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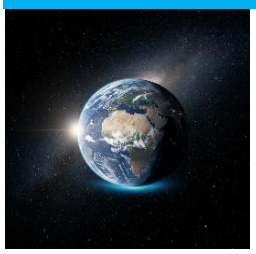

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Use of GLP-1 Analogues in Patients with Schizophrenia and Other Neuropsychiatric Disorders: A Literature Review

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Abstract:

Background: Schizophrenia is a chronic mental disorder associated with an increased risk of metabolic disturbances such as obesity, insulin resistance, and type 2 diabetes, as well as cognitive impairment. This is due to both the pathophysiology of the disease and the use of second-generation antipsychotics.

Aim of the study: To review the literature on the use of GLP-1 analogs in the treatment of metabolic and cognitive disorders in patients with schizophrenia and other neuropsychiatric diseases.

Methodology: The analysis was based on publications from PubMed and Google Scholar, using keywords related to schizophrenia, GLP-1 analogs, and metabolic disorders. Studies from 1999 to 2026 were analyzed.

Results: GLP-1 analogs show beneficial effects on weight reduction and improvement of glucose and lipid parameters in patients with schizophrenia. There are also indications that they may impact cognitive functions and could be used in other neuropsychiatric disorders. They have a good safety profile and do not exacerbate psychotic symptoms.

Conclusion: GLP-1 analogs are a promising therapeutic strategy in schizophrenia and may have broader applications in neuropsychiatric diseases; however, further clinical studies are required.

Keywords: schizophrenia, GLP-1 analogs, metabolic syndrome, adverse effects of antipsychotic drugs, mental disorders, cognitive disorders

1. Introduction

Schizophrenia is a serious mental disorder characterized by positive and negative symptoms as well as significant impairment of general cognitive functioning. Antipsychotic drugs are a key component of schizophrenia therapy; however, their use, especially second-generation agents, is often associated with side effects such as weight gain, lipid abnormalities, and impaired glucose regulation, which consequently increases the risk of developing MetS. Among drugs used in the treatment of schizophrenia, the highest risk of weight gain is associated with clozapine and olanzapine.

Although lifestyle modification and the use of metformin have shown a beneficial effect on MetS parameters, reviews to date indicate insufficient evidence to confirm the efficacy of most pharmacological strategies for reducing antipsychotic-related weight gain. GLP-1 analogs represent a promising therapeutic strategy in the treatment of MetS in individuals with schizophrenia, and an increasing number of studies, particularly concerning semaglutide and liraglutide, confirm their beneficial effects on metabolic parameters.

GLP-1 analogs also represent a promising method for treating cognitive disorders in individuals with schizophrenia, as preliminary research suggests their potential beneficial effect on processes such as memory, attention, and executive functions. The mechanisms of this action may be related, among other things, to modulation of neurotransmission, neuroprotective effects, and influence on inflammatory processes in the central nervous system. Nevertheless,

this issue remains the subject of ongoing research and requires further, large-scale, and well-designed clinical studies to definitively assess the efficacy and safety of this form of therapy.

The aim of this paper is to review the current literature on the use of GLP-1 analogs in patients with schizophrenia, with particular attention to their impact on metabolic disorders and cognitive functions. Furthermore, the paper aims to assess the potential mechanisms of action of these drugs and their safety in this population. Additionally, the possibility of using GLP-1 analogs in the treatment of other neuropsychiatric disorders such as Alzheimer's disease, alcohol use disorder, and depression is discussed.

2. Methodology

A literature search was conducted in electronic databases such as PubMed and Google Scholar. The search focused on keywords such as "schizophrenia", "GLP-1 analogs", "metabolic syndrome", "adverse effects of antipsychotic drugs", "mental disorders" and "cognitive disorders." The search included publications from 1999 to 2026. Additionally, the bibliographies of selected articles were analyzed to identify further relevant studies.

2.1 Inclusion criteria

The following inclusion criteria were used to ensure the quality and relevance of the selected literature.

- Study design: systematic reviews, meta-analysis, and large-scale cohort studies. The studies concerned: the effect of GLP-1 analogs on the treatment of metabolic syndrome in people with schizophrenia, the effect of GLP-1 analogs on cognitive improvement, the use of GLP-1 analogs in Alzheimer's disease, depression, and alcohol use disorder, and the safety of GLP-1 analogs in people taking antipsychotic drugs.
- Only articles published in reputable, peer-reviewed scientific journals were included to ensure the high quality and reliability of the studies. This criterion was crucial to maintaining the scientific integrity of the review.
- The time interval was limited to publications from 1999–2026. This ensured that the review was based on recent and up-to-date research findings, reflecting the current state of knowledge in the field.

2.2 Exclusion criteria

Exclusion criteria mainly encompassed studies not directly related to the topics of GLP-1 analogs, schizophrenia, and other neuropsychiatric disorders.

2.3 Data extraction and synthesis

Key information was extracted from the selected publications, including: type of study, sample size, participant characteristics, variables analyzed (e.g., type of GLP-1 analog used, antipsychotic medication taken during treatment), main study outcomes, and conclusions regarding the effects of GLP-1 analog treatment in people with schizophrenia and selected neuropsychiatric diseases.

Data extracted from the included studies comprised:

The effect of GLP-1 analogs on the treatment of metabolic syndrome in people with schizophrenia

The effect of GLP-1 analogs on cognitive improvement in people with schizophrenia

The use of GLP-1 analogs in Alzheimer's disease, depression, and alcohol use disorder

The safety of GLP-1 analogs when used with antipsychotic drugs

This approach enabled a comprehensive analysis of the current state of knowledge and the identification of areas that require further research.

3. Schizophrenia

Schizophrenia is a mental disorder characterized by the coexistence of various groups of psychopathological symptoms, which must persist for at least six months, including at least one month in an acute form. The chronic course of the disease and significant deterioration in patient functioning make early diagnosis and the initiation of appropriate treatment crucial [1].

In the treatment of schizophrenia, positive and negative symptoms are distinguished; positive symptoms may decrease over time, whereas negative symptoms tend to persist or even worsen. [1]. Positive symptoms include, among others, hallucinations, delusions, and disorganized behavior and speech [2]. Descriptions of negative symptoms highlight two main aspects:

reduced emotional expression and loss of motivation [3]. These include diminished functioning, affective flattening, alogia, avolition, asociality, and anhedonia [4].

Chlorpromazine, the first antipsychotic introduced in 1951, is effective for positive symptoms of schizophrenia, while clozapine and other atypical drugs may also alleviate negative symptoms [5]. Four antipsychotics - cariprazine, olanzapine, clozapine, and amisulpride - are recommended as first-line drugs for patients with predominantly negative symptoms. Furthermore, in adjunctive therapy, the strongest evidence supports the effectiveness of memantine, 5-HT_3 receptor antagonists (setrons), minocycline, and antidepressants [6]. Introducing a drug with a different mechanism of action into the treatment regimen may allow for a reduction in the dose of the current medication and improve tolerance in patients experiencing side effects, such as weight gain [7].

In addition to the characteristic symptoms, schizophrenia is also associated with an increased susceptibility to comorbid conditions [8].

4. Incidence of Metabolic Syndrome in Patients with Schizophrenia

Patients with schizophrenia who are receiving pharmacological treatment show a significantly increased risk of metabolic disorders, with more than a fourfold higher risk of abdominal obesity and more than double the risk of metabolic syndrome (MetS), hypertriglyceridemia, and low HDL cholesterol levels compared to the general population. Moreover, they also have nearly twice the risk of developing type 2 diabetes (T2D) [9]. It is estimated that 45-55% of individuals with schizophrenia will develop obesity, and 37-63% will develop MetS [10].

Weight gain may occur even at relatively low effective doses of medication, and increasing doses can be associated with greater weight gain with some drugs [11]. Among the drugs used in schizophrenia, clozapine [12] and olanzapine [13] have the greatest potential to induce weight gain. In addition to their impact on body weight, olanzapine and clozapine most significantly increase glucose and cholesterol levels [14]. Australian studies have shown that between 2006 and 2018, olanzapine was among the most prescribed medications for schizophrenia [15].

It is suggested that weight gain induced by antipsychotics may contribute to nonadherence and treatment discontinuation [16]. Weight gain worsens quality of life for patients, impairs social

interactions, and lowers self-esteem [17]. These findings underscore the strong need to seek methods that limit the adverse effects of these drugs, especially metabolic disorders and the resulting therapeutic failures. Weight gain affects not only physical health but also reduces quality of life, hinders social interactions, and lowers self-esteem, which can lead to nonadherence, relapses, and worse mental health outcomes [18].

However, results from studies summarized in a meta-analysis suggest that disrupted glucose homeostasis can be present already in the early stages of the disease, even before treatment initiation [18], and may lead to increased BMI and obesity [19]. Other studies show that glucose metabolism may be regulated by the dopaminergic pathway in patients with schizophrenia. A positive correlation has also been found between the severity of negative symptoms and higher fasting blood glucose levels in antipsychotic-naïve patients with schizophrenia [20].

Further research has demonstrated that schizophrenia and T2D have partly shared genetic risk factors related to insulin resistance (IR). Furthermore, disturbances in glucose metabolism, such as elevated fasting glucose and insulin levels, increased IR, and reduced glucose tolerance, can already be observed in patients experiencing their first episode of psychosis prior to starting antipsychotic treatment, suggesting a link between hyperinsulinemia and increased risk of schizophrenia [21].

5. Mechanism of Action of GLP-1

Analogs Glucagon-like peptide 1 (GLP-1) is an incretin hormone produced mainly by enteroendocrine L-cells located in the ileum, as well as in other parts of the small and large intestine. It is secreted in response to food intake and the presence of nutrients in the intestinal lumen [22]. GLP-1 increases insulin secretion by pancreatic β-cells, while simultaneously inhibiting glucagon secretion by α-cells, limiting gluconeogenesis in the liver, and improving tissue sensitivity to insulin. It is also responsible for slowing gastric emptying and enhancing satiety. GLP-1 receptors are present in the cardiovascular system, central nervous system, and digestive tract [23].

The first clinically approved GLP-1 receptor agonist (GLP-1 RA) was exenatide, introduced in 2005 for the treatment of T2D. Subsequent years saw the development of other longer-acting preparations, such as liraglutide, lixisenatide, semaglutide, dulaglutide, as well as tirzepatide,

the first co-agonist of glucose-dependent insulinotropic peptide (GIP) and GLP-1 receptors. Currently, dulaglutide, semaglutide, and tirzepatide are among the most commonly used drugs in this group for the treatment of T2D [24].

Administration of semaglutide subcutaneously is recognized as a significant aid in the treatment of obesity, in conjunction with behavioral therapy and a low-calorie diet [25]. The SUSTAIN, PIONEER, and STEP clinical trials have demonstrated greater efficacy of semaglutide in reducing body weight compared to other antidiabetic drugs, which led to its approval for the treatment of obesity. Another advantage of semaglutide is the possibility of its long-term use for weight control [26].

6. Treatment of Obesity and Metabolic Disorders in Schizophrenia Using GLP-1 Analogs

Currently, indications for the use of GLP-1 RAs approved by the U.S. Food and Drug Administration (FDA) include T2D, weight management, reduction of cardiovascular events and progression of chronic kidney disease, obstructive sleep apnea, and nonalcoholic fatty liver disease. These indications can have various impacts on individuals with severe mental disorders, contributing to the deterioration of their health [27]. Despite the high prevalence of obesity among patients with schizophrenia, options for effective treatment and knowledge in this area remain limited. Previous reviews have indicated insufficient evidence to confirm the effectiveness of most pharmacological strategies for reducing antipsychotic-induced weight gain [28].

Behavioral programs based on diet changes and increased physical activity can help individuals with schizophrenia reduce their body weight; however, their effectiveness is often diminished due to low participant engagement and high dropout rates [28].

On the other hand, the studies we reviewed demonstrate a significant effect of semaglutide in reducing body weight in patients with schizophrenia [17,28,29]. The HISTORI study observed a positive impact of semaglutide on improving insulin sensitivity, reducing IR, lowering fasting glucose levels, and significantly reducing body weight in patients treated with second-generation antipsychotics. Weight loss partially accounted for the metabolic improvements in patients, while pancreatic β-cell function remained unchanged [28]. Another study showed that subcutaneous use of semaglutide at 1 mg once weekly for 30 weeks lowered glycated

hemoglobin (HbA1c) below 5.7% in 81% of participants with schizophrenia [29]. Semaglutide does not affect psychotic symptoms nor the concentration of clozapine used in treatment [17]. These findings indicate that semaglutide is promising in mitigating metabolic disorders in patients with schizophrenia [30].

In addition to semaglutide, liraglutide has also been shown to be effective in reducing body weight in metabolic disorders, as demonstrated in a study involving the treatment of female rats receiving subcutaneous infusions of olanzapine with liraglutide [30]. In another study, this time conducted on male mice, it was shown that concomitant administration of liraglutide effectively protected against acute olanzapine-induced hyperglycemia, while alleviating glucagon elevation and increasing serum insulin levels [31].

7. Treatment of Cognitive Impairments in Schizophrenia Using GLP-1 Analogs

The prevalence of T2D and IR in patients with schizophrenia is higher than in the general population [9, 32]. Studies have shown alterations in molecules related to IR as well as glucose homeostasis in patients with schizophrenia, including those previously untreated with antipsychotics [33, 34, 35]. As is known, coexisting disorders of glucose regulation are associated with worsening cognitive function [36].

In a study conducted on 159 people with schizophrenia, those with MetS scored lower on tests measuring attention/vigilance, working memory, and problem-solving compared to those without MetS [37].

The influence of GLP-1 RAs on metabolic outcomes in people with schizophrenia is well known [29, 38]. There is currently limited clinical evidence to support the impact of GLP-1 RAs on improving cognitive function; however, a 2018 study involving 106 patients with T2D showed that lower serum GLP-1 levels closely correlated with cognitive dysfunction in patients with T2D [39].

The probable neuroprotective effect may result from the action of GLP-1 RAs in modulating cellular processes such as neuroinflammation, oxidative stress, apoptosis, and mitochondrial dysfunction [40]. There is also frequent discussion about the potential of GLP-1 RAs in treating cognitive functions themselves in people with schizophrenia; however, further research in this field is needed [41].

8. Use of GLP-1 Analogs in Other Neuropsychiatric Disorders

GLP-1 RAs also appear to have promising potential in other mental disorders, neurodegenerative diseases, or in the treatment of addiction to psychoactive substances [42, 43, 44]. GLP-1 RAs are gaining attention among researchers as potential treatments for addictions to alcohol, tobacco, and opioids, as well as for mood disorders [45, 46]. There is also evidence to suggest that GLP-1 RAs may play a role in the modulation of pain perception, indicating their potential as a novel analgesic strategy [47].

8.1 Treatment of Alzheimer's Disease

Studies on the neuroprotective effects of GLP-1 RAs in Alzheimer's disease (AD) have shown that GLP-1 enhances the ability of astrocytes to support neuronal function and neuron survival under β-amyloid conditions. The observed effects included increased growth of neuronal structures and the expression of synaptic proteins, which was dependent on the glycolytic activity of astrocytes. The above study explains that the neuroprotective effect of GLP-1 may result from the regulation of cellular energy metabolism, including enhanced glycolytic processes and activation of the PI3K/Akt pathway. This suggests that targeting therapy toward modulation of the cells' energy homeostasis may represent a promising strategy to slow the progression of AD [42].

8.2 Treatment of Alcohol Use Disorder

In a randomized clinical trial, semaglutide was shown to reduce alcohol consumption in a controlled self-administration task and to lower the intensity of alcohol craving compared to placebo, although not all measures of consumption changed significantly. These effects suggest that GLP-1 RA-based therapies have clinical potential as a new approach to treating alcohol use disorders; however, larger clinical studies are needed to fully confirm their effectiveness and therapeutic significance [48].

In another placebo-controlled study in male vervet monkeys, liraglutide administration led to reduced voluntary alcohol consumption [49]. Additionally, in studies on female and male rats, liraglutide was shown to attenuate nicotine self-administration and reinstatement, as well as reduce hyperphagia and weight gain [50].

Furthermore, in a randomized study conducted on 127 patients, exenatide did not reduce the overall number of heavy drinking days in patients with alcohol use disorder but did reduce brain activity in reward areas responding to alcohol-related cues. In obese patients, the drug was associated with a significant decrease in alcohol consumption, suggesting a possible metabolism-dependent effect. Treatment also affected dopamine transporter availability, indicating modulation of the reward system, although further studies are needed to assess clinical efficacy [51].

8.3 Treatment of Depression

GLP-1 RAs also have potential in the treatment of depression due to their impact on neuronal activity. Of the 18 studies considered, most demonstrated an antidepressant effect of GLP-1 RAs, while the results of observational and clinical studies were inconclusive, with a significant antidepressant effect observed in only 1 out of 3 clinical trials [52]. Also, in a study conducted on mice, semaglutide proved effective in alleviating depressive symptoms and improving cognitive function in mice with T2D [53].

9. Safety of GLP-1 Analogs

The safety and side effects of GLP-1 RAs used in patients with schizophrenia are still the subject of research [54]. In one study in Denmark, the risk of worsening mental health in patients with schizophrenia initiating GLP-1 RA therapy was examined in comparison with sodium-glucose co-transporter 2 inhibitors (SGLT-2) and dipeptidyl peptidase inhibitors (DPP-4). In a study of 354 individuals, GLP-1 RA use was not associated with an increased risk of psychiatric hospitalization compared to other antidiabetic drugs, and GLP-1 RAs proved to be at least as psychiatrically safe as DPP-4 and SGLT2 inhibitors in patients with schizophrenia and T2D [55].

In another randomized clinical trial conducted in Australia, the safety of semaglutide use in individuals with schizophrenia taking clozapine was studied. No effect of the treatment was observed either on the severity of psychotic symptoms or on clozapine concentrations and its metabolite, suggesting a lack of clinically significant pharmacological interactions. The therapy was well tolerated and not associated with the occurrence of serious adverse events, indicating a favorable safety profile, although the obtained results require confirmation in studies with

larger participant numbers [17]. In yet another study on semaglutide administration in people with schizophrenia, no deterioration in patients' mental state was observed [29].

In a meta-analysis of randomized clinical trials, GLP-1 RAs were shown to effectively reduce metabolic disturbances caused by antipsychotic treatment, improving body weight and glycemic control with good therapy tolerance. These data confirm their potential role as adjunctive treatment in psychiatric patients with cardiometabolic risk [56]. In a randomized double-blind clinical trial, adding exenatide to antipsychotic therapy proved to be safe and well-tolerated in patients with schizophrenia on antipsychotic medications; however, it did not provide additional weight reduction compared to placebo. The results suggest a possible modulation of the action of GLP-1 RAs by dopaminergic mechanisms blocked by antipsychotic medications [57].

A case was described of a 43-year-old patient with schizophrenia, treated with ziprasidone, in whom semaglutide increased the concentration of the antipsychotic drug and intensified psychotic symptoms, indicating a potential interaction requiring careful monitoring of drug levels and psychotic symptoms [58]. Available evidence indicates that GLP-1 RAs are generally safe and well-tolerated drugs in patients with schizophrenia, do not worsen psychotic symptoms, and improve metabolic parameters. At the same time, single cases and potential pharmacokinetic interactions with antipsychotic medications suggest the need for further research to fully determine the safety and optimal use of these drugs.

10. Conclusion

Schizophrenia is a chronic mental disorder characterized by the coexistence of positive and negative symptoms, as well as cognitive impairment, which significantly deteriorate patients' functioning. Pharmacological treatment, especially with atypical antipsychotic medications, forms the foundation of therapy; however, it is often associated with adverse effects, including metabolic disturbances. Patients with schizophrenia exhibit a significantly increased risk of obesity, MetS, and T2D, which results both from the effects of antipsychotic medications and from the underlying pathophysiology of the disorder.

GLP-1 RAs represent a promising therapeutic strategy for treating metabolic disorders in patients with schizophrenia. Study results indicate that drugs such as semaglutide or liraglutide

can effectively reduce body weight, improve glycemic control, and increase insulin sensitivity in patients treated with antipsychotic drugs. However, there is a lack of studies evaluating the effectiveness of these drugs in patients with schizophrenia who are not taking antipsychotic medications with high metabolic risk, in order to fully determine the impact of GLP-1 RAs on the metabolism of those affected. At the same time, data suggest that the use of GLP-1 RAs does not negatively impact psychotic symptoms or the concentrations of antipsychotic medications used, indicating a favorable safety profile for this therapy.

Moreover, growing evidence points to the potential neuroprotective activity of GLP-1 analogs. These mechanisms may include, among others, modulation of neuroinflammatory processes, reduction of oxidative stress, and an impact on neuronal energy metabolism. For this reason, their use is being considered not only in the treatment of metabolic disorders in patients with schizophrenia but also in the therapy of cognitive disorders and other neuropsychiatric diseases, such as AD, MD, or alcohol use disorder. In summary, GLP-1 RAs constitute a promising and potentially effective therapeutic strategy for treating metabolic disturbances accompanying schizophrenia and may also have broader applications in the treatment of neuropsychiatric disorders. However, further clinical studies involving larger patient populations and longer observation periods are necessary to fully assess their efficacy, safety, and potential impact on cognitive functions and the course of psychiatric disorders.

Disclosure:

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