use in adolescents undergoing MBS

Studies on the use of AOMs in adolescents date as back to 2005, initially consisting of review articles and most recently including a systematic review and meta-analysis as well as consensus guidelines [55,56]. The recommendations specifically call for the use of AOMs in adolescents with obesity in the setting of a multidisciplinary team and in combination with an established weight loss program with diet and lifestyle modification as well as activity counseling. The literature from more recent years describes the use of various medications to treat adolescents with excess body weight and co-morbidities [57–60]. No studies focus on the use of AOMs in the pre- or postoperative settings of MBS in adolescent patients, though in the updated consensus algorithm published in *Surgery for Obesity and Related Diseases* in 2019, it was noted that consideration needs to be given to AOMs in the post-MBS period because relapses and recurrence of weight gain can occur along the spectrum of chronic disease [56]. This area of research would benefit from further study.

Conclusions

1. AOMs are indicated for patients with BMI ≥ 30 kg/m² or ≥ 27 kg/m² with 1 or more obesity-related co-morbidities and may prove to be a useful adjunct to MBS. AOMs should be used in combination with nutritional and lifestyle interventions.
2. Phentermine is one of the most commonly used AOMs in patients undergoing MBS and has the advantage of low cost and oral administration. Pairing phentermine with topiramate may be advantageous in terms of weight loss efficacy through combinatory mechanisms and cost considerations in the post-MBS patient.
3. GLP-1 agonists offer a long duration of therapy, few medication interactions, and few side effects, but cost can be a deterrent for some patients when they are not covered by insurance.
4. AOMs can be used prior to MBS to help increase preoperative weight loss. The impact on postoperative outcomes is unknown.
5. In patients with weight recurrence after MBS, AOMs can be a particularly useful therapy. Patients who have undergone RYGB compared with patients who have undergone other types of MBS may benefit the most from non-GLP-1 receptor agonist-based AOMs.

Disclosures

A. Fitch is on the scientific advisory boards for Jenny Craig, Novo Nordisk, Gelesis, and Found. The other authors of this paper have no commercial associations that might be a conflict of interest in relation to this article.

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