What are the pros and cons of weight loss medications?

January 19, 2016

Background

Weight gain and obesity are issues of great concern, affecting >140 million adults (or two-thirds of adults) in the United States (US).[1] These issues are also affecting children and adolescents at an increasing rate. According to Wang et al, the obesity/weight gain epidemic is projected to affect 80% of US adults by 2020, and the prevalence of these conditions in children and adolescents is expected to double by 2030.[2] In the US, the prevalence of obesity varies by gender, race, and ethnicity.[1] The highest prevalence has been noted among non-Hispanic black women. Those from families of low-education (less than high-school) are also thought to be at greater risk for obesity, as are patients of older age (maximum prevalence reached at the age of 80 years).

Obesity and weight gain result from an increase in energy storage (i.e., fat) due to an imbalance between energy intake and expenditure over time.[1] Imbalance may be attributed to several causes, including genetic and environmental factors, medical conditions, and use of certain medications. Several genetic mutations have been identified as potential contributors to extreme obesity; however, these mutations are rare, accounting for a small proportion of obesity cases. Other alleles and contributing genes are under investigation. With regard to the environment, obesity has been more frequently observed among individuals with a close social network, particularly if a member of the network is obese. Cultural factors, socioeconomic status, and religious beliefs may also influence dietary habits and contribute to issues with body weight. Several medical conditions have been associated with weight gain, including Cushing's syndrome, growth hormone deficiency, hypothyroidism, and psychiatric conditions such as depression, binge-eating disorder, and schizophrenia. Several medications have also been associated with weight gain. These include anticonvulsants (e.g., carbamazepine, gabapentin, pregabalin, valproic acid), antidepressants (e.g., tricyclic agents), atypical antipsychotics (e.g., clozapine, olanzapine, quetiapine, risperidone), conventional antipsychotics (e.g., haloperidol), and hormones (e.g., corticosteroids, insulin, medroxyprogesterone). The mechanism by which drugs may cause weight gain is specific to the agent used; for most drugs, the specific mechanism is unknown.

Treatment options

There are several options for treatment of obesity, including nonpharmacologic options, such as lifestyle interventions and procedures (i.e., bariatric surgery), and medications.[1] Lifestyle interventions include behavioral therapy, reduction in caloric intake, and increase in physical activity. Medications approved by the Food and Drug Administration (FDA) to treat obesity may be seen in Table 1. Most of the available medications target appetite mechanisms and promote satiety.[3] The exceptions are orlistat, which inhibits fat absorption through reversible inhibition of gastric and pancreatic lipases,[4] and sodium-glucose co-transporter-2 [SGLT-2] inhibitors, which promote weight loss by preventing reabsorption of glucose and water in renal tubules.[3] With regard to bariatric surgery, there are several procedures, all of which promote weight loss by restricting or reducing food intake through reduction of stomach volume, or by malabsorption through reduction in the absorptive area of the gastrointestinal tract.[1]

Table 1. FDA-approved drugs for treatment of obesity.[3-11]

Generic name (trade name)	Mechanism of action	FDA-approval	Maximum dosage, administration	Mean weight loss and study duration
Bupropion ER/ naltrexone (Contrave®)	Bupropion: reuptake inhibitor of dopamine and norepinephrine Naltrexone: opioid antagonist	2014; chronic weight management	360 mg/32 mg total daily dose (2 tablets PO BID)	4.8% 1 year
Diethylpropion (Tenuate®)	Norepinephrine-release	1960s; short-term use (3 months) for weight loss	75 mg PO daily	3.0 kg 6 – 52 weeks
Liraglutide (Saxenda®)	GLP-1 agonist	2014; chronic weight management	3 mg SC daily	5.8 kg 1 year
Lorcaserin (Belviq®)	5-HT_{2c} receptor agonist	2012; chronic weight management	10 mg PO BID	3.6 kg 1 year
Orlistat (Xenical®, Alli®)	Pancreatic and gastric lipase inhibitor	1999; chronic weight management (Alli®: OTC, Xenical®: Rx)	Xenical®: 120 mg PO TID Alli®: 60 mg PO TID	2.9 – 3.4 kg 1 year
Phentermine (Adipex-P®)	Norepinephrine-release	1960s; short-term use (3 months) for weight loss	37.5 mg PO daily	3.6 kg 2 – 24 weeks
Phentermine/ topiramate ER (Qsymia®)	Phentermine: norepinephrine release Topiramate: GABA receptor modulation	2012; chronic weight management	15 mg/92 mg PO daily	6.6 – 8.6 kg 1 year

5-HT=5-hydroxytryptamine (serotonin); BID=twice daily; ER=extended-release; GABA=gamma-aminobutyric acid; GLP-1=glucagon-like peptide-1; OTC=over the counter; PO=by mouth; Rx=prescription; TID=3 times daily

Guideline recommendations

Multiple organizations have published clinical practice guidelines on the management of overweight and obese patients. In 2013, the American College of Cardiology/American Heart Association (ACC/AHA), in collaboration with The Obesity Society (TOS), published guidelines for management of weight in adult patients.[12] More recently, in 2015, guidelines were issued by the Endocrine Society (ES), co-sponsored by TOS and the European Society of Endocrinology,[3] and the Canadian Task Force on Preventive Health Care.[13] The ACC/AHA/TOS and Canadian Task Force recommend identification of patients who need to lose weight using measurements of height and weight, to calculate body mass index (BMI), and waist circumference.[12,13] Patients at increased risk for cardiovascular disease and mortality include those who are overweight (BMI 25 to 29.9 kg/m^2) and obese patients (BMI ≥30 kg/m^2). All 3 guidelines recommend lifestyle interventions as first-line treatment for most patients who are overweight or obese.[3,12,13] These include comprehensive lifestyle programs or weight maintenance programs, reduction in caloric intake to 1,200 to 1,500 kcal/day for women and 1,500 to 1,800 kcal/day for men, and 30 minutes of moderate-intensity activities on most days of the week.

With regard to pharmacologic therapy, the recommendations of the aforementioned organizations slightly differ. The ACC/AHA/TOS chose not to assess the evidence, considering only 1 medication approved by the FDA for weight loss (orlistat) at the time of preparation.[12] However, on the basis of expert opinion, they state that pharmacotherapy could be considered as an adjunct to lifestyle interventions in patients with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 obesity-associated comorbidity who are motivated to lose weight. Their rationale was that medications could reinforce lifestyle changes by helping patients to adhere to a lower-calorie diet more consistently.

The Canadian Task Force recommends that practitioners **not** routinely offer pharmacotherapy aimed at weight loss.[13] The medications they reviewed were orlistat and metformin. The Canadian Task Force further states that there are several concerns with the use of weight loss medications; citing a meta-analysis of clinical trials involving pharmacotherapy and behavioral therapy, they determined that patients using pharmacotherapy were more likely to experience adverse events and withdraw from therapy due to adverse events.

Similar to the ACC/AHA/TOS, the ES recommends the use of FDA-approved weight loss drugs in patients with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 obesity-associated comorbidity (specifically, hypertension, dyslipidemia, type 2 diabetes mellitus [T2DM], or obstructive sleep apnea).[3,12] Per the ES, medications may improve comorbidities, increase adherence to behavioral changes, and allow for greater physical activity in these patients.[3] If medication is prescribed, the ES suggests initiating therapy at a lower dose and increasing the dose as tolerated to the manufacturer-recommended dose. The ES recommends assessing the efficacy and safety of therapy at least monthly for the first 3 months, then every 3 months. Therapy is considered effective if weight loss of ≥5% is observed at 3 months. If effective, continuation of the medication is recommended; if ineffective or the patient develops safety/tolerability issues at any time, discontinuation of the medication is recommended, along with consideration for an alternative medication or treatment approach.

With regard to specific medications, the ES states that antidiabetic agents known to promote weight loss (e.g., glucagon-like peptide-1 [GLP-1] analogs or SGLT-2 inhibitors, in addition to metformin) should be considered in patients with T2DM who are overweight or obese.[3] In patients with cardiovascular disease, the ES recommends avoiding the use of sympathomimetics such as lorcaserin and orlistat. The ES also recommends avoiding off-label use of medications approved to treat conditions other than obesity solely for the purpose of weight loss.

As for bariatric procedures, the ACC/AHA/TOS and ES recommend consideration in certain patients with BMI ≥35 kg/m^2 with an obesity-related comorbidity or BMI >40 kg/m^2.[3,12] The Canadian Task Force suggests consideration for bariatric programs in patients with BMI >40 kg/m^2.[13]

Comparison of pharmacologic options for weight loss

There are a variety of weight loss medications which differ in efficacy, safety, and cost. The ACC/AHA/TOS, Canadian Task Force, and ES do not specify first-line medications for general treatment of obesity.[3,12,13] Among the organizations, only the ES addresses the use of several FDA-approved medications for weight loss, in their 2015 guideline.[3] The ES suggests that there are advantages and disadvantages associated with the medications. These are listed in Table 2.

Additional considerations, outlined in the *Pharmacist's Letter*,[14] are included in this table. In terms of potential weight loss, the available evidence suggests that the greatest weight loss may be observed with phentermine/topiramate (Qsymia®). However, this product is somewhat costly and is associated with several safety concerns. As noted in both resources and by the Canadian Task Force, the risks associated with medication use must be considered.[3,13,14] Safety concerns, including common side effects and contraindications, are described in Table 3. Also, some of these drugs are associated with potential abuse and dependence and have been classified as controlled substances.[8,10,11]

Table 2. Points of consideration regarding selected weight loss medications.[3,14]

Drug	Advantages*	Disadvantages*	Cost per month	Study withdrawal rate**
Bupropion ER/ naltrexone	• >3-5% weight loss • Long-term data (1-2 years)	• Side effect profile • Cost	$200	1 in 9
Liraglutide	• Well-tolerated • Long-term data (1-2 years)	• Route of administration (injection) • Cost	$1,100	1 in 18
Lorcaserin	• Well-tolerated • Long-term data (1-2 years)	• Cost	$200	1 in 53
Orlistat	• Non-systemic • Long-term data (1-2 years) • Inexpensive (OTC)	• 2-3% weight loss • Side effect profile	$45	1 in 26
Phentermine	• Inexpensive • >3-5% weight loss	• Side effect profile • No long-term data	$30	1 in 9
Phentermine/ topiramate ER	• >5% weight loss • Long-term data (1-2 years)	• Teratogenic • Cost	$200	1 in 12

*Based on recommendations from the Endocrine Society
**Drug discontinuation due to adverse effects
ER=extended-release; OTC=over-the-counter

Table 3. Safety concerns of selected weight loss drugs.[3-5,7-11]*

Drug	Common side effects	Contraindications	Controlled substance
Bupropion ER/naltrexone	Nausea, constipation, headache, vomiting, dizziness	Uncontrolled hypertension, seizure disorders, anorexia nervosa, bulimia, drug or alcohol withdrawal, use of MAOIs	N/A
Liraglutide	Nausea, vomiting, pancreatitis	History of medullary thyroid cancer or multiple endocrine neoplasia type 2	N/A
Lorcaserin	Headache, nausea, dry mouth, dizziness, fatigue, constipation	Pregnancy and lactation**; Caution advised when using SSRIs, SNRIs, MAOIs, St John's wort, triptans, bupropion, dextromethorphan	Schedule IV
Orlistat	Decreased absorption of fat-soluble vitamins, steatorrhea, oily-spotting, flatulence with discharge, fecal urgency, oily evacuation, increased defecation, fecal incontinence	Chronic malabsorption syndrome, pregnancy and lactation**, cholestasis, use of levothyroxine, warfarin, antiepileptic drugs, or cyclosporine	N/A
Phentermine	Headache, elevated BP, elevated HR, insomnia, dry mouth, constipation, anxiety, palpitations, restlessness, urticaria, impotence	Anxiety disorders, history of cardiovascular disease, uncontrolled hypertension, seizures, pregnancy and lactation**, hyperthyroidism, glaucoma, history of drug abuse, use of MAOIs or sympathomimetic amines	Schedule IV
Phentermine/topiramate ER	Insomnia, dry mouth, constipation, paresthesia, dizziness, dysgeusia	Pregnancy and lactation, hyperthyroidism, glaucoma, use of MAOIs or sympathomimetic amines	Schedule IV

*Adapted from the Endocrine Society guideline on management of obesity
**Contraindicated because weight loss thought to be of no potential benefit in pregnancy. Teratogenicity unknown.
BP=blood pressure; ER=extended-release; HR=heart rate; MAOIs=monoamine oxidase inhibitors; N/A=not applicable; SNRIs=serotonin-norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors

Notably, none of the available weight loss medications have been shown to exert permanent changes on the underlying physiology of weight regulation.[3] Previously, patients and prescribers have thought that weight loss observed upon initiation of medication therapy could be sustained by behavioral means alone. However, clinical trials have demonstrated that weight loss is sustained only for the duration that the medications are administered.

Conclusion

In summary, obesity and weight-related conditions are of great concern, affecting a substantial proportion of adults and children in the US. There are various treatment options, which may be further categorized as lifestyle interventions, pharmacologic therapy, or surgical procedures. Several organizations have recently published guidelines addressing management of obese and overweight patients; all agree on lifestyle modification as first-line therapy for most patients.[3,12,13] With regard to pharmacotherapy, the Canadian Task Force recommends against routine use, based on concerns for adverse events.[13] The ACC/AHA/TOS and ES suggest that medications for weight loss be considered in patients with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 obesity-associated comorbidity who are motivated to lose weight.[3,12]

While the ACC/AHA/TOS only considered orlistat in their guideline, the ES reviewed several additional agents.[3,12] The ES recommends use of antidiabetic agents associated with weight loss in patients with T2DM; however, they do not recommend 1 agent over another for management of obesity in the general population.[3] Instead, advantages and disadvantages should be considered for all approved drugs. For example, while the greatest weight loss has been observed with phentermine/topiramate, the combination is associated with several safety concerns and potential abuse/dependence. Additionally, it should be noted that none of these drugs will lead to permanent weight loss. In patients who are started on weight loss medication, prescribers are advised to monitor for weight loss and drug-specific safety concerns, and consider discontinuation of the medication if the patient develops intolerance or weight loss ≥5% is not achieved after 12 weeks on maximum doses.

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