REVIEW ARTICLE

Obesity Pharmacotherapy: Present & Future

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Obesity is a common, serious problem affecting many patients in every osteopathic family physician's practice and is also quickly becoming a pressing public health concern. The proper treatment of the obese patient rests on three pillars: proper nutrition, increased physical activity, and behavioral modification. Pharmacotherapy is an option to be considered in patients that don't respond adequately to a sensible treatment regimen targeting the above three elements. This article will review current approved short and long-term medications for the treatment of the obese patient, and briefly discuss some options that might be available in the future.

INTRODUCTION

Obesity is a common, serious problem affecting many patients in every family physician's practice. It is also quickly becoming a pressing public health concern, and imposes a tremendous economic burden on society. The Centers for Disease Control and Prevention reports that more than one-third of U.S. adults are obese (defined as a body mass index ≥30), and the estimated annual medical cost of obesity in 2008 was $147 billion dollars.[1]

As a complex, multifactorial disease, obesity is very challenging to treat, particularly in the setting of a busy primary care practice. A multidisciplinary approach is often needed to tackle the challenge of the obese patient, with the help of behavioral counselors, dietitians, and physical therapists. One cannot effectively treat obesity unless the condition is considered in the context of the whole patient (an "obese patient" instead of "obesity"). All aspects of the patient need to be addressed: mind, body, and spirit, as well as the patient's socioeconomic environment. By adopting a holistic approach to the care of the obese patient, family physicians are well-positioned to be at the forefront of medical bariatrics.

The proper treatment of the obese patient rests on three pillars: proper nutrition, increased physical activity, and behavioral modification.[2,3] Pharmacotherapy is an option to be considered in patients that don't respond adequately to a sensible treatment regimen targeting the above three elements. This article will review current approved medications for the treatment of the obese patient, and briefly discuss some options that might be available in the future.

PRESENT THERAPIES

Currently there are several approved medications for short and long-term management of the obese patient. As mentioned previously, these medications are not to be used as monotherapy, but should only be considered as adjunctive treatment in patients that don't respond adequately to a proper diet and exercise regimen. The obese patient should be required to continue with diet, exercise, and behavior modification efforts while under treatment with one of these medications. Table 1 *(pages 14 & 15)* provides a summary of all the medications discussed in this review.

SHORT-TERM MEDICATIONS

Sympathomimetic medications available for short-term treatment of the obese patient include phentermine, diethylpropion, and benzphetamine.[4,5,6] It's important for the physician to ensure he's complying with state laws when prescribing any of these medications, as many states have specific laws regulating the use of these agents. Phentermine and diethylpropion are schedule IV controlled substances, and benzphetamine is a schedule III controlled substance.

These medications act as appetite suppressants by stimulating the hypothalamus to release norepinephrine in the central nervous system. Phentermine has been shown to promote an average weight loss of about 8%.[7] They are available as once-daily doses, preferably to be taken in the morning to avoid insomnia. They are approved for short-term use only, typically no longer than 12 weeks, and only on patients with a BMI ≥ 30, or with BMI ≥ 27 with medical comorbidities (such as hypertension or diabetes). Once the medication is started, the physician should reassess the patient in 4 weeks and decide if response is adequate to justify continuing the medication.

Sympathomimetics should be avoided in patients with heart disease or uncontrolled hypertension. In patients with well-controlled hypertension, blood pressure should be monitored frequently. These agents should also be avoided in patients with severe psychiatric disease or a history of drug/substance abuse, pulmonary hypertension, hyperthyroidism, or glaucoma. If the patient has started taking monoamine oxidase inhibitors, 14 days should elapse prior to starting a sympathomimetic.

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These agents are absolutely contraindicated in pregnancy, and appropriate contraception needs to be in place prior to prescribing these medications to women of child-bearing age. The prescribing physician should consider documenting a negative pregnancy test prior to prescribing these agents.

Most common adverse reactions include palpitations, tachycardia, tremors, insomnia, and hypertension.

These agents are among the most affordable for patients. They also carry the advantage that patients are not allowed to take these medications long-term, making them ideal as adjunctive treatment, forcing the patient to eventually rely on lifestyle changes for long-term weight loss.

LONG-TERM MEDICATIONS

Long-term medications are available for those patients with a BMI ≥ 30 (or with BMI ≥ 27 with medical comorbidities) who might need a longer course of treatment to achieve their weight loss goals. Although these agents are approved for treatment courses that exceed those of sympathomimetics, prudent use of these agents is still recommended. Patients should not rely solely on long-term weight loss medications and need to eventually modify their lifestyle and habits in order to continue to lose weight or to maintain their current weight. Physicians need to engage in a holistic treatment plan with their patients in order to avoid reliance on long-term pharmacotherapeutic agents for weight loss. No pill can take the place of proper nutrition, increased physical activity, and behavioral modification.

Orlistat, a pancreatic lipase inhibitor, stimulates weight loss by inhibiting the absorption of dietary fats,[8] and has been shown to promote a 10% weight loss.[9] Due to its minimal systemic absorption, this is the safest of all weight loss medications, and is also available over-the-counter without a prescription. At the recommended dose of 120mg three times daily prior to meals, this agent can inhibit absorption of dietary fats by approximately 30%. Orlistat is contraindicated in patients with chronic malabsorption syndromes or cholestasis. It's recommended that patients take a multivitamin due to the possibility of reduced absorption of fat-soluble vitamins while taking orlistat. Most common adverse reactions experienced are oily spotting, flatulence, and fecal urgency. Although this medication is the safest and is also available without a prescription, its use is limited due to the adverse effects patients experience.

Phentermine/topiramate, a combination agent approved in 2012, stimulates weight loss by the combined action of low-dose extended release phentermine, and the anorexiant effects of topiramate,[10] and has been shown to promote an average 10.5% weight loss,[11] making this combination agent the most effective weight loss medication currently available. This medication should be started at the lowest dose of 3.75mg/23mg for 14 days, then increased to the usual daily dose of 7.5mg/46mg. If after 12 weeks of treatment the patient has not lost at least 3% of body weight, the treating physician may choose to discontinue the medication or to increase the dose first to 11.25mg/69mg for 14 days and then to the maximum dose of 15mg/92mg. The medication should be tapered off and discontinued if the patient does not achieve at least 5% weight loss after 12 weeks of treatment at the maximum dose. This agent is contraindicated in pregnancy, or those patients with glaucoma, hyperthyroidism, or within 14 days of starting a monoamine oxidase inhibitor. Most common adverse reactions are paresthesias, dizziness, dysgeusia, insomnia, constipation, and dry mouth.

Naltrexone/bupropion is another combination agent available. It stimulates weight loss by affecting the appetite regulatory center of the hypothalamus, as well as the mesolimbic dopamine reward system. Naltrexone is an opioid antagonist, and bupropion is a weak inhibitor of dopamine and norepinephrine reuptake. The exact neurochemical effects of this drug combination that lead to weight loss are not fully understood.[12] Patients can expect an average of 7% weight loss.[13] Its typical daily dosage is 2 tablets of 8mg/90mg twice daily, but this dose should be arrived at after a slow titration period. This medication should not be used in pregnancy, uncontrolled hypertension, seizure disorder, or within 14 days of taking monoamine oxidase inhibitors. Because of the naltrexone component, this agent should also be avoided in patients taking opioids for chronic pain. Most common adverse reactions are nausea, constipation, headache, vomiting, dizziness, insomnia, and dry mouth. This combination agent carries a black box warning due to a risk of increased suicidal thoughts and behaviors, and increased risk of neuropsychiatric reactions.

Lorcaserin, a serotonin 2C receptor agonist, has an unknown mechanism of action, but is believed to stimulate weight loss by promoting satiety.[14] It has been shown to promote an average 6% weight loss.[15] It's dosed at 10mg twice daily. Response to therapy should be evaluated by week 12, and lorcaserin should be discontinued if the patient has not lost at least 5% body weight. This agent is contraindicated in pregnancy. Patients taking other serotonergic drugs, should be advised on the possibility of serotonin syndrome while on this agent. Previous medications in this class (i.e. fenfluramine) affected the 5-HT2B receptors in the heart, which caused valvular issues. Lorcaserin is selective for the 5-HT2C receptor, which is not present in the heart. However, patients should be monitored for the development of new heart murmurs while on this medication. Its use should be avoided in patients that have valvular heart disease or congestive heart failure. Most common adverse effects are headache, dizziness, fatigue, nausea, dry mouth, and constipation

Liraglutide, the most recent agent to be approved for weight loss, is an injectable glucagon-like peptide-1 (GLP-1) receptor agonist. It stimulates weight loss by affecting appetite regulation areas in the brain and slowing gastric emptying,[16] and has been shown to promote a 6-10% weight loss.[17] It's started at 0.6mg daily, and the dose is increased weekly until the maximum daily dose of 3mg is achieved. This medication should be discontinued if the patient has not lost at least 4% body weight after 16 weeks of treatment. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2, for which it carries a Black Box warning. There is also a risk of developing pancreatitis with this product. It should not be used in patients taking insulin or other GLP-1 receptor agonists. Most common adverse reactions are nausea, hypoglycemia, gastrointestinal upset, and headaches.

FUTURE THERAPIES

Two future therapies in development are worth mentioning: beloranib and fecal microbiota transplantation.

TABLE 1:

Drug Name (approximate monthly cost)	Mechanism of Action	Average Weight Loss	Contraindications
Phentermine ($36.99) Diethylpropion ($49.19) Benzphetamine ($140.89)	Appetite suppressant	8%	Heart disease Uncontrolled hypertension History of drug abuse Pulmonary hypertension Glaucoma Hyperthyroidism Pregnancy
Orlistat ($56 - $173)	Pancreatic Lipase Inhibitor	10%	Cholestasis Chronic Malabsorption Syndromes
Phentermine / Topiramate ($100.89 - $276.99)	Appetite suppressant	10.5%	Pregnancy Glaucoma Hyperthyroidism
Naltrexone / Bupropion ($230)	Affects appetite regulatory center of the hypothalamus & mesolimbic reward system	7%	Pregnancy Uncontrolled Hypertension Seizure Disorder
Lorcaserin ($170.75)	Promotes satiety	6%	Pregnancy Valvular heart disease Congestive heart failure
Liraglutide ($1231.64)	Affects appetite regulation areas in the brain & slows down gastric emptying	6 - 10%	Personal/family history of medullary thyroid carcinoma MEN type 2

Beloranib, an agent developed as a novel, first-in-class obesity therapy, is an inhibitor of methionine aminopeptidase 2 (MetAP2). It works by affecting the way the body metabolizes fat. This medication is currently being tested to treat Prader-Willi syndrome with plans to eventually have approval for severe and complicated obesity as well as obesity due to hypothalamic injury.[18] During Phase 1b studies, the drug demonstrated impressive weight loss, averaging about 2Lb per week. During its Phase 3 trials for treatment of Prader-Willi syndrome the drug was placed on complete clinical hold by the Food and Drug Administration (FDA) due to serious thromboembolic events leading to death in two study participants.[19] At the time of publication, it is unclear whether this agent will make it to routine clinical practice.

Fecal microbiota transplantation (FMT) is a fascinating, possible future adjunctive therapy in the treatment of obesity. A complete explanation of the role of the human intestinal microbiome in obesity is beyond the scope of this review article. The basic premise of FMT is that the human intestinal microbiome affects several of our body's processes, and an imbalance in the microbiome composition is associated with certain diseases (including obesity). With the introduction of donor feces into the patient's intestine, this balance can be restored or altered in order to effect weight loss.[20] This treatment is under investigation and is not FDA approved for weight loss. Currently the FDA only allows the use of FMT for treatment of recurrent C-difficile infections,[21] although not many institutions are capable of performing the procedure.

CONCLUSION

There are currently multiple medication options for the treatment of the obese patient, each with a unique mechanism of action and side-effect profile. The osteopathic physician is encouraged to consider these as adjunctive treatment in patients that are not successful in losing weight with a regimen of proper nutrition, increased physical activity, and behavioral modification. Consideration should be given to the cost of the medications and their insurance coverage, their contraindications and side effects, and the motivation of the patient to continue with their non-pharmacologic regimen, as these medications do not replace a holistic, multidisciplinary approach to the treatment of the obese patient.

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Adverse Events	Criteria to Continue Treatment	Comments
Palpitations, Tremors, Tachycardia, Hypertension, Insomnia	Assess for adequate response after 4 weeks of treatment	Most affordable medication (Phentermine) Dose in the morning to avoid insomnia
Oily spotting, Flatulence, Fecal urgency	5% weight loss by 12 weeks of treatment	Safest medication Adverse effects limit compliance
Paresthesias, Insomnia, Dizziness, Constipation, Dysgeusia, Dry mouth	Must lose 5% body weight by 12 weeks of treatment at maximum dose	Most effective agent Cost/coverage limits its use
Nausea, Dizziness, Vomiting, Insomnia, Headaches, Dry mouth	Must lose 5% body weight by 12 weeks of treatment	Black Box Warning due to increased risk of psychiatric adverse effects
Headache, Nausea, Dizziness, Dry mouth, Fatigue, Constipation	Must lose 5% body weight by 12 weeks of treatment	Least incidence of adverse effects
Nausea, Hypoglycemia, GI upset, Headaches	Must lose 4% body weight by 16 weeks of treatment	Black Box Warning on medullary thyroid carcinoma and MEN-2 Cost is a limiting factor

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