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Obesity Management: Balancing Lifestyle, Medications, and Future Innovations

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Abstract

Obesity is a global health issue that significantly affects quality of life and increases the risk of developing type 2 diabetes, heart disease, osteoporosis, reproductive disorders, and certain cancers. While weight loss is crucial, relying solely on diet and exercise may not be sufficient. An emerging strategy involves repurposing (also called drug repositioning) existing drugs—initially developed for other medical conditions—for weight management. The U.S. Food and Drug Administration (FDA) has approved a number of medications for long-term use in weight management. Originally developed for the treatment of type 2 diabetes, these medications have proven effective in facilitating weight loss in obese patients. The efficacy of liraglutide, semaglutide, and tirzepatide underscores the potential of repurposed medications in addressing obesity—a complex, multifactorial condition. This review aims to discuss the importance of balancing lifestyle modifications and to highlight the significance and benefits of approved medications for obesity control. By examining the mechanisms, efficacy, and safety of these drugs, we aim to enhance the understanding of their role in obesity management and their ability to improve the quality of life for those affected by obesity.

Keywords: Metabolic disorders; Weight reduction; Drug repurposing; Modifiable risk factor.

Introduction

Obesity is a medical condition characterized by an excessive accumulation of body fat that can negatively impact an individual's health. It is typically assessed using the Body Mass Index (BMI), a standardized measure of body weight relative to height [1]. According to the World Health Organization (WHO), overweight and obesity are defined differently based on age groups. For adults, being overweight is classified as having a BMI of 25 or higher, while obesity is defined as having a BMI of 30 or higher. For children under five, overweight is determined by a weight-for-height measurement exceeding two standard deviations above the WHO Child Growth Standards median, and obesity is indicated by a weight-for-height measurement exceeding three standard deviations above the same median. In children aged 5–19 years, overweight is defined as a BMI-for-age greater than one standard deviation above the WHO Growth Reference median, and obesity is classified as a BMI-for-age greater than two standard deviations above the same reference [2].

In 2022, approximately 2.5 billion adults aged 18 years and older were classified as overweight, including over 890 million who were living with obesity. This accounts for 43% of the global adult population, comprising 43% of men and 44% of women, marking a significant increase from 1990, when only 25% of adults were overweight. The prevalence of overweight varied by region, ranging from 31% in the South-East Asia Region and the African Region to 67% in the Region of the Americas. Globally, 16% of adults aged 18 years and older were obese in 2022, with the worldwide prevalence of obesity more than doubling between 1990 and 2022. In the same year, an estimated 37 million children under the age of five were classified as overweight. Once predominantly a concern in high-income countries, overweight and obesity have become increasingly prevalent in low- and middle-income countries. For example, in Africa, the number of overweight children under five has increased by nearly 23% since 2000. Nearly half of the

children under five who were overweight or obese in 2022 resided in Asia. Furthermore, over 390 million children and adolescents aged 5–19 years were classified as overweight in 2022. The prevalence of overweight (including obesity) in this age group has risen dramatically from 8% in 1990 to 20% in 2022, with similar increases observed in both boys and girls—19% of girls and 21% of boys were overweight in 2022. Obesity within this group has also seen a sharp rise, growing from just 2% (31 million young people) in 1990 to 8% (160 million young people) in 2022 [2].

1. Etiology and risk factors of obesity

The global increase in obesity rates over the last decades is best explained by a complex interplay between genetic predispositions and environmental factors. Essentially, obesity arises from a sustained positive energy balance, where the calories consumed exceed those expended. However, this traditional view is likely an oversimplification. Important factors include hypothalamic regulation of appetite and energy expenditure, the impact of sugar consumption on these regulatory mechanisms (including insulin and leptin resistance), and the intricate interactions between appetite and metabolic pathways and the gut (such as gut peptides, the autonomic nervous system, and gut microbiota). These mechanisms, and how our genes interact with environmental factors to influence body weight, are not yet fully understood [3]. Although genetic, behavioral, metabolic, and hormonal factors influence body weight, obesity occurs when calorie intake surpasses the amount burned through daily activities and exercise. The body then stores these excess calories as fat. In the United States, most diets are high in calories, often from fast food and sugary drinks. Individuals with obesity may consume more calories before feeling full, experience hunger more quickly, or eat more due to stress or anxiety. Many jobs are less physically demanding, leading to fewer calories burned at work. Additionally, modern conveniences like remote controls, escalators, online shopping, and drive-through services reduce the calories burned during daily activities [4].

Many etiologies and risk factors contribute to the development of obesity, including genetic predisposition, lifestyle choices, diseases and medications, social and economic factors, age, smoking, and pregnancy. The following section provides more details about these factors (Figure 1).

a. Genetic predisposition

Genes can influence body fat storage and distribution, as well as how efficiently the body converts food into energy, regulates appetite, and burns calories during exercise. Obesity often runs in families, not only due to shared genes but also because of similar eating and activity habits [5].

b. Lifestyle choices

Unhealthy Diet: A high-calorie diet that is low in fruits and vegetables, rich in fast food, and includes high-calorie drinks can lead to weight gain.

Liquid Calories: High-calorie drinks, such as alcohol and sugary sodas, can contribute to weight gain without providing a sense of fullness.

Inactivity: A sedentary lifestyle, including prolonged screen time, results in consuming more calories than are burned through daily activities and exercise [6].

c. Diseases and medications

Medical Conditions: Conditions like hypothyroidism, Cushing syndrome, and Prader-Willi syndrome can lead to obesity. Medical issues like arthritis can decrease activity and result in weight gain.

Medications: Some medicines, including steroids, antidepressants, anti-seizure drugs, diabetes medications, antipsychotics, and certain beta blockers, can cause weight gain if not balanced with diet or activity.

d. Social and economic factors

The lack of safe areas for exercise, inadequate cooking knowledge, limited access to healthy foods, and influence from friends or relatives with obesity can contribute to weight gain.

e. Age

Obesity can occur at any age, but hormonal changes, decreased activity, and loss of muscle mass with age increase the risk. These factors reduce metabolism and make weight control harder.

f. Other factors

Pregnancy: Weight gain during pregnancy can be difficult to lose post-birth, potentially leading to obesity.

Quitting smoking: Weight gain is common after quitting smoking due to increased food intake as a coping mechanism.

Lack of sleep: Insufficient or excessive sleep can alter hormones, increasing appetite for high-calorie, carbohydrate-rich foods, leading to weight gain.

Stress: External stressors can lead to increased consumption of high-calorie foods.

Microbiome: The composition of gut bacteria, influenced by diet, can affect weight gain and weight loss difficulty [7].

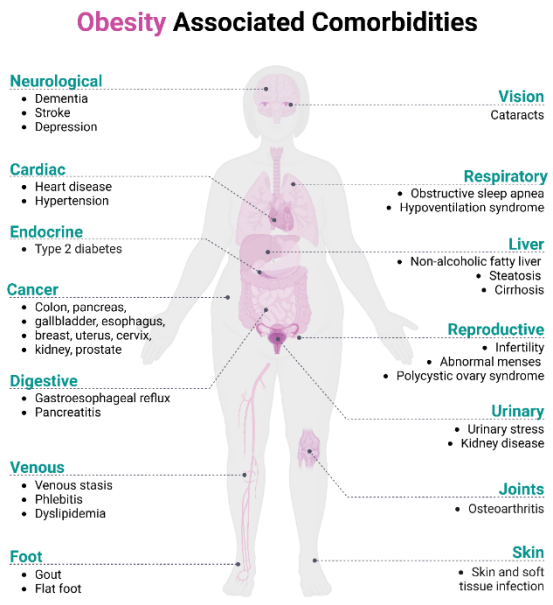

Figure 1. Obesity-associated comorbidities throughout the human body. Adopted from [4].

2. Complications of obesity

Obesity in both children and adults is linked to several health issues, including:

High blood pressure and cholesterol can lead to heart disease, type 2 diabetes, respiratory problems like asthma and sleep apnea, joint issues such as osteoarthritis and musculoskeletal pain, gallstones and gallbladder disease.

For children, obesity is also connected to:

Mental health challenges like anxiety and depression, low self-esteem and diminished quality of life, social issues, including bullying and stigma and the higher likelihood of obesity in adulthood. In adults, obesity raises the risk of: stroke, various cancers, early death, mental health conditions such as clinical depression and anxiety [8].

3. Obesity management and prevention

Management and prevention of obesity can be achieved by adopting healthy eating habits. Here are some diet regimes that can support weight loss and prevent obesity [9].

a. Enriching fruits and vegetables intake

Consuming a diet rich in fruits and vegetables lowers the risk of obesity. These foods are packed with beneficial nutrients and fiber, which help you feel full with fewer calories and regulate your digestive system. Fill your plate with a variety of colorful fruits and vegetables at every meal.

b. Reduce processed foods

Highly processed foods, like white bread and snack foods, are often high in empty calories. A study found that people who ate a minimally processed diet consumed fewer calories and lost weight compared to those on a highly processed diet. Healthy snacks like nuts, roasted chickpeas, and yogurt-covered blueberries can be consumed as an alternative to processed food [10].

c. Sugar and artificial sweeteners limitation

Keeping the minimal intake of added sugars low is fundamental. Escaping major sources of added sugar is also useful including sugary beverages, grain desserts, fruit drinks, candy, and dairy desserts. Even some natural sweeteners, like agave, should be used in moderation.

d. Reduce saturated fats

Foods high in saturated fats contribute to obesity. These include pizza, cheese, butter, and processed meats. Instead, focus on healthy fats found in avocados, olive oil, nuts, and fish. However, these fats should still be limited to about 20% to 35% of daily calories.

e. Being mindful of the beverages consumption

Soft drinks, energy drinks, and juices can quickly add up in sugar and calories. Even sugar-free and low-calorie drinks can contribute to health problems. Make water or unsweetened drinks your go-to beverages.

f. Home Cooking

Preparing meals at home can help prevent weight gain and reduce the risk of type 2 diabetes. Studies show that people who frequently eat home-cooked meals are less likely to have an overweight BMI [11].

g. Exercise regularly

Aim for at least 150 minutes of moderate-intensity physical activity per week. Walking at a brisk pace can help maintain a healthy weight. Staying active throughout the day with activities like using a standing desk or taking stretch breaks is also beneficial.

h. Reduce stress

Chronic stress can lead to weight gain by increasing cravings for high-calorie foods. Finding healthy ways to manage stress, such as walking, yoga, meditation, listening to music, and spending time with friends, can help prevent obesity.

i. Improve sleep

Getting enough sleep is crucial for overall well-being and preventing obesity. Aim for seven or more hours of sleep per night. Establishing a consistent bedtime routine, creating a comfortable sleep environment, and avoiding large meals and caffeine before bed can improve sleep quality. By making these changes to your diet and lifestyle, you can effectively prevent obesity and maintain a healthy weight [12].

j. Surgery

Weight-loss surgery, also called metabolic and bariatric surgery, includes several types of operations that help you lose weight by making changes to your digestive system. Your doctor may recommend weight-loss surgery if you have a BMI of 35 or higher. Some doctors and professional groups recommend weight-loss surgery for people with a lower BMI if

they have a serious health problem related to obesity, such as type 2 diabetes or sleep apnea [12].

4. FDA-approved medications for weight management

The FDA has authorized six medications for long-term use in weight management, presented in Figure 2: orlistat (Xenical, Alli), phentermine-topiramate (Qsymia), naltrexone-bupropion (Contrave), liraglutide (Saxenda), semaglutide (Wegovy), and tirzepatide (Zepbound). Four of these medications are approved for use in adults and adolescents aged 12 years and older. Another drug, setmelanotide (IMCIVREE), is specifically approved for individuals diagnosed with one of four rare genetic disorders, which must be confirmed through genetic testing. These medications can be continued as long as they provide therapeutic benefits without causing significant adverse effects [13].

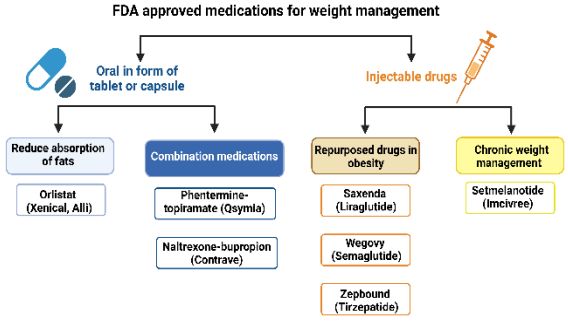

Figure 2. U.S. Food and Drug Administration (FDA) approved medication for weight management.

4.1. Types of pills that reduce absorption of fats

Few types of pills reduce the absorption of fats, primarily used for weight management. Here are the main ones:

4.1.1. Orlistat (Xenical, Alli):

Orlistat is the most commonly used medication in this category. It works by inhibiting the enzyme lipase, thereby reducing the amount of fat absorbed from food. *Mechanism of action:* Lipase, an enzyme produced in the pancreas and stomach, is responsible for breaking down dietary fats into smaller molecules, such as fatty acids and monoglycerides, which can be absorbed in the intestines. By inhibiting lipase activity, orlistat prevents the breakdown and absorption of approximately 25–30% of the fat consumed in meals. The undigested fat is then excreted in the stool. Since fats are calorie-dense, reducing fat absorption leads to a lower overall calorie intake, which can aid in weight loss and management.

Side effects: The most common side effects are gastrointestinal issues, including oily stools, flatulence, and frequent bowel movements. These effects are typically associated with the unabsorbed fat passing through the digestive system. Orlistat can reduce the absorption of fat-soluble vitamins (A, D, E, and K). Therefore, taking a multivitamin supplement is often advised to prevent potential deficiencies.

Regulatory approval: In 2007, orlistat as an oral, 60 or 120 mg tablet (marketed as Alli) was approved for over-the-counter (OTC) use in overweight adults aged 18 years and older. Its use is recommended in combination with a reduced-calorie, low-fat diet [14].

4.2. Combination medications

4.2.1. Phentermine-topiramate (Qsymia)

Mechanism of action: This medication is available as an extended-release capsule taken orally once daily. It combines two active ingredients that work together to suppress appetite and promote a feeling of fullness. It is typically recommended in conjunction with lifestyle modifications, including dietary changes and increased physical activity. This combination act by activating both noradrenergic and gamma-aminobutyric acid (GABA) receptors while inhibiting kainate and AMPA glutamate receptors. If significant weight loss is not achieved after 12 weeks, discontinuation may be advised.

Side Effects: Common side effects include tingling or numbness in the extremities or face, dizziness, changes in taste, dry mouth, constipation, and difficulty sleeping. It is contraindicated in pregnancy.

Regulatory Approval: This medication was approved by the FDA on July 17, 2012. Phentermine has long been used for weight loss, while topiramate, an antiepileptic agent, is known to induce weight loss as a side effect [15, 16].

4.2.2. Naltrexone-bupropion (Contrave)

Contrave, a medication marketed under this brand name, is available as an extended-release tablet that is administered once or twice daily. It is a combination of bupropion, an antidepressant and an inhibitor of dopamine and norepinephrine reuptake, and naltrexone, an opioid receptor antagonist. Together, these active ingredients work synergistically to reduce appetite and cravings by targeting specific areas of the brain involved in hunger regulation. While generally well-tolerated, some mild side effects have been reported, including nausea, vomiting, dizziness, dry mouth, headache, and constipation [17].

4.3. Injectable drugs used in obesity:

These drugs are repurposed (also called drug repositioning, reprofiling or retaking) which is a strategy to identify new uses for approved or investigational medicines that are outside the scope of the original medical indication.

4.3.1. Saxenda (Liraglutide)

Saxenda is a GLP-1 agonist used for type 2 diabetes

that aids in weight loss by reducing appetite and slowing gastric emptying. Which prolongs feelings of fullness and reduces calorie intake, it mimics a hormone that naturally occurs in the body, helping to control blood sugar, insulin levels, and digestion. Patients can achieve an average weight loss of 5-10% over a year. It was approved by FDA for weight loss, since December 2014 [18, 19].

4.3.2. Wegovy (Semaglutide)

Wegovy mechanism as Saxenda, It reduces glucagon secretion, slows gastric emptying, and promotes satiety by acting on appetite-regulating areas of the brain. Patients can achieve weight loss of 15% or more over a year. It was approved by FDA in March 2021 for weight loss and reduce risk of stroke in type 2 diabetes patients [20, 21].

4.3.3. Zepbound (Tirzepatide)

Zepbound is an injectable GLP1 receptor agonist used for type 2 diabetes , stimulates insulin release in response to high blood glucose levels. It regulates appetite by stimulating the release of insulin and glucagon, reducing hunger, and promoting satiety (feeling of fullness). Patients can achieve weight loss of 20% or more over a year. It was approved by the FDA for weight loss in November 2023 [22].

Common side effects of injectable drugs in Obesity

Saxenda (Liraglutide), Wegovy (Semaglutide), and Zepbound (Tirzepatide) are widely recognized for their efficacy in weight management; however, they come with some common side effects (Figure 3), distinct restrictions, and contraindications that must be taken into account (Table 1). While Saxenda is approved for adolescents aged 12 and older, both Wegovy and Zepbound remain restricted to adult patients and are not authorized for individuals under 18. Additionally, none of these medications are appropriate for those with type 1 diabetes, as their mechanism of action depends on enhancing insulin regulation, which is ineffective in individuals who do not produce insulin. Another important consideration is the increased risk of pancreatitis associated with all three drugs, necessitating careful monitoring in patients with a history of the condition and immediate reporting of any severe abdominal pain [1, 23]. Furthermore, Saxenda and Wegovy have been linked to a heightened risk of medullary thyroid carcinoma (MTC), making them unsuitable for individuals with a personal or family history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN2). Notably, this risk has not been identified with Zepbound. Since all three medications function by targeting the GLP-1 receptor, concurrent use is not recommended, as it may intensify adverse effects without offering additional therapeutic benefits. Moreover, Saxenda and Wegovy have been associated with gallbladder-related complications, including gallstones, which should be considered in patients with a history of gallbladder disease. While these medications provide substantial benefits in promoting weight loss, their use should be tailored to each patient's medical profile, with healthcare professionals overseeing treatment to ensure optimal safety and effectiveness [18, 21, 22, 24].

Table 1. Limitations and contraindications of injectable obesity drugs.

Limitation/ Contraindication	Saxenda (Liraglutide)	Wegovy (Semaglutide)	Zepbound (Tirzepatide)
Not for Pediatrics (Below 18 years)		✔	✔
Not for Type 1 Diabetes Patients	✔	✔	✔
Pancreatitis (Pancreas Inflammation)	✔	✔	✔
Thyroid Cancer Risk	✔	✔	
Not Co-administered with Other GLP-1 Agonists	✔	✔	✔
Gallbladder Disease	✔	✔	

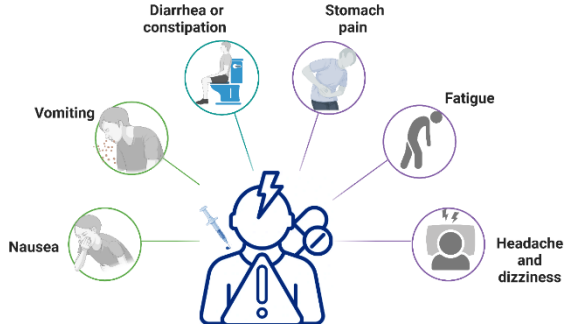

Figure 3. Common side effects of injectable weight management drugs.

4.4. Setmelanotide (Imcivree)

Mechanism of action: This medication is classified as melanocortin-4 (MC4) receptor agonist designed to address obesity resulting from deficiencies in proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or the leptin receptor (LEPR). It is approved by the FDA for use in severely obese adults and children over the age of six, specifically in cases where obesity is caused by certain genetic conditions confirmed through genetic testing. The medication is administered as a daily subcutaneous injection. If a patient does not experience weight loss after several months, discontinuation of treatment may be recommended.

Side effects: Imcivree requires careful monitoring due

to potential risks, including prolonged erections in males, suicidal thoughts, depression, and skin pigmentation changes. Regular dermatological assessments are recommended. Common side effects include skin hyperpigmentation, injection site reactions, gastrointestinal issues (nausea, vomiting, diarrhea), and spontaneous penile erections.

Regulatory approval: The FDA approved this medication in November 2020 for chronic weight management in adult and pediatric patients (aged six years and older) with obesity due to genetic conditions such as POMC deficiency, PCSK1 deficiency, or LEPR deficiency. These conditions result in severe obesity that begins at an early age [25].

5. Future Perspectives

The future of obesity management is shifting toward more personalized, accessible and effective treatment options. Advances in pharmacology are already reshaping the field, with next-generation drugs targeting multiple metabolic pathways for improved weight loss and long-term maintenance. Beyond medications, personalized treatment plans integrating genetic and metabolic profiling could help identify the most effective strategies for each individual, reducing trial-and-error approaches. Digital health technologies, including AI-driven coaching, mobile health applications, and wearable devices, are also expected to play a vital role in improving adherence to lifestyle changes and treatment plans. Moreover, addressing disparities in obesity care will be crucial. Expanding healthcare policies to ensure broader access to medications, preventive programs, and multidisciplinary obesity management in primary care can help close the gap between available treatments and patient outcomes. As research continues to explore the complex biology of obesity, the combination of pharmacotherapy, behavioral interventions, and innovative healthcare models will shape a future where sustainable weight management is more achievable.

6. Conclusion

Obesity is more than just a weight issue—it is a chronic, multifactorial disease that requires a long-term, individualized approach. While diet and exercise remain essential, they are often not enough for many individuals, making pharmacological and surgical interventions important tools in obesity management. Recent advancements in repurposed drugs, particularly GLP-1 receptor agonists and dual-acting medications, have shown promising results in reducing body weight and improving metabolic health. However, the challenge of long-term maintenance highlights the need for continuous care, patient education, and access to multidisciplinary support. Moving forward, the integration of innovative treatments, digital health solutions, and improved healthcare accessibility will be key in transforming obesity management from a reactive approach to a proactive, sustainable solution. By embracing a combination of lifestyle modifications, medical treatments, and emerging technologies, we can create a more effective and inclusive approach to tackling obesity and its associated health risks.

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