Effectiveness and safety of drugs for obesity

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ABSTRACT

Recent publicity around the use of new antiobesity medications (AOMs) has focused the attention of patients and healthcare providers on the role of pharmacotherapy in the treatment of obesity. Newer drug treatments have shown greater efficacy and safety compared with older drug treatments, yet access to these drug treatments is limited by providers' discomfort in prescribing, bias, and stigma around obesity, as well as by the lack of insurance coverage. Now more than ever, healthcare providers must be able to discuss the risks and benefits of the full range of antiobesity medications available to patients, and to incorporate both guideline based advice and emerging real world clinical evidence into daily clinical practice. The tremendous variability in response to antiobesity medications means that clinicians need to use a flexible approach that takes advantage of specific features of the antiobesity medication selected to provide the best option for individual patients. Future research is needed on how best to use available drug treatments in real world practice settings, the potential role of combination therapies, and the cost effectiveness of antiobesity medications. Several new drug treatments are being evaluated in ongoing clinical trials, suggesting that the future for pharmacotherapy of obesity is bright.

Introduction

The prevalence of obesity (defined as a body mass index ≥30) has increased significantly in recent decades. Although most definitions of obesity are based on body mass index, body mass index is now widely acknowledged to be an imperfect measure of adiposity and should not replace clinical judgment in the assessment of adiposity related health risks.[1 2] Additionally, adjustments of body mass index based cut points need to be made for some racial and ethnic groups. Regardless of its shortcomings for predicting individual health, having a body mass index ≥30 is associated with increased morbidity and mortality at a population level and for many individuals.[3] This association is manifested in large part by the increased risk of weight related complications such as type 2 diabetes,[4] hypertension,[5] obstructive sleep apnea,[6] and degenerative joint disease.[7] In light of the burden obesity places on human health and a growing understanding of the physiologic processes underlying weight regulation, scientific organizations including the American Medical Association, the National Institutes of Health, and others now recognize it as a relapsing, remitting chronic disease.[8-11] Accordingly, modern guidelines recommend a long term treatment approach, which can include the use of antiobesity medications (AOM).

The goal of this review is to summarize recent guideline documents, systematic reviews, and emerging randomized controlled trials and observational studies related to the safety, efficacy, and health outcomes of antiobesity medications, to help guide practicing physicians in their clinical decision making. We also alert clinicians to emerging trends in treatment and major unanswered research questions to help guide conversations with patients. Two recently published reviews and guideline documents have provided a detailed summary of the relative efficacy and safety of these drug treatments.[10 12] We augment these papers by presenting post-approval evidence on antiobesity medication effectiveness and comparative effectiveness in real world settings, and proposing future avenues for research. When patients meet guideline based criteria for consideration of an antiobesity medication, clinicians should feel comfortable initiating conversations about antiobesity medications and responding to their patients' questions. In a busy clinical practice, conversations about antiobesity medications need to be efficient and to touch on several key points that can drive clinical decision making. Key points that can guide the discussion are listed in box 1.

Box 1: Key considerations for providers considering antiobesity medication prescribing

1. Antiobesity medications approved by the Food and Drug Administration are an evidence based **adjunct to lifestyle treatment**. Antiobesity medications should be considered a standard tool to help people with obesity to lose weight and keep it off.
2. Because obesity is a chronic disease, like diabetes or hypertension, patients who want to maintain weight loss **should understand that antiobesity medications will likely need to be continued long term**, because weight is usually regained after antiobesity medications are discontinued.
3. Many insurance companies in the United States currently do not cover antiobesity medications, so **out-of-pocket costs usually play a role in the selection of antiobesity medication**. Clinicians should be prepared to discuss insurance coverage and drug treatment affordability with their patients.
4. Antiobesity medications vary in average effectiveness, cost, and side effect profile. The **clinician and patient should together identify which factors are most important**, and tailor prescribing around those priorities.
5. Antiobesity medications can cause a variety of side effects. A useful initial strategy is to **prescribe the selected antiobesity medication at a low dose and titrate upwards** based on the weight response and side effects.
6. The initial antiobesity medication selected should be **discontinued and replaced with an alternative if the patient does not have ≥5% weight loss** in 3-6 months.
7. Antiobesity medications improve several markers of health, including blood pressure, lipid levels, and glycemic control. **Among patients with diabetes, glucagon-like peptide-1 receptor agonists reduce incident cardiovascular events,** and one trial has shown reduced cardiovascular events with semaglutide in patients with pre-existing cardiovascular disease without diabetes.

Epidemiology

In 2017-18, 42% of US adults were living with obesity (body mass index ≥30), with a similar prevalence among men and women.[13] Obesity shows marked racial and ethnic disparities, with the lowest prevalence among non-Hispanic Asian adults (17.4%) and the highest prevalence among non-Hispanic black (49.6%) and Hispanic (44.8%) adults.[13] The global prevalence of obesity nearly doubled in 70 countries between 1980[14] and 2015. The Global Burden of Disease study found in 2019 that roughly 41% of all deaths from metabolic diseases were attributable to obesity.[15]

While public interest in antiobesity medications seems to be increasing rapidly in recent years, published data on current levels of use are lacking. Historically, use of antiobesity medications has been relatively low compared with the numbers of eligible patients. In 2012-16, the United States Government Accountability Office reported that out of the estimated 72 million US adults with obesity, only 0.9% had been prescribed an FDA approved antiobesity medication in any given year.[16] Numerous studies have reported similarly poor uptake, ranging from 1-3% both in the US and Europe.[17-27] Patients who report wanting to lose weight, have a history of bariatric surgery, or are enrolled in intensive weight loss programs might be more likely to be prescribed antiobesity medications,[16 19 26] but uptake is low even in these groups. The high cost of these drug treatments, many of which are not covered by health insurance in the US, is likely to lead to uneven access to them, which could further exacerbate obesity related health disparities.[28]

Methods

Sources and selection criteria

We based this review on articles found by searching PubMed and the Cochrane Library since inception through June 2023, using the terms "systematic review", "randomized controlled trial", "guideline", "weight-loss", "obesity", "antiobesity medication", "obesity pharmacotherapy", "phentermine", "orlistat", "phentermine-topiramate", "bupropion-naltrexone", "semaglutide", "liraglutide", "tirzepatide", "setmelanotide", "cagrilintide", "orforglipron", "retatrutide", "pemvidutide", "survodutide" "mazdutide", "danuglipron", "apitegromab", "taldefgrobep", and "HU6". Our search was limited to English language articles and focused on drug treatments that are available in the US. Priority was given to evidence obtained from the most recent systematic literature reviews, meta-analyses, and when possible, any subsequently published randomized controlled trials. Where possible, we prioritized studies of at least one year in duration. Patient stakeholders were engaged in the creation of the manuscript (see box 'How patients were involved in the creation of this article').

Current antiobesity medications FDA approved for use in the US

Owing to differences in approval processes for drug treatments and in the opinions of regulatory bodies across the globe, the array of antiobesity medications available for prescribing varies between nations. This review primarily focuses on drug treatments available in the US. Several FDA approved antiobesity medication options are now available for US providers and patients to consider when initiating pharmacotherapy. Table 1 provides an overview of the efficacy, side effects, costs, and practical considerations of these antiobesity medications, with an emphasis on data from meta-analyses and randomized trials. For ease of description, we have grouped available antiobesity medications according to the year when they were approved by the FDA as treatments for weight loss. Importantly, although an increased understanding of obesity physiology has recently led to the introduction of some highly effective antiobesity medications, a newer antiobesity medication is not always inherently better or more effective for a given patient than an older one. Individual heterogeneity in response to these drug treatments is substantial, and many patients will have a clinically meaningful response to older antiobesity medications.

Table 1 | Overview of antiobesity medications approved by the Food and Drug Administration

Generic name (year approved, approval type*)	Mechanism of action	Route of administration	Placebo subtracted % weight loss (95% CI) at 12-24 months	Proportion of patients achieving 5% weight loss at 12-24 months, %	Other weight loss estimates	Side effects	Contraindications	Cost for 1 month supply, $†	Ideal use case (special benefits)
Phentermine (1959, short term use, DEA schedule IV)	Sympathomimetic amine; increases norepinephrine (primarily), dopamine, serotonin in hypothalamic nuclei that regulate hunger	Oral; options for daily or three times daily dosing	Unknown	Unknown	5-15% total weight loss at 6 months[29-32] (uncontrolled studies) 7.2% average total weight loss at 24 months[33] (observational cohort) 32-80% of patients lose at least 5% over 3 months[29 33-37]	**Common**: Dry mouth, insomnia, constipation, anxiety, headache; **Possible/ rare**: elevated blood pressure, tachyarrhythmia; **Theoretical**: cardiovascular events such as myocardial infarction, stroke	Cardiovascular disease including arrhythmia, history of substance use disorder, hyperthyroidism, poorly controlled hypertension, cardiac valvulopathy	5-20	Young or middle aged patient with no cardiovascular disease history and for whom affordability of drug treatments is a concern (**Affordability**)
Orlistat (1999, long term use)	Reversible inhibitor of gastric and pancreatic lipases; inhibits absorption of dietary fats	Oral; three times daily ingestion with meals	3.2 (95% CI 2.8-3.5)[12]	49.7[12]	2.8% (95% CI 2.4-3.2)[10] placebo subtracted % weight loss up to 4 years	**Common**: flatulence, oily stools, fecal urgency, fecal incontinence. **Rare/theoretical**: liver failure	Pregnancy, chronic malabsorption syndrome (eg, celiac disease, inflammatory bowel disease, previous bariatric surgery), cholestasis	0-60	Patient for whom cost is a concern but who is not worried about gastrointestinal adverse effects or is adhering to a very low fat diet‡ (**Few contraindications**)
Phentermine-topiramate extended release (2012, long term use, DEA schedule IV)	Phentermine: as above; topiramate: GABAergic agent used for epilepsy, carbonic anhydrase inhibitor	Oral; once daily dosing	7.9 (95% CI 6.7-9.3)[12]	74.4[12]	7.8-9.8% total weight loss at 12 months and 9.3-10.5% total weight loss at 24 months (depending on dose)[38 39]	**Common**: Same as phentermine + paresthesias, dysgeusia, cognitive dysfunction **Possible/ rare**: same as phentermine + glaucoma, nephrolithiasis§	Same as phentermine + pregnancy category X (topiramate); consider avoiding in patients with glaucoma, nephrolithiasis	100-150	Young or middle aged patient with no cardiovascular disease history, with history of migraine headache and no risk of becoming pregnant (**Migraine prophylaxis**)
Naltrexone-bupropion sustained release (2014, long term)	Naltrexone pure opioid antagonist. Bupropion: weakly inhibits neuronal reuptake of dopamine and norepinephrine Mechanism leading to weight loss not fully understood	Oral; twice daily dosing	4.1[12] (95% CI 3.0-5.2)	64.6[12]	3.0% (95% CI 2.5-3.5)[10] Placebo subtracted % weight loss at 56 weeks	**Common**: headache, dizziness, nausea, vomiting, depression, initial increase in blood pressure that resolves by 12 weeks in RCTs. **Rare**: seizure, cholecystitis, suicidal ideation	Seizure disorder or high risk of seizures; opioid use; uncontrolled hypertension; hepatic cirrhosis; current or recent (<14 days) use of monoamine oxidase inhibitor, pregnancy	500	Patient with alcohol use disorder, tobacco use disorder, and/ or depression and no history of hypertension, who would be willing to take two separate pills if cost was a concern (**Alcohol use disorder, depression, tobacco cessation**)
Liraglutide (2014, long term)	GLP-1 receptor agonist; acts centrally to improve satiety and slows gastric emptying	Subcutaneous injection; daily	4.7 (95% CI 4.1-5.3)[12]	64[12]	Average total weight loss 8.0% +/- 6.7 (SD) at 56 weeks[40]	**Common**: nausea, vomiting, constipation **Possible/rare**: pancreatitis	Family history of MEN type 2 syndrome; personal history of medullary thyroid cancer	1090	Patient with type 2 diabetes whose insurance will not cover weekly injectables (**Type 2 diabetes**)
Setmelanotide (2020, long term use)	Melanocortin-4 receptor agonist for monogenic obesity syndromes	Subcutaneous injection; daily	Unknown	Unknown	Average total weight loss 5-20%, 45-80% achieved a 10% reduction at 1 year depending on gene defect[41]	**Common**: hyperpigmentation, injection site reactions, gastrointestinal upset, headache, sexual adverse reactions	None	20 904	Individuals with an approved monogenic obesity indication (***POMC*, *PCSK1*, or *LEPR* deficiency, Bardet-Biedl syndrome**)

(*Continued*)

Table 1 | Continued

Generic name (year approved, approval type*)	Mechanism of action	Route of administration	Placebo subtracted % weight loss (95% CI) at 12-24 months	Proportion of patients achieving 5% weight loss at 12-24 months, %	Other weight loss estimates	Side effects	Contraindications	Cost for 1 month supply, $†	Ideal use case (special benefits)
Semaglutide (2021, long term use)	GLP-1 receptor agonist; acts centrally to improve satiety and slows gastric emptying	Subcutaneous injection; once weekly dosing	11.4 (95% CI 10.3-12.5)[12]	78.1[12]	Average total weight loss 14.9% at 68 weeks[42]	**Common**: nausea, vomiting, constipation **Possible/rare**: pancreatitis	Family history of MEN type 2 syndrome; personal history of medullary thyroid cancer	1100	Patient with at least 10% weight loss clinically indicated, with cardiovascular disease, or diabetes/insulin resistance who cannot take a phentermine-containing agent (**Type 2 diabetes; cardiovascular-disease; substantial weight loss**)
Tirzepatide (2023, long term)	Dual agonist to GLP-1 and glucose dependent insulinotropic polypeptide receptors; and slows gastric emptying	Subcutaneous injection; once weekly dosing	11.9 (95% CI 10.4-13.4) to 17.8[43] (95% CI 16.3-19.3) depending on dose	85-91 depending on dose	Average total weight loss 15-21% at 72 weeks (depending on dose)	**Common**: nausea, vomiting, constipation **Possible/rare**: pancreatitis	Family history of MEN type 2 syndrome; personal history of medullary thyroid cancer	1060	Patient with at least 10% weight loss clinically indicated and diabetes or insulin resistance who cannot take a phentermine containing agent. (**Type 2 diabetes; substantial weight loss**)

CI=confidence interval; DEA=Drug Enforcement Administration; GABA=γ-aminobutyric acid; GLP-1=glucagon-like peptide-1; MEN=multiple endocrine neoplasia; RCT=randomized controlled trial; SD=standard deviation.
*Short term indicates three months; long term indicates 12 months or longer.
†In US dollars, 2023 reported average wholesale prices (does not account for potential insurance coverage).
‡Also recommended to prescribe a daily multivitamin with orlistat owing to resulting malabsorption of fat soluble vitamins.
§In clinical trials, no difference in serious adverse event rate was observed for active drug participants compared with placebo.

Antiobesity medications approved before 1999

The group of antiobesity medications approved before 1999 which are still available on the market is small and includes phentermine and the other older sympathomimetic amines (eg, phendimetrazine). Having been available on the market for over half a century, phentermine is currently the most widely prescribed antiobesity medication in the US because of its low cost; however, long term data to guide outcome comparisons with newer antiobesity medications are almost completely lacking. Of note, unlike newer antiobesity medications, phentermine is only FDA approved for three months of use, although recent guideline documents do provide guidance for longer term prescribing (as summarized later).

Antiobesity medications approved from 1999 to 2014

This group of antiobesity medications have varying mechanisms of action, reflecting an evolving understanding of obesity physiology during the period. The group includes orlistat, which blocks dietary fat absorption and was approved in 1999, the combination of phentermine and topiramate extended release approved in 2012, the combination of naltrexone and bupropion, and the glucagon-like peptide (GLP-1) receptor agonist liraglutide, both approved in 2014. These drug treatments are dosed daily or more frequently, and provide a wide range of average weight loss, as low as 3% and up to 11% depending on dose and duration of use. Importantly, two of the antiobesity medications in this category represent combinations of drug treatments which, when used alone in an off-label fashion, can independently promote weight loss. Topiramate, for example, was previously studied as a standalone antiobesity medication, but formal FDA approval for weight management was never sought. The doses used in the initial trials of topiramate monotherapy were as high as 192 mg daily and produced 6-8% placebo subtracted weight loss in patients with obesity.[44-46] In a 48 week clinical trial of bupropion monotherapy 300-400 mg daily for patients with obesity, the average weight loss in patients was 2.4-3.2% higher than placebo.[47 48]

Antiobesity medications approved in 2015 or later

This group of antiobesity medications, which includes those currently awaiting approval, contains highly effective drug treatments (mean weight loss 11-21%) that primarily target incretin pathways such as the GLP-1 receptor agonist semaglutide (approved for obesity in 2021), and the novel combination GLP-1 receptor agonist/glucose dependent insulinotropic polypeptide (GIP) receptor agonist tirzepatide

(approved for obesity in 2023). In their current formulations, these drug treatments (semaglutide and tirzepatide) are injected weekly, and in placebo controlled clinical trials, resulted in greater weight loss than was seen with older antiobesity medications. They are also substantially more expensive than older antiobesity medications. Several additional highly effective antiobesity medications and combinations that leverage nutrient sensitive hormone pathways are in late phase clinical trials, and will likely become available over the coming years. These antiobesity medications include oral versions of GLP-1 receptor agonists, which could be important for patients who are hesitant to use injectable drug treatment.

Antiobesity medications developed for the treatment of genetic syndromes resulting in obesity

The only drug treatment currently in this final category is setmelanotide. This agent is not approved for treatment of general obesity but is specifically useful in monogenic and syndromic obesity.

Overview of non-FDA approved options for obesity pharmacotherapy

Several drug treatments that are not specifically approved by the FDA as antiobesity medications have been found to cause weight loss in some people (table 2). Here, we summarize the existing evidence around weight loss efficacy and safety considerations

Table 2 | Overview of selected drug treatments used in an off-label fashion for weight loss

Generic name or class	Mechanism of action	Route of administration	Placebo subtracted % weight loss (95% CI) at 12-24 months	Proportion of patients achieving 5% weight loss at 12-24 months, %	Other weight loss estimates	Side effects	Contraindications	Cost for 1 month supply, $*	Ideal use case (special benefits)
Metformin	Multiple mechanisms, including AMPK dependent and AMPK independent mechanisms	Oral; options for daily or twice daily dosing	2.5 (95% CI, 1.7-3.3) in patients with pre-diabetes or diabetes[12]	43.2[12]		**Common**: nausea, vomiting, diarrhea **Possible/rare**: lactic acidosis in people with heart failure, kidney or liver disease, alcohol use disorders	Renal dysfunction; decompensated congestive cardiac failure; acute or chronic metabolic acidosis; impaired hepatic function	11-50	Patients with diabetes or pre-diabetes (**Polycystic ovary syndrome**)
Topiramate	GABAergic agent used for epilepsy, carbonic anhydrase inhibitor	Oral; options for daily or twice daily dosing	2.4-8.0 at 6 months depending on dose and study[49 50]	36-67	10% weight loss achieved by 29-44% of patients, depending on dose	**Common**: paresthesias, dysgeusia, cognitive dysfunction **Possible/rare**: glaucoma, nephrolithiasis	Pregnancy category X; consider avoiding in patients with glaucoma, nephrolithiasis	3-244	Patients with history of migraine headache or on antipsychotics and no risk of becoming pregnant (**Migraine prophylaxis; antipsychotic induced weight gain**)
Bupropion	Weakly inhibits neuronal reuptake of dopamine and norepinephrine. Mechanism leading to weight loss not fully understood	Oral; options for daily or twice daily dosing	2.8-3.2 in patients with major depression[51] at 26 weeks	40		**Common**: headache, dry mouth, insomnia, tachycardia, tremor, hypertension **Rare**: seizure, suicidal ideation	Seizure disorder or high risk of seizures; uncontrolled hypertension; hepatic cirrhosis; current or recent (<14 days) use of monoamine oxidase inhibitor	17-230	Patient with tobacco use disorder and/or depression and no history (**Depression, tobacco cessation**)[52]
SGLT2 inhibitor drug treatments (canagliflozin, dapagliflozin, and empagliflozin)	Reduces renal tubular glucose reabsorption, producing a reduction in blood glucose without stimulating insulin release	Oral; daily dosing	2.1 (95% CI, 1.1-3.0) in patients with diabetes	51.1		**Common**: nausea, fatigue, polyuria, polydipsia, and xerostomia **Possible/rare**: acute renal injury	Severe renal dysfunction	300-500	Patients with diabetes and heart failure who might have mild to moderate renal dysfunction (**Safe for use in patients with mild to moderate renal dysfunction**)
Lisdexamfetamine	Blocks the reuptake of norepinephrine and dopamine; primary approval for ADHD treatment	Oral; daily dosing	Unknown	Unknown	Average total weight loss in patients with binge eating disorder 3.1-4.3 kg at 11 weeks[53]	**Common**: Decreased appetite; headache nausea; upper abdominal or stomach pain; vomiting	Monoamine oxidase inhibitor use	100-400	Patients with obesity and binge eating disorder or ADHD (**ADHD treatment**)

ADHD=attention deficit hyperactivity disorder; AMPK=adenosine monophosphate activated protein kinase; CI=confidence interval; GABA=γ-aminobutyric acid; SGLT2=sodium glucose cotransporter 2.
*In US dollars, 2023 reported average wholesale prices (does not account for potential insurance coverage).

for some of these options. As noted above, guidelines generally recommend against the off-label use of these drug treatments exclusively for weight loss purposes.

Metformin

Metformin is a generic biguanide agent commonly used to treat type 2 diabetes, but it can also lead to modest weight loss (eg, 2.5% more than placebo).[12 54] Metformin is best used in patients with type 2 diabetes, pre-diabetes, or polycystic ovarian syndrome who are unable to tolerate or afford a GLP-1 receptor agonist.

Sodium glucose cotransporter 2 (SGLT2) inhibitors

SGLT2 inhibitors are drug treatments that are FDA approved for use in patients with type 2 diabetes, heart failure, and chronic kidney disease. They are associated with modest weight loss (eg, 2.1% more than placebo).[12] SGLT2 inhibitors could be particularly useful in patients with heart failure, for whom phentermine is contraindicated. Metformin can also be useful in patients with decompensated heart failure. In patients with diabetes, the glucose lowering properties of SGLT2 inhibitors could also help reduce doses of insulin, a known contributor to weight gain. Side effects of SGLT2 inhibitors include genitourinary tract infections and urinary frequency.

Lisdexamfetamine

Lisdexamfetamine is an amphetamine derivative, FDA approved for binge eating disorder and attention deficit hyperactivity disorder, and is associated with modest weight loss.[55] Lisdexamfetamine might be a preferred treatment for adults with obesity and binge eating disorder. Importantly, this is a Drug Enforcement Administration schedule II drug treatment (high potential for abuse), which has implications for restrictions on prescribing. Additionally, based on its mechanism of action, lisdexamfetamine has similar cardiovascular contraindications to phentermine.

Antiobesity medication use in practice: current patterns of use and real world evidence on effectiveness

Rates of antiobesity medication prescriptions tend to be specific to the clinician and the site of practice, with a subset of clinicians and certain sites prescribing a majority of antiobesity medications.[19 20 56] For example, in 2010, antiobesity medication prescription rates for US veterans with obesity ranged from 0-21% of eligible patients across 140 Veterans Health Administration facilities nationwide.[19] Clinicians who do prescribe antiobesity medications appear to frequently do so in an off-label fashion, with, for example, up to half of phentermine prescriptions lasting >3 months and one third lasting >1 year.[20] In surveys, physicians and advance practice providers describe several major barriers to prescribing antiobesity medications, including high costs and lack of insurance coverage, side effects, medication interactions, insufficient knowledge, lack of time for weight loss counseling, and a perceived lack of efficacy.[57-59] Longstanding bias and stigma towards patients with obesity is probably an important contributing factor as well. Providers might think that obesity represents a failure of character and that prescribing antiobesity medications is giving patients the "easy way out." Patients can have internalized stigma, blame themselves for their weight, and even avoid healthcare altogether[60-65] (table 3).

Observed effectiveness of antiobesity medication in real world settings

Most studies evaluating the real world effectiveness of FDA approved antiobesity medications are single arm retrospective observational studies that compare post-drug treatment weights with pre-drug treatment weights.[75 79] Two thirds of these studies were conducted in specialty weight management clinics or centers, where access to and knowledge of antiobesity medications is typically higher than in primary care settings. The majority were conducted in the US. Most of these studies were aggregated in two reviews published in 2021.[75 79] Twenty nine additional studies have since been published.[80-108]

In general, the efficacy of antiobesity medications persists in real world scenarios across many different groups of patients; however, estimated weight loss is highly variable between studies, even within a single antiobesity medication. In three long term studies evaluating the effectiveness of taking any antiobesity medication at any dose, weight loss was 2.2-9.3% at 12 months and 10.5% at 24 months.[83 84 109] A common finding was that patients experienced greater weight loss when they consistently took their prescribed antiobesity medications. However, many patients stop using antiobesity medications over time owing to lack of effectiveness, side effects, or difficulty obtaining them because of inadequate insurance coverage and high cost.[75] Long term efficacy estimates in real world settings could reflect a selection for those patients who find the drug treatments useful and are able to acquire them consistently.

Phentermine

Most studies evaluating the effectiveness of phentermine in clinical practice have followed patients for only three months.[29 34 110-116] Total percentage weight loss in these studies was widely divergent, ranging between 2.1-12.8%,[29 34 111-113 115] and similarly, estimated rates of clinical response (proportion of patients experiencing ≥5% weight loss) were also broad, ranging from 21-97%.[29 34 110 111 114] Limited observational data suggest that patients who remain on phentermine for longer than three months are generally able to maintain their weight loss. In a study of 13 972 US patients with obesity who took phentermine for up to two years, those who consistently took phentermine for ≥1 year had an average weight loss of 7.5% two years after initiation.[33]

Naltrexone-bupropion

In a single large study evaluating the effectiveness of naltrexone-bupropion in multiple US primary care

Table 3 | Barriers to evidence based prescribing of antiobesity medications in clinical practice

Barrier	Pertinent data	Possible solutions
Cost of drug treatments, limited insurance coverage, and supply chain problems	• Insurance coverage of antiobesity medications in the US is highly variable and is not required by law.[66-69] • In 2015-2016, among 7378 adults surveyed about their employer based insurance, 21% reported having coverage for antiobesity medications.[66] • As of 2017, only 16 out of 50 state Medicaid plans cover ≥1 antiobesity medication.[68] Medicare Part D does not cover treatment with any FDA approved antiobesity medications at all. • The GLP-1 receptor agonists liraglutide and semaglutide are particularly expensive, costing $324-1619/month before insurance.[70 71] • No consensus exists on the healthcare cost impact of long term antiobesity medication use. Different studies have used various assumptions, with some estimating substantial savings in healthcare costs, while others estimate a net cost increase.[69 72] • Shortages in availability of newer medications have made it difficult to initiate and consistently maintain patients on these treatments as they are first coming to market[73]	• Drug prices are expected to fall as additional highly effective antiobesity medications enter the market in the coming years. • Prices will fall further as the drugs come off patent and become available as generics. Liraglutide is expected to come off patent within the next five years. • States, payers, and employers are increasingly considering and expanding coverage for antiobesity medications
Concerns about safety of long term antiobesity medication use	• Clinicians' concerns about side effects[59] might be related to the recall of several antiobesity medications owing to increased risk of valvular heart disease and pulmonary hypertension (fenfluramine), stroke and myocardial infarction (sibutramine), and cancer (lorcaserin).[74] • In real world effectiveness studies of currently approved antiobesity medications, most adverse events are reported as mild and moderate. That said, how frequently side effects are severe enough to lead to discontinuation is unclear from these studies.[75] • Long term safety of antiobesity medications outside of clinical trials is not well understood[75 76]	• Ongoing clinical trials investigating cardiovascular outcomes and longer term safety of antiobesity medications will likely help reduce concerns. • Additional postmarketing surveillance studies will likely be conducted in the coming years
Lack of clinician awareness/ education	• Primary care physicians' knowledge of obesity guidelines is poor. In one survey of 1506 primary care physicians, only 8% could correctly identify guideline recommended weight and weight loss criteria for starting and continuing antiobesity medications[77]	• Educational interventions that aim to improve clinical knowledge of obesity and its treatment options have been shown to increase comfort with counseling about and prescription of antiobesity medications.[78]
Antiobesity stigma and bias	• Implicit and explicit bias against people with obesity is widespread among physicians, nurses, students, and nutritionists,[62-64] owing to a belief that obesity is primarily caused by poor behavior. • Even obesity specialists who were surveyed at an obesity related medical conference in 2013 revealed implicit and explicit bias, pairing words like "bad" and "lazy" with "obese."[65] These biases have real implications for the care that patients receive. For example, clinicians perceive patients with higher body mass index to have lower drug treatment adherence,[61] and therefore, could be reluctant to prescribe antiobesity medications. • In audiorecorded visits, clinicians provide less empathy, legitimation, and reassurance to patients with overweight and obesity[60]	• Various groups are developing interventions and trainings for healthcare providers to help identify and mitigate bias and stigma

FDA=Food and Drug Administration; GLP-1=glucagon-like peptide-1.

and specialty clinics affiliated with an academic medical center, at three months, the observed percentage weight loss was 2.7%, and 29% of patients had achieved ≥5% weight loss.[112]

Orlistat

In 13 observational studies conducted on four continents,[34 80 117-126] percentage weight loss with orlistat ranged from 2.2-5.0% at three months[34 121 123] and 4.6-10.7% at six months.[34 118 120-122] The proportion of patients achieving ≥5% weight loss in these studies was 22-38%[121 123] at three months, with more variability in this metric at six months (14-51%).[118 124]

Liraglutide

In 17 observational studies evaluating liraglutide's real world effectiveness across North America, East Asia, Europe, and the Middle East,[80 82 85-92 127-133] percentage weight loss ranged from 4.8-9.2% at 4-6 months[85 87 88 90-92 129 130 132 133]; the proportion of patients achieving ≥5% weight loss was 32-44% at three months[130] and 40-65% at six months.[86 127 129] Adherence to liraglutide in real world studies is generally higher than to other antiobesity medications,[80 85-88 90-92 127-132 134] although direct comparisons are difficult to make because of variation in the ways adherence was measured across studies.

Semaglutide

The effect of semaglutide on weight loss has also been evaluated as a secondary outcome in observational studies among patients with type 2 diabetes,[95-105 107 108] where the primary outcome was HbA_{1c}. Among studies reporting this outcome, percentage weight reduction ranged from 2.2-7.5% over 9-18 months of follow-up.[95-108] Only one retrospective study has evaluated weight loss as a primary outcome among patients with obesity without type 2 diabetes. This study[94] used electronic health record data at one academic health system to evaluate 175 patients with obesity who took semaglutide for ≥3 months. Mean weight loss was 5.9% at three months and 11% at six months. The proportion of patients achieving ≥5% weight loss was 54% at three months and 55% at six months. Weight loss was significantly lower among patients with type 2 diabetes, consistent with findings from clinical trials. Only 3% of patients discontinued the drug owing to gastrointestinal side effects. Of note, 148 out of 408 patients who were initially prescribed semaglutide were excluded from the study because they could not access the drug treatment, owing to either insurance denials or pharmacy shortages.

Comparative effectiveness studies

Randomized trials

Because of their high financial and time costs, limited evidence has been published to date from

randomized trials comparing the effectiveness of different antiobesity medications head-to-head. One trial of 338 adults with overweight or obesity and without type 2 diabetes found that once weekly subcutaneous semaglutide resulted in significantly greater weight loss at 68 weeks compared with once daily subcutaneous liraglutide[135] (-15.8% with semaglutide *v* -6.4% with liraglutide (difference -9.4 percentage points (95% confidence interval -12.0 to -6.8), P<0.001)). These findings are consistent with other randomized trials of patients with type 2 diabetes,[136-138] where patients receiving semaglutide had better improvement in weight and HbA_{1c} than those receiving liraglutide. Another randomized trial including 756 adults found that the combination phentermine-topiramate 7.5 mg/46 mg (-8.5%) and 15 mg/92 mg (-9.2%) achieved greater weight loss versus placebo (P<0.0001) and their respective monotherapies (P<0.05) at 28 weeks.[139]

Network meta-analyses

A systematic review and network meta-analysis (search date March 2021) identified 143 trials that enrolled 49 810 participants.[12] The main findings were that placebo subtracted percentage weight loss was highest with phentermine-topiramate (-7.97%; 95% confidence interval -6.7 to -9.3) and GLP-1 receptor agonists (-5.8%; -5.2 to -6.3). In a post hoc analysis that separated the GLP-1 receptor agonists, percentage weight loss was higher for semaglutide (-11.4%; -10.3 to -12.5) than for liraglutide (-4.7%; -4.1 to -5.3). Phentermine-topiramate and naltrexone-bupropion had the highest risk of adverse events leading to discontinuation. A recent analysis of SURMOUNT-1 and STEP 1 trial data concluded that tirzepatide was likely more effective than semaglutide.[140]

Real world comparative effectiveness data

We found insufficient data from observational comparative effectiveness research designs to understand the real world treatment effectiveness and safety of antiobesity medications.[80] More research is needed to help inform treatment decisions in populations that are not typically included in clinical trials, such as those with multiple comorbidities and advanced age.

Cost effectiveness studies

Cost effectiveness analyses use modeling strategies to estimate the value of alternative treatment strategies and relate them on a cost per quality adjusted life year (QALY) scale. A cost effectiveness analysis comparing semaglutide 2.4 mg weekly with three other antiobesity medications (liraglutide 3 mg, phentermine-topiramate, and naltrexone-bupropion)[141] found that semaglutide 2.4 mg was cost effective compared with all other comparators, with the incremental cost per QALY gained ranging from $23 556 to $144 296. A separate model compared costs and outcomes of seven weight loss strategies plus no treatment for five years. The treatments included intensive lifestyle intervention, orlistat, phentermine, phentermine-topiramate, lorcaserin, liraglutide, and semaglutide.[142] Phentermine was found to be the most cost effective strategy, followed by semaglutide, with all other treatment options being dominated by these options (more effective and cheaper). Finally, another model found that phentermine-topiramate in addition to lifestyle modification was the most cost effective option, particularly when prescribed generically.[143] The model also reported that, at current prices in the US, the cost effectiveness of semaglutide or liraglutide in patients without type 2 diabetes exceeded commonly used cost effectiveness thresholds. The health benefit price benchmark for semaglutide (defined as the price range that would achieve incremental cost effectiveness ratios between $100 000 and $150 000 per QALY gained), was estimated at $7500 to $9800 per year, which would require a discount from the wholesale acquisition cost of 44-57%. Given the variability in modeling approaches used across studies and the strong assumptions necessary to conduct these models, further research is necessary before firm conclusions can be drawn about the most cost effective approach to prescribing antiobesity medication.

Remaining gaps in evidence and call to action for future research

Personalized treatment approaches to antiobesity medication prescribing

As is true with other forms of obesity treatment, patient response to antiobesity medications is highly variable. Ideally, clinicians would select the antiobesity medication most likely to lead to clinically significant weight loss in a given patient.[144] The choice is easy in patients with specific forms of monogenic or syndromic obesity where setmelanotide is uniquely beneficial.[145] Unfortunately, the published research is not sufficient to accurately predict individual response to antiobesity medications. However, several principles can be used in clinical practice to make an initial selection of antiobesity medication. First is a consideration of how secondary effects of drug treatments might be beneficial to individual patients (table 1). For example, naltrexone-bupropion might be preferred for a patient with depression, binge eating, or food cravings.[146 147] Phentermine-topiramate extended release might be useful in patients who have another indication for topiramate, such as peripheral neuropathy or migraine headaches. GLP-1 receptor agonists are particularly useful in people with type 2 diabetes. Some evidence suggests that phentermine might be more effective in people who eat excessively owing to hunger (as opposed to emotional stress, boredom, etc).[148] While clinicians can and do use these generalizations, few studies have specifically evaluated the effectiveness of antiobesity medication in these subpopulations.

Another important question for healthcare systems is how to balance effectiveness and cost, given the

large number of people who could potentially benefit from antiobesity medications. Newer antiobesity medications reliably produce more weight loss than older drug treatments, but they cost substantially more. It might not be financially viable in the short term to provide insurance coverage for the newest, most effective drug treatments for all eligible patients. Therefore, it could be seen as reasonable to use the older, less expensive drug treatments in patients with lower body mass index or those without extensive comorbid conditions. Since some individuals will have an excellent response to older drug treatments, it could also be reasonable to try these first, and reserve newer, more effective drug treatments for those who are "non-responders" to older drug treatments and/or need more weight loss for health benefits. For example, patients with a lower body mass index might not need the 15% or 20% weight loss that are more likely to be produced by newer drug treatments. Current guidelines have focused broadly on which patients should be offered treatment for obesity. A consensus on weight loss targets has not yet emerged, other than an established minimum of 5% weight loss.

Combination therapy

In light of the multiple neuroendocrine pathways governing body weight and appetite,[11] a single agent pharmacotherapy approach is likely inadequate to support durable, clinically significant weight loss for all patients. In a nod to this idea, current antiobesity medications in the pipeline include dual agonist and triple agonist agents, drugs that simultaneously target multiple pathways (eg, tirzepatide, which targets GLP-1 receptor agonist and GIP receptor agonist)[43] in an attempt to circumvent these natural redundancies.[149-152]

Whether currently available (and possibly generic, more affordable) agents might be combined in a stepwise, off-label fashion to produce greater total weight loss or more durable weight loss has not been rigorously studied. Given a lack of research on this topic, modern obesity treatment guidelines state that, while promising, off-label combination therapy is not recommended.[153] By contrast, modern treatment guidelines for type 2 diabetes[154] and essential hypertension[155] (also nutrition related chronic diseases), do recommend a stepped care approach to pharmacotherapy. In some cases, guidelines even recommend starting combination therapy as an initial approach to facilitate the more rapid achievement of glycemic or blood pressure targets.

In practice, the lack of a clear guideline around combination therapy for obesity presents a conundrum: how should providers manage a patient who had an initial clinically significant response to a single agent (eg, liraglutide), but has subsequently plateaued or begun to regain weight after longer term exposure? Should the agent be discontinued in favor of another; or, similarly to how we approach hypertension or type 2 diabetes, should an additional agent targeting a different pathway be started? These are critical questions that should be answered as part of future research priorities on antiobesity medications.

Weight loss maintenance

Another unanswered question in obesity medicine is how best to manage antiobesity medications during weight loss maintenance. Increasingly, clinical trials of antiobesity medications follow patients up to 2-3 years after initiation of a drug treatment, and have provided strong evidence that clinically significant weight loss is maintained so long as patients stay on the drug treatment.[38] Following a 20 week run-in on semaglutide, the STEP 4 trial randomized participants to remain on study drug versus placebo until week 68. Those who remained on active drug lost an additional 8% of their body weight, while those on placebo regained 7%, for a final difference between groups of 15% body weight.[156] Thus, much as has been observed for lifestyle interventions,[157] weight regain seems a foregone conclusion for patients who discontinue obesity treatment, including antiobesity medications. Guidelines recommend the long term use of antiobesity medication, yet the practical, clinical, and economic implications of this recommendation are unknown. In particular, the long term safety implications of taking these drug treatments beyond a few months to a few years are not yet known. Long term safety is an important area for future research, especially as antiobesity medication use is increasing among young adults and even adolescents. Additionally, with an average wholesale price of $1619 to $2023 per month,[158] the indefinite use of semaglutide for all but the most economically advantaged patients would present an enormous financial strain under current payment models.[159] Substantial changes to the way payers cover these drug treatments, and/or major reductions in price for the drugs by pharmaceutical companies, could make the widespread long term use of GLP-1 receptor agonists and similar drugs more feasible in the future.

Key research and policy questions that must be resolved moving forward include whether more affordable (albeit likely less efficacious) antiobesity medications, a cycling on/off approach, or a lower dose antiobesity medication could be used for weight loss maintenance; and if so, when best to initiate a trial of these strategies, and in which patients.

Outcomes beyond percentage weight loss

Historically, one challenge to broader uptake of antiobesity medications has been the lack of randomized trial evidence showing that these treatments reduce adverse health outcomes. Recently, however, the SELECT trial reported a 20% reduction in the risk of cardiovascular events with semaglutide 2.4 mg versus placebo over a mean duration of treatment of 34 months among 17 604 patients 45 years of age or older who had pre-existing

cardiovascular disease and a body mass index of 27 or greater but no history of diabetes.[160] A primary cardiovascular endpoint event occurred in 569 of the 8803 patients (6.5%) in the semaglutide group and in 701 of the 8801 patients (8.0%) in the placebo group (hazard ratio 0.80; 95% confidence interval 0.72 to 0.90; P<0.001). Adverse events leading to permanent discontinuation of the trial product occurred in 1461 patients (16.6%) in the semaglutide group and 718 patients (8.2%) in the placebo group (P<0.001).

Another recent study showed that semaglutide 2.4 mg resulted in improvements in symptoms and walking time in people with heart failure and preserved ejection fraction[161] and another analysis showed a reduction in the risk of developing type 2 diabetes.[162] Additional studies are needed to investigate the impact of antiobesity medications on other weight related health outcomes, such as non-alcoholic fatty liver disease and cancer. Another ongoing trial is looking at cardiovascular outcomes of tirzepatide, with results expected in the next 1-2 years.

Along with this line of research, there might need to be a shift in the view of how we define success for a patient following antiobesity medication prescribing. The threshold for clinically significant response to antiobesity medication has traditionally been narrowly defined as 5% weight loss at three months after initiation[11]; however, this goal might not be appropriate for all patients. For example, weight stability and improvement in HbA_{1c} could be a reasonable clinical goal after initiating an antiobesity medication in a patient with pre-diabetes who was previously gaining weight. Similarly, weight stability and improved appetite control in a post-bariatric patient trying to maintain surgical weight loss could also be a clinically significant outcome from initiating antiobesity medication therapy.

Emerging treatments

The arrival of semaglutide and tirzepatide is just the beginning of what promises to be a growing armamentarium of highly effective antiobesity medications. Many drugs in the pipeline are based on incretin hormones which have been found to be useful in the management of type 2 diabetes.[163] While most GLP-1 receptor agonists have been given by injection, a number of newer agents can be delivered orally. A 50 mg oral formulation of semaglutide recently was shown in a phase 3 trial to produce a 12.7% placebo subtracted weight loss from baseline to week 68.[164] Recent phase 2 data on orforglipron, an oral non-peptide GLP-1 receptor agonist given at doses ranging from 12-45 mg/day, produced 7.1-12.4% greater weight loss than placebo at 36 weeks.[165] Danuglipron is another oral small molecule GLP-1 receptor agonist that is undergoing phase 2 trials for the treatment of both obesity and type 2 diabetes.[166]

Tirzepatide is the first approved dual agonist. Dual agonists are single peptide molecules that contain domains conveying receptor agonism for two different receptors, in this case GLP-1 and GIP. Tirzepatide is currently approved for use in type 2 diabetes and obesity. Weight loss with tirzepatide is being evaluated in the SURMOUNT studies. SURMOUNT 1 tested tirzepatide at 5, 10, or 15 mg weekly for 72 weeks, and found that the 15 mg formulation produced a 17.8% placebo subtracted weight loss, and 56.7% achieved >20% weight loss.[167] SURMOUNT 2 tested tirzepatide in people with type 2 diabetes, and at 72 weeks found a slightly lower (11.5%) placebo subtracted weight loss.[168] In SURMOUNT 3, subjects who lost >5% with an intensive lifestyle intervention were randomized to placebo, 10 mg, or 15 mg tirzepatide weekly. After 72 weeks, the placebo subtracted weight loss in the 15 mg group was 19.9%, with a total placebo subtracted weight loss including the lifestyle intervention of 22.8%.[169]

Evidence of the effectiveness of tirzepatide has encouraged the development of other dual agonists, including three GLP-1 receptor agonist/glucagon dual agonists: mazdutide (IBI362 or LY3305677),[170] survodutide (BI456906),[171] pemvidutide (ALT-801), and cotadutide.[172] The fact that multiple large pharmaceutical companies from the US, Europe, Japan, and China all have dual agonists in late phase 2 and early phase 3 programs suggests that dual agonists will be a competitive segment of the market, and gives hope for a range of treatment options and lower prices in the future.

Retatrutide is the first triple agonist with activity directed at GLP-1, glucagon, and GIP receptors.[172] Recent phase 2 trial data on retatrutide administered at doses of 1-12 mg weekly for 48 weeks showed a placebo subtracted weight loss ranging from 6.6-22.1%.[173] In this study, 48% of participants on the highest dose lost >25% of baseline weight and 26% lost >30%. SAR441255 is another triple agonist currently in early human trials.[174]

Pramlintide is an amylin analog that is FDA approved for the treatment of type 2 diabetes, and was studied but never FDA approved as an antiobesity medication. A newer long acting acylated amylin analog named cagrilintide has been studied alone and in combination with semaglutide for the treatment of obesity. In a study of patients with overweight or obesity, the combination of cagrilintide 4.5 mg plus semaglutide 2.4 mg per week produced a 15.4% reduction in body weight at 20 weeks.[152] That study had no placebo arm, and participants were instructed not to change their diet or physical activity. In a more recent study in subjects with type 2 diabetes, this combination produced a 15.6% weight loss at 32 weeks. This study also had no placebo group.[175]

The large weight losses seen with newer highly effective antiobesity medications have raised concerns about the potential for a loss of lean body mass. Results from the STEP 1 trial of semaglutide suggested that 40% of total weight loss was derived from lean mass.[42] In response to this concern, new drug treatments are being examined that could help to maintain lean body mass in the context of weight

loss therapy. Several agents acting in the myostatin/activin A pathway, which regulates skeletal muscle mass, are being tested with this goal in mind. Bimagrumab, a monoclonal antibody that blocks the activin type II receptor, is administered by infusion every four weeks. A 48 week trial of bimagrumab treatment in subjects with obesity and type 2 diabetes produced 6.5% overall weight loss, but with a small increase in lean mass.[176] Additional agents with related mechanisms of action that are in the drug development pathway (phase 2 or earlier) include apitegromab, taldefgrobep, and the mitochondrial uncoupling agent HU6. Whether and when these agents will progress to approval for broad use in patients with obesity is not yet clear.

Many other drug treatments that make use of other mechanisms are in preclinical and phase 1 testing, suggesting that this is only the beginning of a period of remarkable growth in antiobesity medications. Unfortunately, very few of these new agents are currently being tested in children and adolescents.

Guidelines

Over the past decade, several professional societies and even nations have issued clinical guidelines that directly deal with the use of antiobesity medications. In 2013, The Obesity Society, the American Heart Association, and the American College of Cardiology together issued a comprehensive obesity treatment guideline document.[177] While expansive in detail on lifestyle interventions and bariatric surgery, this document was limited with respect to antiobesity medications. An expert recommendation was made for when to initiate antiobesity medications, stating that FDA approved antiobesity medications could be considered as adjunctive treatment for adult patients with body mass index ≥30 or ≥27 with a weight related comorbidity, who were unable to lose weight or sustain weight loss with lifestyle intervention alone. Additionally, it was recommended to consider discontinuation of antiobesity medications in patients not losing at least 5% of their body weight after 12 weeks of treatment. In 2015, following FDA approval of two new antiobesity medications for long term use, the Endocrine Society released its own guidelines outlining the same antiobesity medication initiation criteria as earlier guidelines, but also recommended continuation of antiobesity medications during weight loss maintenance, and suggested a more detailed plan for antiobesity medication monitoring.[11] The Endocrine Society advised against off-label prescribing of drug treatments indicated for other purposes solely to achieve weight loss. Lastly, this guideline allowed for off-label, long term (>3 months) prescribing of phentermine, for patients deemed safe candidates.

In 2016, the American Association of Clinical Endocrinologists and the American College of Endocrinology also issued clinical practice guidelines for obesity.[153] Although largely aligned with earlier documents, these guidelines explicitly recommended against the short term use of antiobesity medications (eg, 3-6 months) owing to lack of durable health benefits. In 2020, Canada issued its own obesity treatment guidelines which have since been replicated in other countries.[178] The Canadian guidelines primarily differ from US based documents in that recommended antiobesity medication options do not include phentermine or phentermine containing compounds, which are unavailable in that country. Finally, in 2022, the American Gastroenterological Association published the most recent guidelines on the pharmacotherapy of obesity.[10] These guidelines are the first to make priority recommendations for antiobesity medication selection on the basis of available evidence from individual agent trials, explicitly recommending the use of semaglutide 2.4 mg because of the magnitude of clinical benefit. The American Gastroenterological Association guidelines next prioritize liraglutide 3.0 mg, followed by phentermine-topiramate, and then naltrexone-bupropion. Like the Endocrine Society, the American Gastroenterological Association guidelines also allow for off-label long term phentermine prescribing, while acknowledging the low quality of evidence in this space. Importantly, they advise against the use of orlistat as an antiobesity medication, given the modern available options that are superior and better tolerated. A summary approach to prescribing FDA approved antiobesity medications based on existing guidelines is provided in figure 1.

It should be noted that, given the expanding array of available antiobesity medication options, treatment guidelines from just 5-10 years ago are already becoming out of date. Most reviews on adult antiobesity medications from high profile groups are also out of date, and do not reflect the available evidence on the most recent antiobesity medication options.[179-182] With more antiobesity medications in the pipeline targeting novel pathways, more frequent updates to clinical guidance documents are needed to ensure safe and equitable antiobesity medication prescribing. Additionally, evidence synthesis groups like Cochrane and USPSTF have an important role, as they can more regularly revise systematic reviews and meta-analyses as new trial results are published.

Conclusions

Obesity is a serious and growing public health problem in the US and around the world. Pharmacotherapy has historically been viewed by many physicians as a fringe treatment, resulting in the persistence of "eat less, move more" advice that fails to produce durable weight loss for most patients. This perception has been reflected in the underuse of antiobesity medications by a minority of clinicians. However, the advent of newer, highly effective antiobesity medications has brought pharmacotherapy of obesity into the mainstream, and patients are increasingly asking their physicians for advice on these drug treatments. Prescription rates are increasing rapidly, leading to challenges in maintaining drug treatment supply.[183] New antiobesity medications are on the horizon and will provide levels of efficacy that were

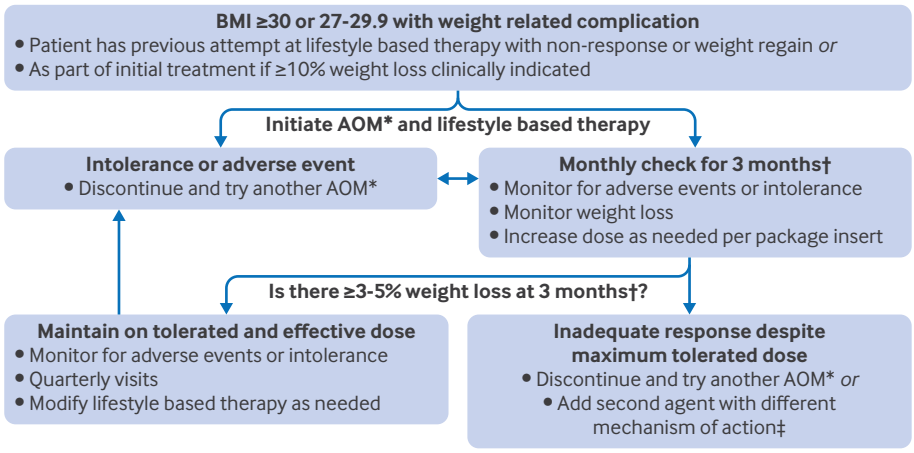

Fig 1 | A guideline informed strategy for antiobesity medication prescribing. AOM=antiobesity medication. *After factoring in patient comorbidities, preferences, and affordability/insurance coverage, clinicians could consider prioritizing based on expected weight loss, such as: - GLP-1 receptor agonist (semaglutide/liraglutide (semaglutide produces more weight loss on average than liraglutide)) or dual agonist (tirzepatide) - Phentermine-topiramate extended release - Bupropion-naltrexone sustained release - Phentermine monotherapy or similar (if patient is an appropriate candidate and in concordance with regulations and guidelines in your institution or location) - Orlistat (if patient is unable to take other, more effective drugs) †Depending on tolerability, some drug treatments can take longer than three months to reach full dosing. In these cases, longer monitoring for weight loss and adverse events is indicated. ‡Current guidelines do not specifically advise this additive approach to pharmacotherapy; however, the approach could be reasonable with individual patients under the care of an obesity medicine specialist (provided that the second agent is well tolerated, affordable, sustainable and appears to benefit the patient). Further research is needed in this area to guide general practice

previously only seen with bariatric surgery. The hope is that competition will bring down the cost of these drug treatments over time, and insurance companies will gradually provide coverage for antiobesity medications much as they do for new drug treatments for other chronic metabolic diseases such as diabetes and hyperlipidemia. Clinicians should work to become comfortable having comprehensive yet efficient conversations with their patients about the benefits and drawbacks of antiobesity medications. Major research gaps remain around examining the optimal clinical definition of obesity that warrants antiobesity medication treatment, the comparative effectiveness of antiobesity medication for outcomes beyond weight loss, the utility of combination therapy, determining how to personalize treatment for individual patients, and showing the cost effectiveness of antiobesity medications.

KEY QUESTIONS FOR FUTURE RESEARCH ABOUT ANTIOBESITY MEDICATIONS

Outcomes beyond weight loss:
- Do antiobesity medications contribute to improved health outcomes beyond weight loss, such as reducing cardiovascular events or mortality?
- Can antiobesity medications affect other weight related health conditions, such as non-alcoholic fatty liver disease and cancer?

Predicting response to antiobesity medications:
- Can individual patient responses to various antiobesity medications be accurately predicted?
- Do specific subpopulations that respond better to certain antiobesity medications?

Balancing effectiveness and cost:
- What is the optimal approach to balance the effectiveness of newer, more expensive antiobesity medications with their high cost of treatment?
- Should older, less expensive antiobesity medications be considered for certain patient groups, and if so, which criteria should guide this selection?

Combination therapy:
- Is it beneficial to combine different antiobesity medications to achieve greater weight loss or maintain long term results?
- How should patients best be transitioned to combination therapy when a patient plateaus on a single antiobesity medication?

Comparison against metabolic/bariatric surgery:
- Are newer antiobesity medications more effective and/or safer than metabolic/bariatric surgery for treating patients with severe obesity?

Weight loss maintenance:
- How can weight loss be effectively maintained in the long term with antiobesity medications?
- Is there a role for more affordable antiobesity medications, cycling on/off approaches, or lower dose antiobesity medications in weight loss maintenance?

Redefining success:
- Should the definition of success with antiobesity medications be individualized, considering factors like weight stability, improved HbA_{1c}, or appetite control?
- How can success criteria be adapted to better meet the unique needs of different patient populations?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

To inform the development of a manuscript that helps clinicians better deal with patients' needs and questions about antiobesity medication use, we consulted patient experts representing individuals with the lived experience of obesity. The Obesity Action Coalition (OAC), a patient advocacy organization based in the United States, was contacted by the authors with a request for help in identifying people living with obesity who might be willing to provide input for this review. The four people listed in the contribution section were identified with the help of the OAC, and they reviewed a draft manuscript and provided input. These people emphasized the importance of recognizing obesity as a chronic disease, the profound impact that stigma and bias play in the ability of people living with obesity to get treatment, and the need for access to antiobesity medications by improving provider comfort with prescribing and insurance coverage.

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