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Glucagon-like peptide-1 receptor agonists as a Therapeutic Option for Antipsychotic-Induced Obesity: A Review of Current Evidence

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ABSTRACT

Introduction

Obesity affects over 650 million adults worldwide and is a major risk factor for cardiovascular diseases and type 2 diabetes. Among those affected are patients treated with antipsychotics, such as clozapine and olanzapine, which often lead to significant weight gain, increasing the risk of metabolic syndrome. Recent advances with glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including semaglutide and liraglutide, show promise in addressing antipsychotic-induced obesity by reducing weight and improving metabolic health.

Purpose

The aim of this review is to present an overview of the current state of knowledge regarding the efficacy of GLP-1 RAs in the treatment of antipsychotic-induced obesity.

Materials and methods

This review is based on both original research studies and review articles identified through a comprehensive search of the PubMed database, using the following search terms: obesity, antipsychotic-induced weight gain, clozapine, olanzapine, adverse effect, GLP-1 receptors agonist.

Description of the state of knowledge

GLP-1 RAs significantly reduce body weight and adipose tissue by suppressing appetite, particularly for high-fat foods. Clinical trials show improvements in lipid profiles, blood

pressure, and inflammation, contributing to better metabolic health. However, their long-term effects, especially with different antipsychotics, remain insufficiently studied.

Conclusions

GLP-1 RAs show significant potential for managing antipsychotic-induced obesity, but further research is needed to assess long-term efficacy and safety in this population.

Keywords

obesity, antipsychotic-induced weight gain, clozapine, olanzapine, adverse effect, GLP-1 receptors agonist.

INTRODUCTION

Antipsychotic medications, also known as neuroleptics, are widely utilized in the treatment of various psychiatric disorders, most notably schizophrenia. These drugs are essential for controlling symptoms such as hallucinations, delusions, and disorganized thinking, significantly improving patient outcomes and quality of life [1]. Antipsychotics are broadly categorized into two generations: first-generation or typical antipsychotics, and second-generation, often referred to as atypical antipsychotics [2]. While first-generation antipsychotics primarily target dopamine D2 receptors, leading to effective symptom control, they are associated with extrapyramidal side effects, such as motor dysfunction and rigidity. In contrast, second-generation antipsychotics not only modulate dopamine receptors but also serotonin receptors, which has led to a reduction in motor-related side effects and an improvement in overall tolerability, thus making them a preferred treatment option for many patients [3].

Despite their advantages, second-generation antipsychotics are associated with a range of metabolic side effects, the most concerning being significant weight gain, which can lead to or exacerbate obesity [4]. This metabolic burden not only contributes to an increased risk of comorbidities, such as type 2 diabetes and cardiovascular diseases, but also negatively impacts treatment adherence, as patients often discontinue medication due to these side effects. Among second-generation antipsychotics, clozapine is recognized as having the highest potential to induce weight gain and metabolic disturbances, including insulin resistance and dyslipidemia [5]. These metabolic effects are particularly concerning given clozapine's otherwise favorable efficacy in treatment-resistant schizophrenia.

Addressing antipsychotic-induced obesity and the associated metabolic abnormalities presents a significant challenge in the long-term management of psychiatric conditions. Various therapeutic strategies have been explored, ranging from lifestyle interventions to pharmacological and surgical options. Lifestyle changes, such as dietary modification and increased physical activity, are often recommended as first-line interventions, but they are frequently insufficient in managing the severe weight gain associated with antipsychotic treatment [6]. In more extreme cases, invasive procedures like bariatric surgery have shown promising results, particularly in patients with morbid obesity, leading to substantial and sustained weight loss, as well as improvements in metabolic health [7].

Pharmacological interventions also play a crucial role in managing antipsychotic-induced weight gain. Metformin, an insulin-sensitizing agent commonly used in the treatment of type 2 diabetes, has been shown to reduce weight gain and improve metabolic parameters in patients taking antipsychotics [8]. Recently, there has been growing interest in glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as liraglutide and semaglutide, as novel therapeutic options for treating both obesity and metabolic dysfunction in patients receiving antipsychotics [9]. GLP-1 RAs, originally developed for managing type 2 diabetes, have shown significant potential in reducing body weight by promoting satiety, delaying gastric emptying, and improving insulin sensitivity [10]. Early clinical trials suggest that GLP-1 RAs may be effective in reducing antipsychotic-induced weight gain and associated metabolic risks, providing a new avenue for treatment in this challenging patient population [11].

Antipsychotic-Induced Obesity: Mechanisms and Clinical Impact

Antipsychotic medications are undeniably one of the cornerstone treatments for various psychiatric disorders, with schizophrenia being the primary condition. Pharmacotherapy in schizophrenia is often long-term, and in many cases, lifelong. Such treatment enables patients to function relatively well in society despite their condition [12]. However, the use of antipsychotic medications carries the risk of significant adverse effects, one of the most concerning being antipsychotic-induced obesity [13]. This condition not only increases the risk of comorbidities such as cardiovascular disease and type 2 diabetes but also contributes to a reduction in quality of life and poor adherence to prescribed therapies, posing a serious challenge. For instance, data from the Clinical Antipsychotic Trials of Intervention

Effectiveness (CATIE) study demonstrated that 74% of patients with chronic schizophrenia discontinued their medication within 18 months, largely due to side effects, including significant weight gain [14].

The life expectancy of individuals with schizophrenia is reduced by an average of 14.5 years, largely due to natural causes such as cardiovascular diseases and a higher risk of suicide [15]. Additionally, antipsychotic medications, although crucial for symptom control, contribute to this reduction through metabolic side effects like weight gain, insulin resistance, and an increased risk of diabetes. Both the natural factors and the side effects of treatment combine to significantly impact the lifespan of people living with schizophrenia [16]. The impact of antipsychotic drugs on body weight varies depending on the specific medication used and the individual biological response of the patient [17]. Weight gain associated with antipsychotic use is primarily attributed to the drug's interaction with various neurotransmitter receptors, including serotonin (5-HT2C), dopamine (D3), histamine (H1), and muscarinic (M3) receptors. Atypical antipsychotics, such as clozapine and olanzapine, are known to have a particularly strong affinity for these receptors, resulting in a higher risk of substantial weight gain [18,19].

Receptor Mechanisms and Weight Gain

Antipsychotic drugs, particularly second-generation antipsychotics, cause weight gain through complex interactions with several neurotransmitter receptors, including serotonin 5-HT2C, dopamine D2, histamine H1, and muscarinic M3 receptors. Blocking 5-HT2C receptors in the hypothalamus impairs satiety signaling, leading to increased appetite and excessive consumption of high-fat, high-calorie foods. At the same time, dopamine D2 receptor antagonism disrupts reward pathways, further exacerbating food-seeking behavior and increasing caloric intake. Antagonism of H1 receptors promotes appetite and reduces energy expenditure, further contributing to weight gain. Additionally, blocking M3 receptors negatively affects insulin secretion and glucose metabolism, increasing the risk of insulin resistance and hyperglycemia. These combined receptor mechanisms lead to increased fat accumulation and decreased insulin sensitivity, resulting in significant metabolic disturbances and rapid weight gain [18,20].

Impact on Adipokines and Metabolic Regulation

Antipsychotic medications also alter the levels of key adipokines, such as leptin and adiponectin, which are essential regulators of appetite and energy metabolism [21]. Studies have shown that patients treated with olanzapine exhibit elevated levels of leptin, which can lead to leptin resistance, a condition where the body fails to respond to the appetite-suppressing effects of this hormone [22]. At the same time, levels of adiponectin, a hormone that enhances insulin sensitivity and has anti-inflammatory properties, are reduced. These changes in adipokine levels contribute to insulin resistance and increased inflammation, further raising the risk of metabolic disorders like type 2 diabetes and cardiovascular disease [23].

Role of Ghrelin

Ghrelin, commonly known as the "hunger hormone," is believed to contribute to the development of obesity in patients undergoing antipsychotic treatment. Elevated ghrelin levels have been observed in these patients, leading to increased appetite and enhanced fat storage. While this suggests a possible link between ghrelin and antipsychotic-induced weight gain, additional research is required to clarify the precise role of ghrelin in this process and to assess whether modulating its activity could provide an effective approach to managing weight gain in this population [24].

Metabolic Consequences

The metabolic side effects of antipsychotic medications, particularly their impact on lipid and glucose metabolism, are closely linked to weight gain, especially the accumulation of visceral fat. Visceral adiposity plays a key role in the development of insulin resistance, contributing to increased levels of circulating triglycerides and very low-density lipoprotein (VLDL) production [25]. This fat accumulation leads to impaired insulin sensitivity in peripheral tissues, promoting further metabolic disturbances.

Moreover, there is growing evidence that antipsychotic medications upregulate the expression of sterol regulatory element-binding proteins (SREBP), which are critical regulators of lipid

biosynthesis. SREBP activation enhances the production and secretion of VLDL particles from adipocytes, exacerbating dyslipidemia and contributing to the development of metabolic syndrome. These changes in lipid metabolism increase the risk of cardiovascular diseases in patients undergoing long-term antipsychotic therapy [26]. The combination of increased fat storage, dysregulated lipid biosynthesis, and impaired glucose metabolism creates a multifactorial challenge for managing the metabolic health of individuals treated with these medications.

Managing Antipsychotic-Induced Obesity

Managing obesity induced by antipsychotic medications remains a clinical challenge. Invasive strategies, such as bariatric surgery, have been shown to be effective in severe cases, but pharmacological interventions are often preferred due to their less invasive nature. Recently, GLP-1 RAs such as liraglutide and semaglutide, have emerged as promising therapeutic options. These agents not only promote weight loss by reducing appetite and caloric intake but also improve metabolic parameters, making them a potential treatment for antipsychotic-induced obesity [27].

GLP-1 Receptor Agonists: Mechanism of Action

GLP-1 RAs are a relatively new class of drugs that have been widely used not only for the treatment of type 2 diabetes but also for obesity management. Initially developed for glycemic control, these drugs have shown remarkable efficacy in reducing body weight and improving metabolic health [28]. Their development began in the early 2000s, with drugs like exenatide and liraglutide, designed to mimic the natural GLP-1 hormone. As researchers observed significant weight loss in patients using GLP-1 analogs, their potential as obesity treatments became increasingly evident. In 2014, liraglutide (at a higher dose) became the first GLP-1 analog approved by the Food and Drug Administration (FDA) specifically for chronic weight management, followed by semaglutide in 2021, marking a new era in obesity treatment. Today, GLP-1 analogs are considered highly effective for weight loss, particularly in patients struggling with obesity-related health risks, offering a promising alternative to traditional weight management therapies [29].

GLP-1 RAs are synthetic analogs of the endogenous incretin hormone GLP-1, produced in the intestines. These drugs are structurally modified to increase stability, extend their half-life, and enhance biological activity compared to the native hormone. The native GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), whereas GLP-1 RAs are resistant to this degradation, allowing them to exert prolonged effects [30].

GLP-1 receptors are widely distributed throughout the body, including in the pancreas, brain, heart, kidneys, and gastrointestinal tract [31]. GLP-1 RAs exert their effects by specifically targeting these receptors. In the pancreas, GLP-1 RAs primarily support glucose homeostasis by stimulating insulin secretion from beta cells in response to elevated blood glucose. This glucose-dependent action minimizes the risk of hypoglycemia, a common side effect in diabetes management. Concurrently, GLP-1 RAs inhibit glucagon secretion from pancreatic alpha cells, which prevents unnecessary glucose production by the liver, thus aiding in overall blood glucose stabilization. This combination of enhanced insulin secretion and suppressed glucagon release makes GLP-1 RAs an effective tool for glycemic control in patients with type 2 diabetes [32,33]. In the gastrointestinal tract, GLP-1 RAs have a pronounced effect on gastric motility by slowing gastric emptying. This delayed gastric emptying prolongs the digestion process, extending the sensation of fullness (satiety) following meals. As a result, patients experience reduced appetite, which can significantly decrease total caloric intake and limit the desire for frequent snacking, especially on energy-dense foods. This mechanism is particularly beneficial for weight management, as it provides a natural form of appetite suppression that promotes gradual and sustained weight loss. Furthermore, slower gastric emptying prevents rapid spikes in blood glucose levels after meals (postprandial glucose spikes) by moderating the rate at which carbohydrates are absorbed from the stomach into the bloodstream [34].

Hypothalamic Action and Appetite Regulation

One of the key mechanisms by which GLP-1 RAs contribute to weight loss is their action on the hypothalamus, a region in the brain responsible for regulating appetite and energy balance [35]. GLP-1 receptors in the hypothalamus modulate neuronal pathways involved in hunger and satiety. By activating specific neuronal circuits, GLP-1 RAs increase the sensation of fullness (satiety) and reduce hunger, leading to decreased caloric intake. This is particularly relevant in reducing the desire for energy-dense foods, such as those high in fat [36]. The prolonged action of GLP-1 RAs on these central nervous system pathways distinguishes them

from other weight-loss medications, as they directly influence the neuroendocrine regulation of food intake [37].

Peripheral Metabolic Effects

Beyond their central effects on appetite and weight control, GLP-1 RAs reduce glucose production in the liver by inhibiting gluconeogenesis, promote lipolysis in adipose tissue, and reduce fat accumulation [38]. These actions improve overall metabolic health. In the cardiovascular system, GLP-1 RAs enhance endothelial function, reduce arterial stiffness, and lower blood pressure, contributing to their cardioprotective effects. These drugs also reduce oxidative stress and inhibit pro-inflammatory cytokines, which are key factors in the development of atherosclerosis [39].

Cardioprotective Effects and Clinical Trials

The cardiovascular benefits of GLP-1 RAs have been confirmed in a series of landmark clinical trials, which evaluated their effects on major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal stroke, and myocardial infarction. These benefits are attributed to both the direct effects of GLP-1 RAs on cardiac tissues and their impact on traditional metabolic risk factors, such as HbA1c, body weight, and blood pressure [40].

The LEADER trial evaluated the impact of liraglutide on cardiovascular outcomes in patients with type 2 diabetes and established cardiovascular disease or high cardiovascular risk. The study found a 13% reduction in MACE confirming the cardioprotective effects of liraglutide in high-risk populations [41].

Semaglutide demonstrated a 26% reduction in MACE, particularly a 39% reduction in non-fatal stroke, in the SUSTAIN-6 trial. This highlights the dual benefits of semaglutide in glycemic control and cardiovascular protection [42].

The REWIND trial, which assessed dulaglutide, showed significant reduction in MACE compared to placebo, extending the evidence for cardiovascular protection to a broader patient population, including those without established cardiovascular disease [43].

Emerging Roles in Non-Diabetic Populations

While GLP-1 RAs were initially developed for the treatment of type 2 diabetes, their effects on weight loss and cardiovascular risk reduction have led to their exploration in non-diabetic populations [44]. Studies are ongoing to assess their utility in treating obesity without diabetes, as well as potential benefits in conditions like non-alcoholic fatty liver disease (NAFLD) and even neurodegenerative disorders due to their effects on inflammation and neuronal protection [45,46].

Adverse Effects of GLP-1 Receptor Agonists

GLP-1 RAs are generally well-tolerated, with a favorable safety profile, particularly given their benefits in weight reduction and cardiovascular health improvement. However, as with any medication, side effects can occur, clinical studies indicate that gastrointestinal symptoms, including nausea, vomiting, diarrhea, and constipation, can affect approximately 40-70% of patients treated with GLP-1 RAs, especially during the initial stages of treatment as the body adjusts to the medication [47]. These symptoms are often dose-dependent and can frequently be managed by gradually increasing the dose, which may help reduce their intensity [28].

Additionally, GLP-1 RAs slow gastric emptying, which contributes to a feeling of fullness and supports weight loss but can exacerbate gastrointestinal discomfort in some patients, leading to sensations of bloating, fullness [30,48].

Although rare, concerns have arisen regarding the potential increased risk of pancreatitis with the use of GLP-1 RAs. However, the evidence remains inconsistent, and further studies are necessary to definitively establish this association [49].

Another potential risk involves gallbladder-related issues, such as gallstones and cholecystitis. These effects may be linked to changes in bile secretion and gallbladder motility, which can lead to bile stasis and the formation of gallstones [50, 51].

It is also important to note that while the risk of hypoglycemia with GLP-1 receptor agonists (GLP-1 RAs) is generally low, certain factors can increase its likelihood. One study indicates that GLP-1 RA-induced hypoglycemia occurs more frequently in middle-aged patients compared to older adults and appears to be more common among women [52]. Additionally,

the risk can rise when GLP-1 RAs are combined with insulin or insulin secretagogues, such as sulfonylureas [53]. In these cases, regular blood glucose monitoring is recommended to prevent hypoglycemic episodes and ensure patient safety.

While GLP-1 RAs present certain adverse effects, particularly gastrointestinal symptoms, their overall safety profile remains favorable. The therapeutic benefits, such as significant weight reduction and improved cardiovascular risk factors, may outweigh the potential risks for many patients. However, the decision to use GLP-1 RAs should involve a careful assessment of both advantages and drawbacks, tailored to each patient's needs. Moreover, there is a clear need for further research to fully understand the long-term safety and efficacy of these agents, especially as their use expands beyond diabetes management into broader applications.

Clinical Evidence: Efficacy of GLP-1 RAs in Treating Antipsychotic-Induced Obesity

The use of GLP-1 RAs in treating antipsychotic-induced obesity has garnered considerable clinical interest due to positive results in both weight reduction and improvement of metabolic parameters. Studies have primarily focused on liraglutide and semaglutide, which have demonstrated potential efficacy and safety in patients suffering from obesity induced by psychiatric medications.

Review of Clinical Studies

In a randomized controlled trial from 2017, 103 patients with obesity induced by antipsychotic medication were enrolled in a 16-week study to evaluate the effectiveness of liraglutide, a GLP-1 RA, as a treatment option. Results indicated that patients receiving liraglutide experienced significant weight reduction compared to the placebo group. Body weight decreased by an average of 5.3 kg in the liraglutide group relative to placebo. Additional improvements were observed in waist circumference (-4.1 cm), systolic blood pressure (-4.9 mm Hg), visceral fat (-250.19 g), and low-density lipoprotein (LDL) levels (-15.4 mg/dL). These findings suggest that liraglutide may offer a viable therapeutic approach for managing weight gain and metabolic complications associated with long-term antipsychotic treatment, thereby helping to mitigate cardiovascular risk factors in this patient population [54].

In a retrospective study from 2023, researchers examined the efficacy of semaglutide, a GLP-1 RA, in managing antipsychotic-associated weight gain (AAWG) among patients with severe mental illness who had not achieved sufficient results with metformin. Conducted at the Metabolic Clinic at the Center for Addiction and Mental Health (CAMH) between 2019 and 2021, this study included twelve patients who received weekly injections of semaglutide. The participants, with a mean baseline weight of 111.4 kg and mean BMI of 36.7 kg/m², showed average weight reductions of 4.56 kg at 3 months, 5.16 kg at 6 months, and 8.67 kg at 12 months. Side effects were generally well-tolerated, indicating that semaglutide could be a promising treatment for AAWG, especially in patients who do not respond to metformin [55]. However, it is important to note that the study sample was very small, highlighting the need for larger trials to confirm these findings.

While GLP-1 RAs have generally shown promise in promoting weight loss and metabolic benefits, some studies suggest that they may not offer significant advantages for obese patients with schizophrenia treated with antipsychotics. One study, for instance, found that despite their effectiveness in other populations, exenatide demonstrated minimal impact on body weight compared to placebo in this group. These findings suggest that the interaction between GLP-1 receptor agonists and antipsychotic medications, particularly their effects on dopamine pathways, could reduce the effectiveness of GLP-1-based treatments in this context [56].

Another article presents a systematic review of approved weight-loss medications for managing antipsychotic-induced weight gain, focusing primarily on liraglutide, semaglutide, and the naltrexone-bupropion combination. The findings indicate that liraglutide provides the strongest clinical evidence for reducing body weight and improving key metabolic markers, including BMI, waist circumference, HbA1c, and LDL cholesterol, in patients with antipsychotic-induced obesity. Semaglutide also shows promising results, particularly for patients unresponsive to metformin, although current research on its effects in this population is limited. The review underscores the need for larger, more comprehensive trials to better assess the efficacy and safety of these medications for patients treated with antipsychotics, considering the unique challenges of antipsychotic-induced weight gain. This review lays the groundwork for future research, aiming to develop effective weight-management strategies for this vulnerable population and emphasizing the importance of mitigating cardiometabolic risks to enhance quality of life and overall health outcomes [57].

In 2024 researchers conducted a comprehensive systematic review and meta-analysis to assess the effectiveness of GLP-1 receptor agonists, specifically liraglutide and exenatide, in managing weight gain caused by antipsychotic medications. The analysis included randomized controlled trials and cohort studies, with a focus on changes in body weight, BMI, and potential side effects. The findings revealed that liraglutide led to a significant average weight loss of approximately 4.7 kg and a BMI reduction of 1.52, whereas exenatide showed moderate weight loss of 2.48 kg and a BMI decrease of 0.82. These outcomes suggest that liraglutide, in particular, may be a more effective option for weight management in this context. Importantly, neither liraglutide nor exenatide aggravated psychiatric symptoms, making them a viable option for patients with schizophrenia or similar conditions experiencing antipsychotic-related weight gain. Common side effects were primarily mild gastrointestinal issues, such as nausea, vomiting, and diarrhea, which were generally manageable and did not significantly interfere with treatment adherence. These results underscore the potential of GLP-1 agonists, especially liraglutide, as safe and effective pharmacological interventions for addressing metabolic side effects associated with antipsychotic therapy. However, the authors note that further studies are necessary to confirm these findings over the long term and to determine the sustainability of weight loss and overall metabolic benefits in this patient population [58].

Potential Neuropsychiatric Benefits

GLP-1 receptors in the central nervous system has been linked to neuroprotective effects, such as reducing cell death, enhancing neuronal growth, and promoting long-term potentiation, which is essential for learning and memory. Clinical and preclinical studies suggest that GLP-1 RAs, like liraglutide, may improve cognitive function and mitigate cognitive decline in individuals with mood disorders, providing a potential avenue for repurposing these medications beyond their metabolic applications [59].

Research has shown that GLP-1 RAs provide robust neuroprotection, shielding neurons from oxidative stress, reducing amyloid-beta accumulation - a key factor in neurodegenerative diseases - and enhancing synaptic plasticity, which is vital for memory and learning. Additionally, GLP-1 RAs have been shown to support neurogenesis by promoting the proliferation and differentiation of neural progenitor cells, which may help offset cognitive decline often associated with mood and metabolic conditions [60].

Limitations of Current Research

While GLP-1 RAs show considerable promise in addressing antipsychotic-induced obesity, several limitations in the existing research warrant attention. A primary limitation is the limited number of randomized controlled trials (RCTs) directly evaluating their long-term efficacy and safety, particularly within psychiatric populations. The available studies are typically short-term and often involve small sample sizes, which limits the generalizability of findings to broader patient groups.

Additionally, while GLP-1 RAs have demonstrated cardiometabolic benefits, there is a need to better understand their impact on the complex needs of psychiatric patients, who may have unique metabolic and behavioral profiles. Another crucial consideration is the potential for drug interactions. Many patients on antipsychotic medications are prescribed additional medications, and the interactions between GLP-1 RAs and other commonly used drugs in this population remain underexplored. Given the polypharmacy frequently observed in psychiatric treatment, future studies should investigate how GLP-1 RAs interact with a range of medications, including antipsychotics, mood stabilizers, and other metabolic agents, to ensure the safety and effectiveness of combined therapies.

Need for Further Research

Future research must prioritize long-term studies on the safety and efficacy of GLP-1 RAs in patients with severe mental disorders, especially those undergoing antipsychotic treatment. Conducting larger RCTs with more extensive follow-up periods is essential for accurately assessing potential adverse effects, optimizing dosing strategies, and identifying any risks associated with prolonged use in this vulnerable population. Research should also focus on the potential cognitive and psychological effects of GLP-1 RAs, exploring how these agents may influence mental health outcomes and overall quality of life.

Expanding research efforts in these areas is critical for establishing GLP-1 RAs as a viable treatment option for antipsychotic-induced obesity. Comprehensive studies that include a diverse patient population and account for potential drug interactions will provide clearer guidance for clinical practice, ensuring that GLP-1 RAs can be safely integrated into complex treatment regimens without compromising patient well-being.

Comparative Efficacy of GLP-1 RAs vs. Other Treatment Modalities

Antipsychotic-induced obesity presents a significant health challenge, with multiple strategies available for management. While lifestyle interventions, such as regular physical activity, are often effective in general obesity management, implementing consistent exercise routines can be particularly challenging for individuals in this patient group due to the nature of psychiatric conditions and medication side effects. Pharmacological options are therefore commonly considered as adjuncts to lifestyle changes. Among these, metformin is commonly prescribed [61]. Acting primarily by improving insulin sensitivity and reducing hepatic glucose production, metformin offers modest weight loss and glycemic control benefits [62]. However, its effects on body weight can be limited, particularly in patients with severe or persistent antipsychotic-induced obesity [55,63]. Another class of medications, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, such as dapagliflozin, works by increasing urinary glucose excretion [64]. This leads to a moderate weight reduction but tends to be less effective than GLP-1 receptor agonists (GLP-1 RAs) in terms of sustained weight management [65]. Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin, indirectly increase GLP-1 levels by inhibiting its breakdown, enhancing postprandial insulin secretion, yet typically have only a mild effect on body weight [66, 67].

In more extreme cases, bariatric surgery may also be considered. These results are promising but require further research to fully understand long-term safety and efficacy in patients with antipsychotic-induced obesity. As with any invasive procedure, bariatric surgery carries increased risks, making it generally reserved for patients with severe obesity who have not responded adequately to pharmacological treatment [68,69].

CONCLUSIONS

Available data suggest that GLP-1 receptor agonists (GLP-1 RAs), such as liraglutide and semaglutide, represent a promising therapeutic option for patients with antipsychotic-induced obesity. Their unique mechanism of action - modulating appetite and metabolism through effects on the central nervous system and endocrine system - enables significant weight reduction and improvement in key metabolic parameters, including lipid profiles, insulin sensitivity, and blood pressure. These characteristics make GLP-1 RAs an effective tool in

addressing the adverse metabolic side effects of antipsychotic therapy, which, if untreated, can lead to severe health outcomes such as metabolic syndrome, type 2 diabetes, and cardiovascular diseases.

However, while the therapeutic potential of GLP-1 RAs is substantial, there remains a critical need for additional research. Future studies should prioritize larger sample sizes and longer follow-up periods to thoroughly evaluate the long-term safety and efficacy of these agents in psychiatric populations. Such research will be essential for refining dosing regimens and understanding potential drug interactions, given the complex medication profiles often present in this patient group. Specifically, the interaction of GLP-1 RAs with antipsychotic medications, mood stabilizers, and other metabolic agents must be investigated to optimize therapeutic outcomes and minimize the risk of adverse effects.

Moreover, further exploration into the impact of GLP-1 RAs on mental health outcomes is crucial to establishing a comprehensive profile of their benefits and limitations. Understanding how GLP-1 RAs affect not only physical but also psychological health outcomes - such as mood stability, cognitive function, and overall quality of life - will be instrumental in shaping future clinical guidelines.

In conclusion, GLP-1 RAs represent an innovative approach to managing antipsychotic-induced obesity, offering benefits beyond weight loss that could significantly enhance the quality of life and health outcomes for patients with psychiatric disorders. Given their efficacy in reducing cardiometabolic risks and potential neuroprotective properties, GLP-1 RAs have the potential to become a standard therapeutic option for this patient group, especially as further research solidifies their safety and efficacy profile in the psychiatric context.

Disclosure

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