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Pharmacological and Non-Pharmacological Strategies for the Prevention and Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia: A Narrative Review

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ABSTRACT

Antipsychotic-induced weight gain (AIWG) is a common problem encountered in the treatment of schizophrenia. This side effect often appears soon after starting treatment and can harm physical health and make it harder for patients to stick with their therapy. This review examines current approaches to preventing and managing AIWG, concentrating on practical strategies for clinical use. The pathogenesis of AIWG is complex. The most important pathways are linked to metabolic imbalance, impaired glucose control, and abnormal lipid levels, as well as modulation of appetite mediated by H1, 5-HT2C, and D2 receptors. Inflammation and the gut microbiome are emerging factors. Together, these mechanisms help explain why some antipsychotics carry a higher metabolic risk than others. Early prevention is critical. Choosing lower-risk antipsychotics and monitoring weight from the beginning of treatment are key initial steps. The most established pharmacological option affecting both body weight and metabolic parameters is metformin. Newer approaches, such as GLP-1 receptor agonists, look promising and may lead to greater weight reduction. Other options, including orlistat and the olanzapine/samidorphan combination (OLZ/SAM), may be useful in selected clinical cases. In the future, more experimental strategies such as targeting the gut microbiome or using neuromodulation could become relevant. Both pharmacological and non-pharmacological approaches are used to prevent and treat AIWG. Regardless of which strategy is used, interventions should be individualized. Despite advances in this field, important questions remain about long-term outcomes and optimal treatment options.

Keywords: antipsychotic agents, drug-related side effects, adverse reactions, schizophrenia, weight gain, management of obesity, obesity treatment

1. INTRODUCTION

Schizophrenia affects approximately 20 million people all over the globe and causes many difficulties for the individuals themselves as well as other people who care for or are involved with the individual (World Health Organization, 2022). Antipsychotics are the primary treatment used for schizophrenia. They help manage symptoms for individuals and prevent relapses. There are multiple side effects from being prescribed antipsychotics, and these side effects can be a barrier for many patients to maintaining a healthy weight (Pillinger et al., 2020). According to Huhn et al., (2019), there are 12 commonly used antipsychotic medications, which are consistently associated with significant weight gain in comparison to placebo, as noted in a meta-analysis that analyzed data from 116 published studies. Many patients begin to gain weight very early in their treatment course (Pillinger et al., 2020). The mechanisms by which antipsychotic medications cause significant weight gain involve changes in appetite, hormones, metabolism, and behavior (Niță et al., 2022; Wu et al., 2022).

Since antipsychotic agents are associated with significant differences in risk for weight gain, the selection of the appropriate antipsychotic agent to treat the individual with schizophrenia must be individualized and closely monitored (Stogios et al., 2025). AIWG increases the risk of metabolic syndrome, type 2 diabetes, and heart disease, resulting in more illness and death among people with schizophrenia (Bak et al., 2022). Weight gain can also make patients less likely to adhere to their treatment (De et al., 2025) and may harm self-esteem and social life (Solmi et al., 2024). Lifestyle changes like diet and exercise are recommended, but they often do not work well for people with schizophrenia. There are still no well-established or widely accepted drug strategies to prevent or manage this weight gain. More research is needed to find and evaluate effective treatments.

This review looks at current evidence on drug options for preventing and managing AIWG in schizophrenia, with a focus on how well they work, their safety, and new approaches.

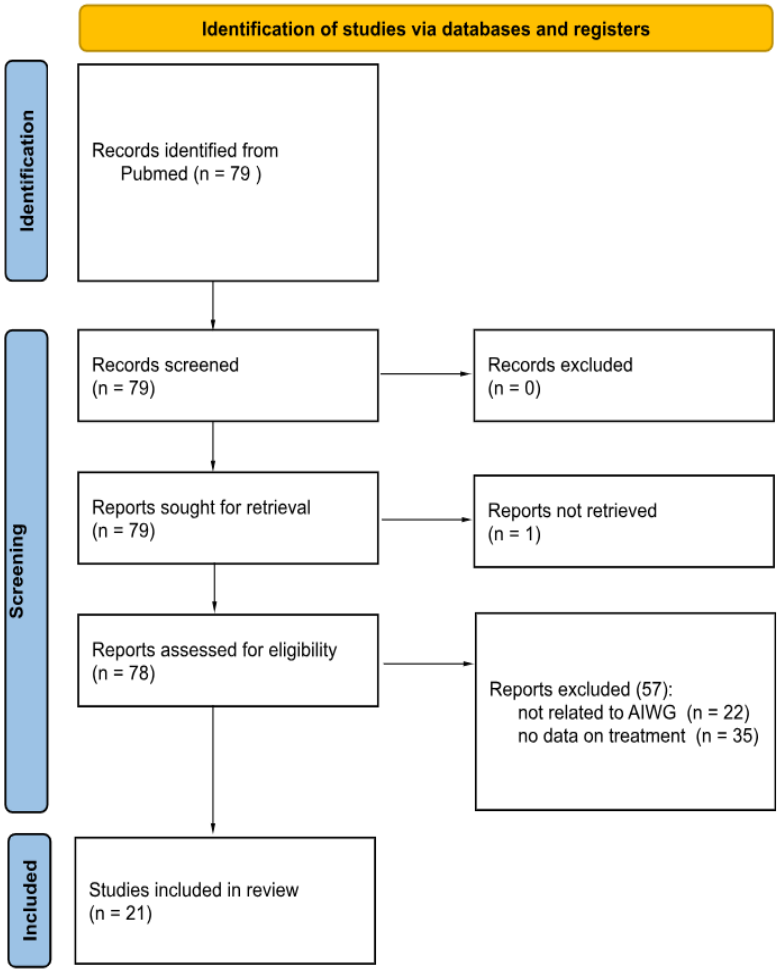

Figure 1. Flow chart

2. REVIEW METHODS

This narrative literature review was conducted using the PubMed database. The PubMed database was searched using an established strategy to locate articles using MeSH (Medical Subject Headings) and free-text words. The following MeSH terms were used: antipsychotic agents, drug-related side effects, adverse reactions, and schizophrenia. Free-text terms included: obesity, weight gain, management of obesity, and obesity treatment.

Three separate search queries were developed covering antipsychotic treatment and adverse effects, weight gain and obesity, and schizophrenia. These queries were subsequently combined using the AND operator in the advanced search function. Filters were applied to include articles available as free full text, written in English, and limited to clinical trials, randomized controlled trials, meta-analyses, systematic reviews, and review articles.

The search using those three initial queries found 79 records. Titles and abstracts were reviewed for relevance. Studies that did not focus on managing obesity or weight gain in patients with schizophrenia were excluded. Full-text articles were then assessed for eligibility. In the end, 21 studies were included in the narrative review (Figure 1).

3. RESULTS

Mechanisms of AIWG

AIWG is caused by a combination of factors involving neurotransmitter receptors, metabolic changes, inflammation, and the gut microbiome (Stogios et al., 2025).

Role of receptors

AIWG is closely linked with the effects of antipsychotic medications on histamine H1, serotonin 5-HT2C, and dopamine D2 receptors. Blocking H1 and 5-HT2C receptors increases hunger and reduces satiety, thereby leading to overeating (Wu et al., 2022; Niță et al., 2022). Blocking D2 receptors alters reward pathways, which can increase food intake, especially when combined with H1 and 5-HT2C effects (Niță et al., 2022). Drugs like olanzapine and clozapine, which strongly affect H1 and 5-HT2C receptors, are most likely to cause weight gain. Medications with weaker effects on these receptors have less impact on metabolism (Wu et al., 2022; Niță et al., 2022).

Metabolic pathways

AIWG is commonly associated with metabolic disturbances involving glucose and lipid regulation. Drugs such as olanzapine can impair insulin sensitivity, leading to elevated blood glucose levels (Manta et al., 2025; Toledo et al., 2022). They also alter lipid processing, elevating triglycerides and altering cholesterol levels (Xie et al., 2024; Manta et al., 2025). These issues can lead to metabolic syndrome, which is common in people with long-term antipsychotic use (Manta et al., 2025). Starting treatment early and attentively monitoring metabolic health are important (Wu et al., 2022; Agarwal et al., 2022).

Emerging mechanisms

The gut microbiome has recently been suggested as a possible modulator of energy balance, adiposity, and inflammation, with a putative exacerbation of AIWG (Tufvesson-Alm et al., 2026; Huang et al., 2022). Mild inflammation is also associated with abnormalities in insulin and lipid metabolism (Niță et al., 2022; Manta et al., 2025). Hence, modulation of the gut microbiota with probiotics and dietary fiber may represent a promising approach to attenuate weight gain and enhance metabolic response, although the evidence remains limited (Huang et al., 2022).

Pharmacological prevention strategies

As the rapid onset of AIWG generally occurs with initiation of an antipsychotic medication, efforts to apply prevention methods should occur as soon as practicable. Metformin has been found to provide a slight reduction in the amount of weight gained in patients who begin metformin immediately after starting an antipsychotic medication (Agarwal et al., 2022). Prevention efforts may also include selecting an antipsychotic medication that has little to no potential for contributing to weight gain as a way to limit weight-related problems to a minimum. If rapid weight gain occurs, clinicians may consider switching to an antipsychotic drug with lower metabolic risk (Stogios et al., 2025).

Metformin

Metformin is one of the most commonly used medications for treating AIWG. It increases insulin sensitivity and may support appetite control. Therefore, it may be a beneficial add-on to the treatment of patients who are using antipsychotic medications (Peng et al., 2025; Wu et al., 2022). It has been reported that metformin decreases the rate of weight gain among patients on antipsychotic drugs. A meta-analysis of 20 studies and 1070 patients showed a significant reduction in AIWG incidence among those receiving metformin 1000–2000 mg, especially when therapy was commenced early (Peng et al., 2025). Real-world studies have shown improvements in glycemia and lipid levels, especially when combined with lifestyle changes (Fitzgerald et al., 2022; Lee et al., 2022). Guidelines state that metformin should be considered for individuals with significant weight gain from the use of antipsychotic medications or who are developing early signs of metabolic problems while taking antipsychotic drugs. Decisions should take into account both the risks/benefits for each individual patient, and patients should be diligently monitored for improvement (Fitzgerald et al., 2022).

GLP-1 receptor agonists

Semaglutide is becoming a new treatment option that could help patients manage weight gain associated with antipsychotic medications. It works by stimulating insulin secretion in response to blood glucose levels, delaying gastric emptying, and suppressing appetite. These actions combine to promote weight loss as well as improve metabolic function. Based on the latest clinical trial results, semaglutide was found to clinically reduce body weight and improve cardiac and metabolic function in patients with AIWG (Uhrenholt et al., 2026). What is more, there were significant reductions in both body weight and blood glucose with semaglutide, indicating that it is a potential therapeutic option. Another GLP-1 agonist, liraglutide, was associated with clinically significant reductions in body weight across included studies. Improved glycaemic control and lipid metabolism were also noted. In patients with pre-existing mental health conditions, no worsening of psychiatric symptoms or mental well-being was observed when they took liraglutide versus those who did not have those conditions (Lee et al., 2022).

Orlistat

Orlistat is an agent that inhibits the absorption of dietary fats in the gastrointestinal tract. It is typically used to reduce body weight (Xie et al., 2024). A multi-site double blind, placebo-controlled study evaluated the safety and efficacy of orlistat (360 mg/day for 8 weeks) in patients with schizophrenia or bipolar disorder who gained at least 7% of their baseline body mass as a result of antipsychotic medication treatment. Although differences in mean change from baseline to week 8 were observed in weight and adipose tissue measures, some outcomes did not reach statistical significance (Xie et al., 2024).

Olanzapine / Samidorphan combination

To maintain the antipsychotic efficacy of olanzapine but at the same time to reduce weight gain, the idea of combining olanzapine with samidorphan emerged. In the ENLIGHTEN-2 trial, patients receiving OLZ/SAM gained less weight over 24 weeks compared with those on olanzapine alone, and fewer patients experienced weight gain (Correll et al., 2023). Similarly, findings from the ENLIGHTEN-Early study found that patients who received OLZ/SAM experienced less weight gain after 12 weeks of treatment than patients who were receiving olanzapine alone. In addition, OLZ/SAM-treated patients had less increase in waist circumference and a lower risk for experiencing a ≥7% gain in body weight than those who received olanzapine alone (Kahn et al., 2023). Over 52 weeks, patients receiving OLZ/SAM had more stable body weight and waist circumference than those receiving only olanzapine, and were at significantly lower risk of developing metabolic syndrome (Kahn et al., 2021). Additional analyses suggest that OLZ/SAM-treated patients may have a lower risk of weight and metabolic dysregulation than patients treated with olanzapine alone (Correll et al., 2023). OLZ/SAM results in less weight gain than olanzapine alone. Yet, the strength of this effect varies across studies, and clinical trial data are scant (Lee et al., 2025).

Other and adjunctive interventions

Berberine, a naturally occurring chemical, was also examined in association with metabolic syndrome and schizophrenia to see if berberine could prevent patients from gaining weight while taking antipsychotic medications. In a randomized controlled trial, adjunctive berberine 600 mg once daily was found to prevent patients from gaining weight, effectively reducing cholesterol levels (LDL and total), reducing body mass index (BMI), and decreasing glycated hemoglobin (HbA1c) compared to placebo. Patients did not have any serious adverse effects while using berberine (Chan et al., 2022).

Probiotics and dietary fibers were examined for their effects on the gut microbiota. In this study, those treated with probiotics and dietary fiber gained much less weight and had many fewer metabolic problems over a 12-week period than those who received placebo treatments. The authors concluded that these microbiota-related therapies may be beneficial for treating or preventing obesity associated with AIWG (Huang et al. 2022).

Emerging and experimental approaches – neuromodulation, gut microbiome modulation, and future directions

New treatments for AIWG go beyond standard drugs and include brain stimulation and changes in the gut microbiome. Non-invasive brain stimulation, like continuous theta burst stimulation (cTBS), has been tested to help control eating and weight. One trial found that cTBS over certain brain areas prevented weight gain and BMI increases in people new to antipsychotics, possibly by helping them control their eating (Kang et al., 2024a). Faster cTBS methods have even led to weight loss in overweight people with schizophrenia, showing promise for treating obesity (Kang et al., 2024b).

There is great promise in targeting the gut microbiota through interventions that alter its composition. What we currently understand is that several studies have linked alterations in the gut microbiota to metabolic disturbances associated with antipsychotic medications (Tufvesson-Alm et al., 2026). Evidence supports the idea that adding fiber and/or probiotics to a person's diet can help decrease the incidence of AIWG and other associated metabolic disorders, further supporting targeting the gut microbiota as a treatment modality (Huang et al., 2022).

4. DISCUSSION

Management of AIWG includes (1) careful selection of an appropriate early antipsychotic medication, (2) close metabolic monitoring of patients taking antipsychotics, and (3) timely transitions to alternative therapies or switching to alternative antipsychotic medications when necessary. An overview of the discussed strategies and their clinical implications is presented in Table 1. Among the available pharmacological interventions, the most extensively studied treatment for AIWG remains metformin. When used together with changes in lifestyle, its efficacy becomes even higher (Peng et al., 2025; Fitzgerald et al., 2022). Additionally, metformin has been suggested in clinical practice guidelines as a first-line medicine, especially for those patients who experience some metabolic abnormalities (Fitzgerald et al., 2022). Besides metformin, novel pharmacological agents, such as GLP-1 receptor agonists, are emerging as potential treatments for AIWG. Semaglutide and liraglutide have limited data on efficacy in weight loss and cardiometabolic parameters. Nevertheless, until now, there is a paucity of data about semaglutide in patients with schizophrenia (Uhrenholt et al., 2026). Still, combining these medications with diet and behavior changes is important to get the best results for AIWG. Compared with metformin, GLP-1 receptor agonists may provide greater weight loss. However, more studies are needed in this patient group.

Table 1. Key findings and clinical implications of strategies for the prevention and treatment of antipsychotic-induced weight gain

Strategies	Key findings	Clinical implications
Early prevention	Early intervention, weight monitoring, selection of lower-risk antipsychotics, and switching to antipsychotic with lower metabolic risk may reduce metabolic burden.	Prevention should begin at treatment initiation whenever possible.
Metformin	Most extensively studied pharmacological treatment for AIWG. Associated with reduced weight gain and improvements in glycemic and lipid parameters, particularly when started early and combined with lifestyle interventions.	Recommended in clinical guidelines as first-line adjunctive therapy for patients with significant weight gain or metabolic abnormalities.
GLP-1 receptor agonists (semaglutide, liraglutide)	Promote weight loss and improve metabolic outcomes through appetite suppression and improved glucose regulation.	Promising alternative to metformin, although long-term evidence in schizophrenia remains limited.
Orlistat	May reduce weight by inhibiting fat	May be considered in selected

	absorption.	patients, but further research is needed.
OLZ/SAM	Demonstrates less weight gain and lower risk of metabolic disturbances compared with olanzapine alone while maintaining antipsychotic efficacy.	Useful option for patients requiring olanzapine treatment but at risk of weight gain.
Berberine	Small clinical trials suggest improvements in body weight, BMI, lipid profile, and HbA1c.	Promising adjunctive treatment, but evidence remains limited.
Experimental approaches	Neuromodulation and gut microbiome modulation have shown encouraging preliminary results.	Larger, long-term clinical trials are required before routine clinical use.

The olanzapine/samidorphan combination is a pharmacological approach tailored towards mitigating weight gain while preserving the antipsychotic efficacy. Clinical studies have shown less weight gain and better metabolic parameters as compared to olanzapine alone (Correll et al., 2023; Kahn et al., 2021; Kahn et al., 2023). However, the degree of benefit varies across studies, and long-term data are limited. In sum, OLZ/SAM has the potential to mitigate antipsychotic-related metabolic burden, but more studies are warranted.

Orlistat is another pharmaceutical agent that may help with weight loss and lipid balance, but more research is needed to determine its long-term effectiveness. Berberine has also been shown to have some benefit in the area of weight loss and improving metabolic parameters, but research has mostly been limited to small clinical trials (Chan et al., 2022).

Novel approaches such as the modulation of the gut microbiome and neuromodulation techniques are promising but still investigational therapeutic avenues. These approaches need to be confirmed in large and robust clinical studies before being used in clinical practice (Huang et al., 2022; Kang et al., 2024a; Tufvesson-Alm et al., 2026).

Much of the existing evidence for the treatment of AIWG comes from short-term, heterogeneous clinical trials. Final conclusions on the efficacy of treatment methods have not yet been established. Future research on treating AIWG should focus on the long-term efficacy of therapies, head-to-head comparison of therapeutic alternatives, and personalized medicine approaches. The development of therapy based on individualized, patient-specific factors, such as metabolic profile, treatment response, and potentially gut microbiota composition, is likely to enhance efficacy but requires more rigorous evaluation.

5. CONCLUSION

AIWG is still a major challenge in clinical practice when treating schizophrenia patients. Based on current knowledge and available evidence, metformin is the most established pharmacological intervention. GLP-1 receptor agonists and OLZ/SAM broaden available treatment options. Both show promising effects on body weight and metabolic parameters. There are new perspectives on emerging therapies, such as targeting the gut microbiome or neuromodulation. However, important gaps still remain. Evidence on the long-term effectiveness of interventions discussed above remains limited. Comparative studies evaluating their relative effectiveness are needed. Studies clarifying the optimal sequencing of therapy would also help answer many clinically relevant questions. Future studies should focus on more personalized approaches and develop targeted strategies to improve metabolic outcomes in patients receiving antipsychotics.

Abbreviations:

AIWG – Antipsychotic-Induced Weight Gain
H1 – Histamine H1 receptor
5-HT2C – Serotonin 5-HT2C receptor
D2 – Dopamine D2 receptor
MeSH – Medical Subject Headings
GLP-1 – Glucagon-Like Peptide-1
OLZ/SAM – Olanzapine/Samidorphan combination
LDL – Low-Density Lipoprotein

BMI – Body Mass Index
HbA1c – Glycated Hemoglobin
cTBS – Continous Theta Burst Stimulation

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Data and materials availability
All data associated with this study will be available based on the reasonable request to corresponding author.

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