MINI REVIEW

PHARMACOTHERAPEUTIC APPROACHES TO OBESITY: NEW DRUG CLASSES AND MECHANISMS OF ACTION

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ABSTRACT:

Obesity remains a global health challenge, linked to numerous comorbidities such as cardiovascular disease, diabetes, and cancer. While traditional management strategies, including lifestyle interventions and bariatric surgery, have shown some success, they are often limited by factors such as patient adherence and availability. In recent years, pharmacotherapy has emerged as a promising adjunct for effective obesity management, with advances in drug development introducing novel mechanisms targeting both central and peripheral pathways involved in appetite regulation, energy expenditure, and metabolic function. This review explores emerging drug classes and mechanisms, including gastrointestinal peptide hormone analogues (GLP-1, GIP/GLP-1 dual agonists), melanocortin receptor agonists, and triple-agonist drugs, alongside newer therapeutic targets like the endocannabinoid system and brown fat thermogenesis. Additionally, it examines clinical efficacy, safety profiles, and potential limitations associated with these therapies. By providing a comprehensive analysis of these pharmacotherapeutic approaches, this review aims to enhance understanding of obesity management and identify areas for future research, including combination therapies and personalized medicine approaches. As obesity rates continue to rise, these novel pharmacotherapies hold promise for more effective and accessible treatment options, potentially transforming the landscape of obesity care.

KEYWORDS: Obesity pharmacotherapy, drug classes, mechanisms of action, appetite regulation, metabolic treatment.

Introduction

The global burden of obesity has reached alarming levels, affecting approximately 2 billion individuals worldwide, with one-third classified as obese. This condition is a significant public health crisis, contributing to various health risks such as diabetes, cardiovascular diseases, and certain types of cancer. In 2019 alone, obesity was linked to around 5 million premature deaths globally, underscoring its status as one of the leading preventable causes of death. The rise in obesity prevalence is not confined to high-income countries; it is increasingly recognized in low- and middle-income nations, where healthcare systems are often less equipped to manage its consequences.[1]

Current treatment approaches for obesity primarily include lifestyle modifications such as dietary changes and increased activity and surgical interventions like bariatric surgery. While these methods can be effective, they often face limitations. Lifestyle changes require sustained motivation and support, which many individuals struggle to maintain over time. Bariatric surgery, though impactful for severe obesity, poses risks and is not accessible to all patients due to cost and eligibility criteria45. Moreover, both approaches may not adequately address the underlying biological factors contributing to obesity.

Given these treatment gaps, there is a growing interest in new pharmacological treatments aimed at obesity management.

Recent advancements in drug classes and mechanisms of action show promise in addressing the multifaceted nature of obesity. These novel medications target various pathways involved in appetite regulation and energy expenditure, potentially offering more effective solutions for weight management compared

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to traditional methods45. The objective of this review is to focus on these emerging pharmacological options, evaluating their efficacy and safety profiles in the context of current obesity treatment paradigms.[2]

OVERVIEW OF PHARMACOTHERAPY FOR OBESITY

The historical perspective on obesity treatments reveals a complex evolution marked by both innovation and challenges. Early pharmacological approaches began in the 1940s with appetite suppressants and thermogenic agents, such as amphetamines and thyroid hormones. The first anti-obesity medication, desoxyephedrine, was approved in 1947, leading to a wave of similar sympathomimetic drugs. However, many of these early treatments were withdrawn due to serious safety concerns, including cardiovascular issues linked to fenfluramine and sibutramine, which were both associated with significant adverse effects that ultimately led to their market removal. By the late 20th century, the introduction of orlistat in 1999 marked a shift towards medications that inhibit fat absorption rather than solely suppress appetite. Despite its efficacy, orlistat is known for gastrointestinal side effects, highlighting ongoing challenges in obesity pharmacotherapy.[3]

Current standards of care for obesity now include several established pharmacotherapies approved by regulatory bodies, each with distinct mechanisms of action. These include:

Phentermine (Adipex, Lomaira): A sympathomimetic agent that suppresses appetite, effective for short-term use.

Orlistat (Alli, Xenical): An intestinal lipase inhibitor that reduces fat absorption by up to 30%, used alongside dietary modifications.

Phentermine-topiramate (Qsymia): A combination drug that decreases appetite and binge eating behaviors through sympathomimetic and carbonic anhydrase inhibition.

Bupropion-naltrexone (Contrave): This combination targets dopamine and norepinephrine pathways to reduce appetite and cravings.

Liraglutide (Saxenda) and Semaglutide (Wegovy): Both are GLP-1 receptor agonists that decrease appetite and increase feelings of fullness; they were initially developed for type 2 diabetes management but have shown significant weight loss effects.

Tirzepatide (Zepbound): A newer medication acting as a dual GLP-1 and GIP receptor agonist, demonstrating substantial weight loss outcomes.

These advancements illustrate the ongoing evolution in obesity treatment options, aiming to address both the physiological and psychological aspects of weight management more effectively than earlier approaches.[4]

EMERGING DRUG CLASSES FOR OBESITY TREATMENT

Recent advancements in obesity pharmacotherapy have introduced several emerging drug classes that show promise for effective weight management. These new treatments primarily focus on innovative mechanisms involving gastrointestinal peptide hormone analogues, melanocortin receptor agonists, and multi-agonist approaches. By targeting various pathways related to appetite regulation and energy expenditure, these drug classes aim to provide more effective solutions for obesity management compared to traditional therapies.

Gastrointestinal Peptide Hormone Analogues

GLP-1 agonists, such as liraglutide and semaglutide, are pivotal in obesity treatment due to their multifaceted mechanisms of action. These agents mimic the action of glucagon-like peptide-1 (GLP-1), a hormone released from the intestines in response to food intake. GLP-1 agonists suppress appetite by enhancing feelings of fullness and reducing hunger. They achieve this by slowing gastric emptying and influencing central nervous system pathways that regulate food intake, particularly through the activation of proopiomelanocortin (POMC) neurons and inhibition of neuropeptide Y (NPY) neurons in the hypothalamus. This dual

action leads to decreased energy intake and improved glucose homeostasis, making GLP-1 agonists effective for both weight loss and glycemic control.

GIP/GLP-1 Dual Agonists are an innovative class that combines GLP-1 with glucose-dependent insulinotropic peptide (GIP) actions. These dual agonists enhance efficacy by leveraging the complementary effects of both hormones on appetite regulation and metabolism. For instance, Tirzepatide, a dual agonist, has shown significant weight loss and improved glycemic control in clinical trials, indicating its potential as a robust treatment option for obesity.[5]

Melanocortin Receptor Agonists

The melanocortin-4 receptor (MC4R) plays a crucial role in appetite regulation and energy homeostasis. Activation of MC4R is associated with reduced food intake and increased energy expenditure, making it a target for obesity treatment. Drugs like Setmelanotide specifically target this receptor and have demonstrated efficacy in treating genetic forms of obesity linked to MC4R deficiencies. Clinical trials have shown that Setmelanotide can lead to significant weight loss in patients with these genetic disorders, highlighting its potential in specialized obesity management.

Triple-Agonist Drugs

New triple-agonist drugs combine GLP-1, GIP, and glucagon actions to stimulate multiple pathways involved in appetite regulation and energy expenditure. This multi-targeted approach aims to provide enhanced weight loss outcomes by addressing various mechanisms contributing to obesity. The mechanistic benefits of these drugs include overcoming resistance often seen with single-agent therapies, potentially leading to improved efficacy in long-term weight management.

Other Novel Pathways and Drug Classes

Emerging drug classes also include Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors, which serve a dual role in promoting weight loss while improving glucose control by preventing glucose reabsorption in the kidneys. This mechanism not only aids in weight management but also benefits patients with type 2 diabetes.

Additionally, endocannabinoid system modulators are being explored for their ability to influence appetite through cannabinoid receptor pathways, potentially offering new avenues for appetite control. Lastly, β3-Adrenergic Receptor Agonists target brown adipose tissue to enhance thermogenesis, thereby increasing energy expenditure as a means of combating obesity.

These diverse approaches reflect the ongoing innovation in pharmacotherapy for obesity, aiming for more effective management strategies tailored to individual patient needs.[6]

MECHANISMS OF ACTION IN DETAIL

Appetite Regulation Pathways

New obesity treatments target various neural and hormonal pathways involved in appetite regulation, particularly focusing on the hypothalamus, which plays a central role in energy balance. Key hormones such as leptin, ghrelin, GLP-1, and insulin interact with hypothalamic neurons to modulate hunger and satiety signals.

GLP-1 agonists, for instance, enhance satiety by activating GLP-1 receptors in the hypothalamus, which reduces food intake through anorexigenic (appetite-suppressing) effects. These drugs also inhibit the secretion of ghrelin, the hormone that stimulates appetite. Additionally, they slow gastric emptying, leading to prolonged feelings of fullness after meals. The integration of these signals helps the body maintain energy homeostasis by balancing caloric intake with energy expenditure.

GIP/GLP-1 dual agonists further enhance appetite regulation by combining the actions of GLP-1 with GIP, which also influences insulin secretion and fat metabolism. This synergistic effect on hypothalamic pathways results in improved appetite suppression and energy regulation.[7]

Energy Expenditure and Thermogenesis

Several new drugs are designed to enhance fat oxidation and thermogenesis, contributing to increased energy expenditure. For example, melanocortin receptor agonists target the melanocortin-4 receptor (MC4R), which is crucial for regulating energy expenditure and appetite. Activation of MC4R leads to increased thermogenesis and fat oxidation, promoting weight loss.

Additionally, β3-adrenergic receptor agonists stimulate brown adipose tissue (BAT), which plays a significant role in thermogenesis. By activating these receptors, these drugs enhance heat production through increased metabolic activity in BAT, thereby promoting energy expenditure.[8]

Metabolic Effects on Glucose and Lipid Metabolism

Emerging obesity treatments also exhibit beneficial effects on glucose and lipid metabolism. GLP-1 agonists improve insulin sensitivity and promote glucose-dependent insulin secretion while reducing glucagon levels, leading to better glycemic control. This mechanism not only aids in weight management but also helps prevent type 2 diabetes in individuals with obesity.

Furthermore, SGLT2 inhibitors contribute to weight loss by promoting glycosuria excretion of glucose through urine thereby reducing blood sugar levels while simultaneously aiding in weight management. These drugs help lower triglyceride levels and improve overall lipid profiles by enhancing fat oxidation.[9]

CONCLUSION

Advances in pharmacotherapy offer promising new options for obesity management, with novel drug classes targeting appetite regulation, energy expenditure, and metabolic health. While these treatments enhance the efficacy of traditional approaches, challenges like cost, long-term safety, and individual response remain. Continued research and personalized strategies will be key in making these therapies widely accessible and effective.

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