



PHARMACOLOGICAL STRATEGIES FOR REDUCING METABOLIC COMPLICATIONS INDUCED BY SECOND-GENERATION ANTIPSYCHOTICS IN PATIENTS WITH SCHIZOPHRENIA

Farmakologiczne strategie redukcji powikłań metabolicznych wywołanych przez leki przeciwpsychotyczne drugiej generacji u pacjentów ze schizofrenią



Hanna Weronika Wołodkiewicz, Weronika Caban

Medical University of Warsaw, Poland

Hanna Weronika Wołodkiewicz – 0009-0000-5166-6855

Weronika Caban – 0009-0002-1530-4392

Abstract

The aim of this paper was to review the current literature on pharmacological treatments for metabolic complications induced by second-generation antipsychotics in patients with schizophrenia and to compare their efficacy. Data from meta-analyses, randomized studies, cohort studies and systematic reviews were analysed, focusing on the use of metformin, topiramate, GLP-1 agonists, SGLT2 inhibitors, opioid receptor antagonists, bupropion, and aripiprazole. The largest body of evidence for efficacy was found for metformin, especially in patients after the first episode of the disease. Topiramate and bupropion also cause weight loss, although their use may be associated with some adverse effects. GLP-1 agonists have a beneficial effect on body weight and metabolic parameters, but require continuous therapy. SGLT2 inhibitors and aripiprazole improve the metabolic profile, but clinical data remain limited. Samidorfan is effective only in combination with olanzapine. Pharmacological strategies to reduce metabolic complications due to second-generation antipsychotics are promising but require further long-term studies and evaluation of combination therapy. Personalized treatment and close patient monitoring remain crucial to improve the safety and efficacy of antipsychotic therapy.

Streszczenie

Celem pracy jest przegląd najnowszej literatury dotyczącej farmakologicznych metod leczenia powikłań metabolicznych indukowanych przez leki przeciwpsychotyczne drugiej generacji u pacjentów ze schizofrenią oraz porównanie ich skuteczności. Analizie poddano dane pochodzące z metaanaliz, badań randomizowanych, kohortowych oraz przeglądów systematycznych, koncentrujące się na stosowaniu: metforminy, topiramatu, agonistów GLP-1, inhibitorów SGLT2, antagonistów receptorów opioidowych, bupropionu oraz aripiprazolu. Najwięcej dowodów potwierdzających skuteczność dotyczy metforminy, szczególnie u pacjentów po pierwszym epizodzie choroby. Topiramate oraz bupropion również powodują redukcję masy ciała, choć ich stosowanie może wiązać się z działaniami niepożądanymi. Agoniści GLP-1 wpływają korzystnie na masę ciała i parametry metaboliczne, jednak wymagają ciągłej terapii. Inhibitory SGLT2 oraz aripiprazol poprawiają profil metaboliczny, lecz liczba danych klinicznych jest ograniczona. Samidorfan wykazuje skuteczność jedynie w połączeniu z olanzapiną. Farmakologiczne strategie redukcji powikłań metabolicznych wywołanych przez leki przeciwpsychotyczne drugiej generacji są obiecujące, lecz wymagają dalszych badań długoterminowych oraz oceny terapii skojarzonej. Personalizacja leczenia i monitorowanie pacjentów pozostają kluczowe dla poprawy bezpieczeństwa i skuteczności terapii przeciwpsychotycznej.

Keywords: schizophrenia; antipsychotic drugs; metformin; aripiprazole; GLP-1

Słowa kluczowe: schizofrenia; leki przeciwpsychotyczne; metformina, aripiprazol; GLP-1

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Corresponding author:

Hanna Weronika Wołodkiewicz
Medical University of Warsaw
e-mail: hwołodkiewicz@gmail.com

Introduction

Schizophrenia is a severe, chronic mental disorder that often requires long-term or lifelong pharmacotherapy. Second-generation antipsychotics (SGAs), which effectively alleviate psychotic symptoms and reduce the risk of relapse, are currently the cornerstone of therapy. However, these treatments have been linked to a substantial risk of adverse reactions, with metabolic complications such as weight gain, insulin resistance, dyslipidaemia, and elevated risk of type 2 diabetes mellitus (T2DM) having major clinical significance [1,2]. These disturbances markedly increase cardiovascular (CV) morbidity in schizophrenic patients, which is up to twofold higher compared to the general population, and contribute to reduced life expectancy [4]. Additionally, antipsychotic-induced weight gain adversely affects patients' quality of life and may negatively influence treatment adherence, potentially leading to premature discontinuation [5, 6].

The risk of metabolic complications depends on both the pharmacological profile of the antipsychotic and individual patient factors. Among drug-related aspects, receptor-binding affinity (particularly for histamine H₁, serotonergic 5-HT_{2C}, and dopaminergic D₂ receptors) is particularly critical, as these play a key role in appetite regulation, energy balance, and metabolic homeostasis [7].

It is crucial to emphasize that the metabolic adverse effects of antipsychotics differ qualitatively from typical obesity, exhibiting a more rapid onset, profounder impact on glucose metabolism, and distinct hormonal and neuroendocrine alterations induced by these agents [8]. Furthermore, schizophrenic patients may be more susceptible to antipsychotic-associated weight gain than individuals with other psychiatric diagnoses [9].

Due to the significant clinical risk, regular monitoring of metabolic parameters is recommended in individuals taking antipsychotics, with particular attention paid to individual risk factors [10]. If significant metabolic adverse effects occur, dose reduction or switching to a drug with a lower metabolic risk, such as aripiprazole, lurasidone, or ziprasidone, may be considered [9]. Although such a therapeutic strategy may benefit some patients [11], it carries a risk of poor psychotic symptom control and does not consistently yield clinically meaningful weight loss [12]. Non-pharmacological interventions, including dietary education and promotion of regular physical activity, are vital for both preventing and managing metabolic complications [8]. However, such interventions often produce only transient effects and may prove inadequate in cases of substantial antipsychotic-induced weight gain [13].

Despite the availability of multiple therapeutic strategies, the optimal management of metabolic adverse effects associated with antipsychotic therapy remains a major clinical challenge.

Aim

This paper summarises the current knowledge on pharmacological treatments for antipsychotic-induced me-

tabolic complications in schizophrenic patients, while comparing their efficacy.

Results

Metformin

Metformin is an antihyperglycaemic agent that inhibits gluconeogenesis and lipid synthesis, leading to improved blood glucose control and reducing triglyceride and low-density lipoprotein (LDL) cholesterol. Its appetite-suppressing effect may be related to increased production of glucagon-like peptide-1 (GLP-1), which promotes satiety, stimulates insulin release, and inhibits glucagon secretion. Metformin's multifaceted actions also reduce glucose absorption from the gastrointestinal tract [15]. These mechanisms reduce insulin resistance and enhance peripheral glucose metabolism, thereby promoting weight loss [14]. Its efficacy in reducing body weight in SGA-treated patients has been extensively investigated and confirmed in many meta-analyses and cohort studies across diverse patient populations, establishing it as a primary adjunctive agent for mitigating antipsychotic metabolic adverse effects [14]. In their meta-analysis of 12 randomised, double-blind, controlled trials, De Silva et al. showed that metformin yielded a mean weight loss of 3.27 kg and a BMI reduction of 1.13 kg/m² ($p < 0.001$) in 743 patients. It additionally induced a mean reduction in the insulin resistance index (IRI) of 1.49 ($p < 0.001$). Metformin was effective in both paediatric and adult populations; however, greater efficacy was observed in first-episode patients (-5.94 kg) compared with those receiving chronic treatment (-2.06 kg) [16]. The association between weight loss and gender varies across studies (Lee et al.; Hakami et al.). However, metformin was more frequently combined with antipsychotic treatment in women, possibly due to the higher prevalence of coexisting indications, such as polycystic ovary syndrome (PCOS), which is often linked to obesity. Metformin has also proven effective in patients on clozapine. Since clozapine reduces GLP-1 levels by disrupting its pathway in the small intestinal epithelium, metformin may be particularly beneficial in these patients. In their meta-analysis of 487 patients on clozapine, Siskind et al. demonstrated reductions in body weight (3.12 kg) and BMI (1.18 kg/m²) with metformin versus placebo. Additionally, patients benefited from improvements in fasting glucose, triglycerides, and waist circumference, which are key components of metabolic syndrome [15]. These studies confirm metformin as an appropriate treatment for weight loss in patients on SGAs, with the added benefit of alleviating metabolic syndrome and thereby reducing CV risk [16].

Topiramate

Topiramate promotes satiety and suppresses appetite, likely by inhibiting carbonic anhydrase; it also reduces lipogenesis and boosts lipoprotein lipase activity [17]. Nickel et al. conducted a 10-week study in women treated with olanzapine. The study group receiving topiramate 250 mg/day showed an average weight loss of

4.4 kg compared with 1.2 kg weight gain in controls. Similar results were reported by Afshar et al. for patients receiving clozapine. The dose-dependent weight loss was highlighted by Ko et al., who stratified patients into two study groups: topiramate 100 mg/day or 200 mg/day, and a control group. Weight loss of 1.68 kg, 5.35 kg, and 0.3 kg was observed across the groups, respectively. Patients receiving topiramate 200 mg/day were more likely to achieve $\geq 5\%$ weight loss. Paraesthesia, with dose-dependent incidence of 60% in the 200 mg/day group vs 25% in the 100 mg/day group, was the most common adverse reaction. Paraesthesia also occurred in the placebo group, but at a significantly lower rate (10%). Additionally, worse control of schizophrenic symptoms was observed in the study groups compared to the placebo group, although this effect has not been reported elsewhere. Therefore, when prescribing topiramate to patients on SGAs, potential adverse effects should be considered, particularly at higher doses, and the symptoms of the underlying disease should be closely monitored. Nevertheless, topiramate still shows promising effects in terms of weight management [14, 17].

GLP-1 receptor agonists

GLP-1, an incretin hormone secreted by intestinal L cells in response to nutrients, stimulates insulin release, inhibits glucagon secretion, and lowers blood glucose levels. GLP-1 receptor agonists (GLP-1RAs) slow gastric emptying, thereby prolonging satiety and reducing appetite, while their glucose-dependent mechanism minimises the risk of hypoglycaemia. GLP-1RAs are commonly used to treat T2DM and often promote weight loss. Studies in patients receiving SGAs have also confirmed this effect [18, 19]. Subcutaneous liraglutide or exenatide treatment resulted in mean weight reductions of 3–5.3 kg. Exenatide proved particularly beneficial for patients on olanzapine and/or clozapine, yielding a mean weight loss of 5.29 kg, significantly greater than in those receiving other antipsychotics [18]. GLP-1 receptor agonists also exert multifaceted benefits on lipid metabolism, fasting glucose, glycated haemoglobin, and waist circumference, which are key components of metabolic syndrome and CV risk factors. However, 12 months after treatment discontinuation, patients returned to baseline metabolic parameters, while partial weight loss achieved with liraglutide was maintained [19]. Gastrointestinal (GI) symptoms, including nausea, vomiting, and diarrhoea were the most common adverse effects; however, these were mild, and the dropout rate was similar in both the study and control group. Potential effects of GLP-1RAs on the risk of suicidal behaviours have also been ruled out. Semaglutide offers greater convenience with once-weekly dosing; however, its use for this indication is still under investigation [19].

SGLT2

Sodium–glucose cotransporter 2 (SGLT2) inhibitors represent another class of medications that may improve body weight in SGA-treated patients. These agents act by inhibiting glucose reabsorption in the proximal renal tubules, leading to glucosuria and a consequent negative caloric balance. Due to their

capacity to reduce blood glucose and glycated haemoglobin (HbA1c), as well as their low risk of hypoglycaemia, T2DM is the primary indication for this class of drugs. In clinical trials, SGLT2 inhibitors induced an average weight loss of 1–3 kg. SGLT2 inhibitors also mitigate CV risk by lowering blood pressure via natriuresis. Additionally, they provide renal benefits by reducing intraglomerular pressure and hyperfiltration. Ertugliflozin is characterized by a favourable safety profile comparable to placebo, while significantly reducing metabolic syndrome components, including body weight. SGLT2 inhibitors are routinely used as second-line therapy alongside metformin, showing clear benefits for weight reduction [20]. However, clinical data regarding their use in patients treated with clozapine or olanzapine remain limited.

Opioid receptor antagonists

Endogenous opioids interact with three main receptor types, i.e. mu (MOR), delta (DOR), and kappa (KOR), which regulate appetite, satiety, energy expenditure, and overall metabolic functions. Given the involvement of the opioid system in these processes, antagonists targeting these receptors could mitigate antipsychotic-induced metabolic disturbances. Three substances are being investigated for this indication: naltrexone, samidorphan, and LY255582. Naltrexone is mainly indicated for alcohol use disorder and opioid dependence, whereas its combination with bupropion is approved for long-term management of overweight and obesity. Preclinical and clinical studies on the effect of naltrexone on weight loss when used concomitantly with antipsychotics are inconclusive. In animal studies, it demonstrated weight-lowering effects despite having no effect on food intake [21]. In a pilot study involving 24 women with schizoaffective disorder or schizophrenia, naltrexone treatment led to weight loss after 8 weeks, but only in those without T2DM [22]. Another study involving patients receiving olanzapine for the same indications showed no weight loss after 12 weeks, but a reduction in fat mass was observed in the naltrexone group [23].

Samidorphan, used in conjunction with olanzapine, uniquely promotes weight loss in this combination while counteracting metabolic adverse effects of olanzapine. In preclinical studies, it consistently reduced olanzapine-associated metabolic adverse effects. The drug primarily acts by reducing body weight and fat mass, with studies also showing appetite suppression. Clinical trials have confirmed these conclusions, additionally demonstrating reduced waist circumference and a positive impact on cholesterol and glucose metabolism. The combination of samidorphan and olanzapine, under the trade name Lybalvi, was approved by the FDA in 2021 for bipolar disorder [21].

In preclinical trials, LY255582 reduced fat mass, total body weight, and appetite. These metabolic effects are based on improved glucose tolerance and lipid profile, which may be related to changes in carbohydrate metabolism. Despite promising results, further studies are needed to confirm the clinical efficacy of LY255582. Differences in effects among individual opioid recep-

tor antagonists likely arise from their varying affinities for specific receptor subtypes, resulting in distinct levels of appetite modulation and impacts on lipid metabolism. Further comparative studies of these substances will help determine their efficacy and optimize therapeutic strategies [21].

Bupropion

Bupropion is a norepinephrine–dopamine reuptake inhibitor with minimal serotonergic activity. It is widely used as an antidepressant and has also been employed as a weight-reducing agent, either as monotherapy or in combination with naltrexone. Its role in supporting smoking cessation is an additional clinically relevant benefit in psychiatric populations. A randomized, double-blind study evaluating the effect of bupropion on body weight included 26 patients receiving SGAs. The study group received bupropion at 150–300 mg/day combined with olanzapine (10–20 mg/day) or risperidone (2–4 mg/day). At treatment week 8, a statistically significant reduction in body weight was seen in the bupropion group, without comparable effect in the placebo group. Given bupropion's dopaminergic and noradrenergic action, psychotic manifestations were systematically monitored post-intervention, with no aggravation in the bupropion group [24].

In a prospective, open-label trial, standard-dose bupropion was given to 8 patients on olanzapine for at least 26 months, with a mean weight gain of 13.3 kg. At 24 weeks, patients achieved a mean weight loss of 3.4 kg, accompanied by improved lipid profiles [25]. Bupropion is also combined with naltrexone, which is also used to treat obesity in the general population. Reports on its efficacy for weight loss in psychiatric patients using SGAs remain ambiguous. Tham et al. demonstrated a significant body weight reduction of 10.9% relative to baseline ($p < 0.001$), accompanied by a decrease in waist circumference at 52 weeks of treatment. However, these findings lack consistent replication, as many other studies failed to demonstrate comparable effects [26]. Although the cited studies showed no significant rise in adverse reactions with bupropion therapy, isolated seizures have been reported in patients concomitantly taking olanzapine and bupropion, both known to lower the seizure threshold. Olanzapine carries an estimated cumulative seizure risk of about 10% after 3.8 years of treatment compared to only 0.4% for bupropion at standard therapeutic doses. To date, there is insufficient evidence to reliably assess the cumulative or synergistic seizure risk associated with the combined use of these two medications. However, caution is warranted in patients with seizure history or other predisposing risk factors; alternative weight-loss pharmacotherapies should be considered in these cases. Although available data on bupropion appear promising, further studies in broader patient populations are needed to confirm its efficacy and better estimate the risk of seizures [27].

Aripiprazole

Aripiprazole acts as a partial agonist at dopamine D₂ and serotonin 5-HT_{1A} receptors and an antagonist at

serotonin 5-HT_{2A} and 5-HT_{2C} receptors. Unlike other SGAs, aripiprazole is not associated with weight gain and may even promote weight loss. In one study, adjunctive treatment with aripiprazole in patients receiving clozapine resulted in a mean weight reduction of 5.1 kg after 34 weeks of therapy. A similar metabolic effect was observed in patients whose primary antipsychotic was olanzapine. However, adjunctive aripiprazole therapy was associated with significant adverse reactions in some patients, including sinus tachycardia, worsened psychotic symptoms, and new-onset auditory hallucinations. These complications were more common in patients receiving combined aripiprazole/clozapine treatment. These adverse effects likely stem from enhanced dopaminergic neurotransmission and increased sympathetic activation due to aripiprazole's partial agonism at D₂ and 5-HT_{1A} receptors, coupled with its antagonism at 5-HT_{2A/2C} receptors. Additional symptoms (nausea, increased anxiety, and ataxia) also occurred more frequently in patients receiving adjunctive aripiprazole. Other than that, no significant differences in Positive and Negative Syndrome Scale (PANSS) scores emerged between the study and control group [28]. In addition to reducing body weight, aripiprazole improves lipid profiles, significantly lowering total cholesterol, LDL cholesterol, and triglycerides while raising HDL cholesterol. Aripiprazole plus olanzapine/clozapine enhances metabolic parameters and mitigates CV risk in these patients [29]. A meta-analysis of 55 randomized controlled trials ($n=4,457$ patients) showed significant mean weight loss of 5.08 kg ($p < 0.00001$) and BMI reduction, without worsening psychotic symptoms. However, the authors stressed the need to validate these findings through higher-quality studies registered in official clinical trial databases [30].

Discussion

Weight gain and metabolic disturbances from SGAs significantly elevate CVD risk and impair patients' quality of life. A 2023 meta-analysis [9] recommends prioritizing lifestyle modifications, supplemented by pharmacological options like metformin, topiramate, or bupropion, to counteract metabolic disturbances from these treatments. If these measures prove ineffective, SGA switching should be considered. The studies presented in this paper assessed the efficacy of both the above-mentioned and other therapies investigated for this indication.

Many studies, including meta-analyses, confirm the efficacy of metformin in mitigating weight gain among SGA-treated patients, especially those in early disease stages. Therefore, metformin constitutes a reasonable primary treatment option for this patient group; however, further long-term studies are needed to assess whether these therapeutic effects persist over time. This may be a particularly suitable option for diabetic patients, given metformin's established effects in reducing insulin resistance, fasting serum glucose and triglyceride levels, and waist circumference. Nevertheless, more comprehensive studies are needed in this patient population.

Topiramate, an antiepileptic agent, also exhibits weight-reducing properties; however, its use is associated with adverse effects such as paraesthesia, hypersalivation, and psychomotor slowing, particularly at higher doses. Due to reports of potential exacerbation of schizophrenia symptoms, its use warrants particular caution and close monitoring of the patient's clinical status.

GLP-1 receptor agonists effectively reduce body weight and, importantly, exert beneficial effects on metabolic syndrome manifestations. This is reflected by improved lipid metabolism, lower fasting serum glucose, reduced glycated haemoglobin levels, and reduced waist circumference. The need for daily subcutaneous injections is a major limitation of liraglutide therapy. Furthermore, the return to baseline metabolic parameters 12 months after treatment cessation highlights the need for continuous administration to maintain therapeutic outcomes. This class of medications is predominantly associated with GI adverse effects, which are generally mild.

A major advantage of SGLT2 inhibitors is their reduced CV risk and beneficial effects on the kidneys. Clinical trials have demonstrated their efficacy in the general population; however, data regarding patients receiving clozapine or olanzapine remain limited. The available data indicate that this drug class warrants consideration in patients with elevated CV risk.

Although opioid receptor antagonists have shown potential anti-weight gain effects, research in this area is inconclusive. Samidorfan has proven efficacy only in combination with olanzapine and was approved by the FDA in 2021. Studies assessing other members of this group (e.g., LY255582, currently in preclinical development), which may expand therapeutic options, are also underway.

Bupropion also supports weight loss, especially when combined with naltrexone. However, research on its efficacy in patients taking SGAs is inconclusive. Although bupropion does not compromise psychotic symptom control, the concomitant reduction in seizure threshold with olanzapine raises safety concerns. Special attention should be paid to aripiprazole, which, unlike most other SGAs, does not cause weight gain and may, in some cases, lead to weight loss. Studies have shown that adding aripiprazole to clozapine or olanzapine can result in significant weight loss and improved lipid profiles. Aripiprazole monotherapy may also be considered. From a practical standpoint, systematic monitoring strategies for patients on antipsychotics are essential, alongside education for psychiatrists regarding the metabolic sequelae of these agents and strategies for their mitigation. This necessitates the development of clear guidelines and protocols for managing these complications. Incorporating pharmacological preventive strategies into routine treatment protocols could enhance the overall health of psychiatric patients, mitigate their CV risk, and lower the risk of treatment discontinuation.

The cost-benefit balance of pharmacotherapy for complications of antipsychotics is another important aspect to consider. Increasing the number of medications taken may contribute to poor adherence. Additional medications may cause other adverse reactions and promote polypharmacy. Therefore, it is crucial to identify situations when antipsychotic therapy is essential and treatment-related complications persist, posing sustained harm to the patient.

However, this review should be interpreted in light of several important limitations. First, most studies are short-term, making it difficult to assess the long-term efficacy and safety of the analysed therapies. Consequently, the observed weight loss effects may prove transient, with their persistence following treatment cessation remaining uncertain. In particular, data on the persistence of favourable metabolic outcomes after discontinuation of pharmacotherapies such as metformin, GLP-1 receptor agonists, or SGLT2 inhibitors are missing. Second, there is a lack of analyses assessing the efficacy of combination approaches, such as metformin and GLP-1 agonists, which could potentially improve treatment outcomes. Furthermore, the methodological heterogeneity across studies (different patient populations, drug dosages, and follow-up durations) precludes direct comparisons of results. Third, the mechanisms underlying individual treatment responses remain unclear. Many studies fail to account for the key factors influencing treatment efficacy, such as comorbidities (e.g., insulin resistance, polycystic ovary syndrome) or prior antipsychotic exposure. Metformin appears to be particularly effective in first-episode patients; however, the mechanisms underlying this observation have not yet been fully elucidated. Fourth, several pharmacological agents discussed are associated with clinically relevant adverse effects despite their proven efficacy. For instance, topiramate may induce psychomotor slowing and exacerbate psychotic symptoms despite its efficacy in inducing weight loss. GLP-1 receptor agonists may cause GI adverse effects, whereas the combination of bupropion and olanzapine may elevate the risk of reduced seizure threshold. Furthermore, robust data on the long-term safety of some interventions in psychiatric populations remain scarce.

Although existing evidence supports the efficacy of several pharmacological strategies for weight reduction in patients with psychiatric disorders, further long-term, comparative studies are needed to comprehensively delineate their efficacy, safety profiles, and potential drug-drug interactions.

In summary, current pharmacological interventions offer promising approaches for reducing weight gain induced by SGAs; however, the evidence often remains limited and reflects short-term outcomes. Future research should therefore prioritize evaluating long-term efficacy and safety, alongside developing personalised treatment strategies tailored to patients' individual clinical profiles.

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