Therapies for Obesity Management

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Program Overview:

To provide participants with an understanding of obesity management and treatment

OBJECTIVES:

After completing this program, participants will be able to:

- Describe the pathophysiology, epidemiology, and public health impacts of obesity
- Recognize the causes and complications of obesity
- Identify nonpharmacological and pharmacological approaches to obesity management
- Describe the mechanism of action of drugs used for obesity treatment
- Explain the adverse effects of medications used to treat obesity
Introduction

Epidemiology

Since 1997, the World Health Organization has recognized obesity as an important worldwide health epidemic.\(^1\) Over nutrition has surpassed under nutrition as an emerging global health issue with an estimated 15% of the world’s population identified as overweight compared to 5.8% who are underweight.\(^2\) Approximately two thirds of the US population is overweight or obese which translates into over 100 million adult Americans who are above their recommended weight.\(^3\) Figures for the number of deaths attributed to obesity each year range from 100,000 to 300,000, and the economic burden of obesity in the US was estimated at $147 billion in 2008.\(^4,5\) An estimated 9.1% of annual medical spending is due to the medical consequences of obesity which has had a significant impact on the rising overall costs of health care.\(^5\)

Obesity has the highest prevalence in African American, Hispanic, and Native American populations (in descending order), and also disproportionately affects rural areas and individuals with lower socioeconomic status and educational level.\(^6\) Nonetheless, the rise in obesity has had an impact on all geographic areas of the US, as well as crossing racial and socioeconomic divides. By 2010, the obesity rate was greater than 20% in every state, with the lowest rate of 21% in Colorado and the highest rate of 34% in Mississippi.\(^7\) Efforts to address the obesity epidemic, which is a major preventable cause of morbidity and mortality, include greater education to address the causes of obesity and initiatives to promote healthy lifestyle choices.

Pathophysiology

A combination of complex genetic and constitutional factors, along with a host of environmental influences, is known to contribute to obesity. Several hormonal influences are involved in regulating appetite, which have a direct impact on obesity. The role of the leptin gene mutation has been described in studies investigating leptin deficiency resulting in massive obesity, hyperphagia, insulin resistance, hyperinsulinemia, and infertility in murine models.\(^8\) Produced primarily in adipose tissue, leptin is a protein that regulates appetite control centers through negative feedback. Studied extensively in animal models, leptin deficiency in humans occurs only rarely.

Other genetic defects associated with melanocortin-4 receptor and Prader-Willi syndrome, which manifests with elevated levels of ghrelin, are also linked to obesity, in addition to neuroendocrine disorders such as hypothalamic obesity, Cushing’s syndrome, hypothyroidism, insulinoma, and polycystic ovarian syndrome. Several other signals have an effect on food intake, including vagal activity, cholecystokinin, apolipoproteins, insulin, glucagon-like peptides, and various other modulators. Certain metabolic factors are also associated with high risk of obesity including low metabolic rate, increased carbohydrate oxidation, insulin resistance, and low sympathetic activity. Endocrine or metabolic disorders, however, account for less than 1% of obesity in the general population.\(^2\)

Additional causes of obesity include various medications that cause weight gain. A careful review of the patient’s medication history is a necessary part of any treatment plan to identify any exogenous causes of obesity. Many different drug classes promote weight gain. Drugs often cited for causing weight gain
include psychiatric agents (e.g. antidepressants such as amitriptyline [Elavil], imipramine [Tofranil], doxepin [Sinequan], and tranylcypromine [Parnate]; antipsychotics such as clozapine [Clozaril], olanzapine [Zyprexa], and risperidone [Risperdal]; anticonvulsants such as carbamazepine[Tegretol], gabapentin [Neurontin], valproic acid [Depakote]; and mood stabilizers such as lithium); steroid hormones (e.g, glucocorticoids); antidiabetes agents (eg, insulin, rosiglitazone [Avandia], pioglitazone [Actos], glipizide [Glucotrol], and glyburide [Micronase]); antihistamines (eg, diphenhydramine [Benadryl]); alpha-blockers (eg, doxazosin [Cardura] and prazosin [Minipress]); beta-blockers (eg, propranolol [Inderal], metoprolol [Lopressor], and atenolol [Tenormin]); and HIV protease inhibitors. Another cause of weight gain is smoking cessation, which can further complicate therapies to address nicotine dependence.

Diagnosing obesity

A common obesity assessment measure is the body mass index (BMI) which is calculated as follows:

\[ \text{BMI} = \frac{\text{Weight in kg}}{(\text{Height in m}) \times (\text{Height in m})} \]

The classification of BMI ranges is listed in Table 1. The use of BMI as an indicator of obesity can be problematic because it can overestimate the degree of body fat in athletes or result in an underestimation for certain ethnic groups (eg, Asians). A more accurate predictor of obesity-related health risk is the measurement of waist circumference. Disease risk is greater in men with a waist circumference ≥ 102 cm (or 40 in) and in women with a waist circumference ≥ 88 cm (or 35 in).

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>≥25 kg/m²</td>
</tr>
<tr>
<td>Class I obesity (mild)</td>
<td>≥30 kg/m²</td>
</tr>
<tr>
<td>Class II obesity (moderate)</td>
<td>≥35 kg/m²</td>
</tr>
<tr>
<td>Class III obesity (severe; also called morbid obesity)</td>
<td>≥40 kg/m²</td>
</tr>
</tbody>
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Comorbidities

A number of medical conditions associated with obesity increase morbidity and mortality risks for the obese population. The landmark Framingham Study showed a marked reduction in life expectancy for those who were obese and overweight, with a greater reduction in the former category. Obesity has been linked to higher risks of coronary artery disease, venous thromboembolism, hypertension, dyslipidemia, type 2 diabetes, metabolic syndrome and insulin resistance, degenerative joint disease, gastroesophageal reflux, gallstones, nonalcoholic fatty liver disease, obstructive sleep apnea, dermatological conditions, and certain types of cancer, e.g. colorectal, endometrial, renal, breast and colon. The mechanism for the increase in blood pressure caused by obesity involves the associated increases in vascular resistance and sodium resorption. Weight reduction is identified as the most effective lifestyle adaptation to reduce elevated blood pressure. Obesity-associated dyslipidemia is linked to high levels of cholesterol and low-density lipoproteins (LDL), and a reduction in high-density lipoproteins (HDL), elevating the risk of coronary heart disease. Psychological comorbidities are also
associated with obesity, which has been linked to higher rates of depression, bipolar disease, and agoraphobia.

Nonpharmacological obesity management approaches

Physical activity and exercise

Challenges for the treatment of obesity include the chronic nature of disease and the requirements for comprehensive strategies that address behavior modification, diet, and physical activity in conjunction with pharmacotherapy. Having a multidisciplinary team approach can be beneficial to help tailor the obesity management plan according to specific individual needs. Lifestyle factors play a key role in the development of obesity. The root cause of weight gain is excess calorie intake relative to energy expenditure, or the level of physical activity (eg, sedentary lifestyle habits). Initial treatment for obesity management consists of nonpharmacological strategies; patients are counseled on diet, physical activity, lifestyle, and goals for weight loss. Regular physical activity is a key part of any overall health strategy and is especially important for individuals attempting weight reduction. The general target goal is a minimum of 30 minutes of moderate-intensity activity on 5 or more days of the week, and to promote weight and maintain weight loss, this goal should increased to 60 to 90 minutes of moderate-intensity activity daily.

Diet and self-management programs

Popular weight loss approaches are diets either with self-management or commercial weight-loss programs, some of which are listed in Table 2. The rationale behind low-carbohydrate diets is based on lowering insulin levels through a reduction in carbohydrate intake and blood glucose levels. The proposed mechanism for weight loss is the reduction in the anabolic effect of insulin and decreased appetite from ketosis and satiety from fat.10

<table>
<thead>
<tr>
<th>Diet/Technique</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins diet</td>
<td>Very low carbohydrates</td>
</tr>
<tr>
<td>Zone diet</td>
<td>Low carbohydrates</td>
</tr>
<tr>
<td>Ornish diet</td>
<td>High carbohydrates</td>
</tr>
<tr>
<td>Mediterranean diet</td>
<td>Healthy fats, fruits, and vegetables</td>
</tr>
<tr>
<td>Weight Watchers program</td>
<td>Portion size/calorie restriction</td>
</tr>
<tr>
<td>LEARN program</td>
<td>Exercise and low-fat, high carbohydrate diet</td>
</tr>
</tbody>
</table>

The most recommended diet strategy is reducing daily calorie intake as part of a low-calorie diet. A reasonable initial goal and timeline for weight reduction is 5% to 10% over 6 months, which can significantly reduce risk factors for diabetes and cardiovascular disease in higher risk patients.11 Reducing calorie intake by 500 to 1000 kcal daily can produce a weight reduction of about 1 to 2 pounds weekly. Suggestions for calorie intake are 1000 to 1200 kcal/day for women and 1200 to 1600 kcal/day for men while restricting saturated fats and refined carbohydrates (eg, sugar) as part of an overall dietary program according to National Heart, Lung, and Blood Institute guidelines.12 Food habits such as portion control, keeping diet records, and eating regular breakfasts have been shown to facilitate healthy eating patterns and should be incorporated into the weight-loss management program.
Readily available information on these diets and other self-management approaches can be accessed by consumers through the internet, books, magazines, and commercial weight-loss programs. Few, if any, differences in results were shown in a study comparing the effectiveness of the Atkins, Ornish, Zone, and Weight Watchers approaches.\textsuperscript{13}

Pharmacological approaches for obesity management

While nonpharmacologic therapies are recommended by the National Institutes of Health as the preferred initial treatment for weight loss, pharmacologic treatment of obesity is a continuing area of research and development.\textsuperscript{14} Pharmacologic agents for the treatment of obesity span a wide range of drug classes and include both FDA-approved and off-label medications. Knowledge of the efficacy, safety, and limitations of drug therapy and its potential for abuse are important considerations in the clinical management of obesity which requires a thorough evaluation of therapeutic risks and benefits.

Pharmacotherapy for obesity should be considered as an adjunct to diet and exercise for individuals with a BMI $\geq$30 who have not met weight goals with non-pharmacological approaches. Discussion about treatment should communicate that drug therapy is not a cure for obesity. Once a patient ceases medication, weight will be regained. Invasive techniques which may be considered are liposuction or bariatric surgery, and the latter option may be recommended for carefully selected individuals with clinically severe obesity (BMI $\geq$40) failing to achieve target weight loss with diet and exercise and are at high risk for obesity-associated morbidity or death due to severe comorbidities.

Choosing the initial medication for weight loss requires consideration of many factors, including patient comorbidities, concurrent medications, tolerance for potential adverse effects, possible drug interactions, drug approval for long-term use, and medication costs. Premenopausal women undertaking pharmacological treatment of obesity should receive counseling about teratogenic risks and contraception (a pregnancy test should also be considered). A thorough patient assessment is also important to ensure that no contraindications to the proposed therapy exist which would preclude its use.

Currently, orlistat (Xenical) is the only medication approved for the long-term treatment of obesity. Treatment guidelines recommend up to 2 years of treatment with orlistat, and the drug is approved by the FDA for up to 4 years. Orlistat is an inhibitor of gastric lipase, pancreatic lipase, and phospholipase A2 that interferes with fat digestion. Available in 120 mg capsules (taken 3 times daily) and at a lower dose, over-the-counter 60 mg dose version (marketed under the brand name Alli), Orlistat has been shown to result in greater weight loss and slower weight gain compared with placebo. As a potent and irreversible inhibitor of gastric and pancreatic lipases, Orlistat decreases the systemic absorption of dietary fat and may also inhibit the digestion of triglycerides while reducing the incidence of diabetes and improving concentrations of total cholesterol and low-density lipoprotein cholesterol, blood pressure, and glycemic control in patients with diabetes. Common adverse effects include diarrhea, flatulence with discharge, fecal incontinence, abdominal pain, and dyspepsia. Some of the symptoms caused by orlistat can be reduced with the concomitant use of bulk-forming laxatives (eg, psyllium, methylcellulose). Because orlistat interferes with fat absorption, levels of fat-soluble vitamins A, D, E, and K may be lowered in individuals taking this medication and taking a daily multivitamin is recommended with long-term use of the drug.
Recently taken off the US market in October 2010 due to concerns about minimal efficacy and cardiovascular risks, sibutramine (Meridia) was previously approved for long-term management of obesity. A mixed noradrenergic-serotonergic agent, sibutramine is a potent inhibitor of norepinephrine and serotonin and a weak inhibitor of dopamine. Sibutramine was shown to cause increases in cardiovascular events and strokes in patients with a history of cardiovascular disease. Common adverse effects associated with sibutramine included dry mouth, constipation, and insomnia.

Noradrenergic agents including benzphetamine (Didrex), diethylpropion (Tenuate), phendimetrazine (Bonril), and phentermine (Adipex-P, Fastin, Obenix, Oby-Trim) act on central nervous system modulators to suppress appetite. Formerly available as an over-the-counter appetite suppressant, phenylpropanolamine was withdrawn from the market because of its association with hemorrhagic stroke. The most common adrenergic agent used in clinical practice today is phentermine which modulates noradrenergic neurotransmission with minimal effect on dopaminergic neurotransmission thus decreasing the potential for abuse. The side effects of phentermine are dry mouth, headache, insomnia, nervousness, irritability, and constipation; palpitations, tachycardia, and blood pressure elevation may also occur; the use of monoamine oxidase inhibitors is contraindicated during or within 14 days of the use of phentermine because hypertensive crisis may be triggered; other contraindications are hyperthyroidism, glaucoma, moderate to severe hypertension, advanced arteriosclerosis/cardiovascular disease, or a history of substance abuse. Because of issues with tolerance and potential for abuse, diethylpropion and phentermine are classified as Schedule IV drugs and approved for short-term use only (i.e. 3 months).

Serotonergic agents do not currently have FDA approval for weight loss, but are known to promote weight loss through their disruption of central neuromodulators which control food intake. Two of these agents, dexfenfluramine (Redux) and fenfluramine (Pondimin), were withdrawn from the US market in 1997 due to an association with increased risks of valvular heart disease and pulmonary hypertension. The remaining serotonergic agent that is available off-label for weight loss is fluoxetine (Prozac), a highly selective SSRI that may increase energy expenditure by raising basal body temperature. Fluoxetine was shown in initial studies to be effective in the treatment of obesity at a dose of 60 mg daily (or three times the therapeutic dose used to treat depression). Because of the high dose required and the lack of long-term data, fluoxetine is not currently recommended for weight reduction.

An atypical antidepressant that inhibits reuptake of dopamine, norepinephrine, and serotonin, bupropion (Wellbutrin) has been demonstrated to result in weight loss when used in doses of 300 to 400 mg q daily. Bupropion is also approved for use as a smoking cessation therapy. The adverse effects of bupropion include dry mouth, insomnia, diarrhea, and constipation, and the drug is contraindicated in individuals with seizure disorders. Similar to fluoxetine, bupropion is not recommended for obesity treatment due to the high dose needed for therapeutic effect.

Topiramate (Topamax) is an antiepileptic drug which has shown efficacy as an anti-obesity agent in clinical trials. Because of its significant side effects including paresthesias, somnolence, difficulty with concentration, dizziness, fatigue, and association with metabolic acidosis, topiramate is not currently recommended for obesity management.
Zonisamide (Zonegran) is a novel antiepileptic drug with serotonergic and dopaminergic activity. In clinical trials, zonisamide at 600 mg daily resulted in weight loss compared with placebo. Similar to topiramate, zonisamide is associated with side effects such as dizziness, confusion, and difficulty with concentration, and is not recommended for use for treating obesity.

Varying degrees of weight loss have been shown with medications approved for the treatment of diabetes, such as metformin (Glucophage), pramlintide (Symlin), exenatide (Byetta), and liraglutide (Victoza). Shown to produce significant weight loss in patients with impaired glucose tolerance, metformin, an oral biguanide, is the drug of choice for overweight individuals who are at high risk for diabetes, but is not approved as a weight-loss drug alone. For patients who experience weight gain when taking antipsychotic medications, metformin is also a suitable choice. Pramlintide is an injectable synthetic analog of the peptide hormone amylin which improves HbA1c concentrations in patients with type 1 and type 2 diabetes and is also associated with modest weight loss. Other injectable diabetes medications that act on the GLP-1 pathway, exenatide and liraglutide, were associated with greater weight loss compared to that seen with pramlintide. Nausea and vomiting were reported as adverse affects associated with the GLP-1 pathway medications, and the weight loss may be partly attributed to the gastrointestinal side effects in addition to any therapeutic effects.

Complementary and alternative medicine

Several widely-used dietary supplements are available over-the-counter but have limited evidence supporting their efficacy and safety. Among these dietary supplements are ephedra (which is no longer available), green tea, guar gum, chitosan, chromium, hoodia gordonii, and others. Ephedrine, a beta receptor stimulator, is available in purified form or in herbal sources of caffeine as ma huang, Guarana, and gotu kola and increases thermogenesis in adipose tissue. Ephedrine’s side effects are related to increased sympathetic activity and include insomnia, tachyarrhythmias, headache, and elevated blood pressure. Ephedra (ma huang) was removed from the market in 2004 because of safety concerns resulting from its association with stroke, tachyarrhythmias, seizures, and death. The stimulant caffeine increases nervous system activity and promotes weight reduction through an increase in metabolic rate and fat oxidation. A major area of safety concerns for caffeine and other related stimulants is the possibility of cardiovascular effects, and patients should be appropriately cautioned and monitored if they choose to use these supplements.

Compounded dietary supplements from Brazil containing amphetamines, benzodiazepines, and fluoxetine have also appeared in the U.S. with reports noting it use among Brazilian immigrant women and a high rate of adverse effects associated with supplement use, prompting a warning issued by the US Food and Drug Administration (FDA).

Acupuncture is another complementary therapy that has been used for the treatment of obesity. A few controlled trials reported in the literature have shown some benefit of acupuncture for weight loss, but the strength of the trial results is limited due to the small size and limited duration of the trials which did not have adequate placebo controls.

Experimental drugs (not currently approved by the FDA):
Other agents are being investigated for treatment of obesity but are not currently approved by the FDA. Approved for obesity treatment in Europe and elsewhere, rimonabant (Acomplia) is a selective antagonist acting on type 1 cannabinoid receptors which is thought to regulate food intake and lead to weight loss. The drug is under investigation but has not been approved due to concerns of increased risk of mood disorders (eg, depression and anxiety) seen in clinical trials.22

Leptin therapy has been studied in obese individuals resistant to leptin. In one of the studies, the greatest amount of weight loss was seen in the highest dose group. While the results of another study suggested that leptin therapy prevents decreases in energy expenditure and may prevent weight regain, leptin’s ability to sustain weight loss effects is not known.

Melanocortin-4 receptor agonists are thought to play an important role in the control of body weight through the hypothalamic melanocortin system. Delivered as an intranasal administration of the melanocortin sequence MSH/ACTH, the drug showed weight loss effects over a short-term period, demonstrating weight loss in normal-weight subjects over 6-week period, but no significant effect in overweight males over a 12-week period.23

Peptide YY (PYY) is a gut hormone that suppresses appetite resulting in decreased food intake. The results of a trial of obese and lean adults receiving short-term PYY suggested that the drug may be a useful weight loss therapy, showing a decrease of approximately 30% in appetite and calorie intake for both groups.24 A longer trial of PYY failed to show similar benefit and also produced intolerable side effects such as nausea and vomiting in 60% of patients which limited the drug’s effectiveness.25

Tesofensine is a sympathomimetic agent initially developed for the treatment of Parkinson’s disease. The drug acts as a presynaptic inhibitor of norepinephrine, dopamine, and serotonin similar to sibutramine and causes appetite suppression and shown to have significant weight loss effects.26 Common adverse effects are dry mouth, nausea, abdominal pain, and diarrhea. In addition, increased heart rate was found in all tesofensine groups in a multi-dose dose-ranging trial as well as a significant increase in blood pressure in the highest dose group. Further investigation is warranted to investigate tesofensine’s efficacy and safety.

Lorcaserin is a selective agonist of the serotonin 2C receptor and results in reduced appetite.27 The drug is effective for weight loss in men and women. Its functional selectivity produces a better side effect profile compared to other serotonergic agents used for obesity management. Although lorcaserin has not been studied long-term, the risk of cardiac effects should be decreased for the drug due to its selective agonism of serotonin receptor 2C over 2B.

Summary

The dramatic rise in obesity both nationally and globally has renewed attention on continuing efforts to address this significant public health issue. The causes of obesity are complex and multifactorial, and obesity is recognized as a chronic medical problem which leads to a host of serious health complications. Treatment to manage obesity should take into account the full range of nonpharmacological and pharmacological options available. While only three medications are FDA approved for weight loss (orlistat for long-term use, and phentermine and diethylpropion for short-term use), several other medications have off-label use for weight loss. Because of the chronic nature of obesity, weight loss
effects of pharmacological therapy cease when medication is discontinued. For obesity management to be effective, lifestyle modification is a necessary part of the overall treatment plan. Medications can promote weight loss, but should be considered an adjunct to nonpharmacological approaches.
References


