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Combining samidorphan with olanzapine to mitigate weight gain as a side effect in schizophrenia treatment

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Abstract

Purpose: This article analyzes clinical trials that provide evidence for the positive effects of using samidorphan to mitigate undesirable weight gain in patients diagnosed with schizophrenia who are undergoing treatment with olanzapine.

Views: Weight gain is a prevalent and problematic side effect of antipsychotic drug therapy, particularly in patients with schizophrenia. To address this issue, extensive research is being conducted to explore new drug therapies that can effectively counteract psychotic symptoms while minimizing the occurrence of unwanted side effects. One promising approach involves the addition of weight-loss substances to existing medications. Studies have indicated that opioid receptor antagonists, such as samidorphan, have the potential to facilitate weight loss. Consequently, a novel therapy combining samidorphan and olanzapine has been developed and is discussed in detail in this article.

Conclusions: The combination of samidorphan and olanzapine has demonstrated its ability to effectively reduce weight gain in patients with schizophrenia, without compromising the drug's primary function of alleviating psychotic symptoms. Moreover, the inclusion of samidorphan in the treatment regimen may contribute to a lower risk of cardiovascular events, though it is worth noting that it could also lead to an increase in digestive side effects. Despite this potential drawback, the introduction of this innovative therapy represents a significant advancement in the management of obesity among individuals with schizophrenia.

Key words: schizophrenia, adverse effects, olanzapine, weight gain, samidorphan.

INTRODUCTION

According to the definition presented in ICD-10, schizophrenic disorders are characterized in general by fundamental and characteristic distortions of thinking and perception, and affects that are inappropriate or blunted. Clear consciousness and intellectual capacity are usually maintained although certain cognitive deficits may evolve over the course of time. The lifetime prevalence of all psychotic disorders was 3.06%, with 0.87% attributed to schizophrenia [1]. Consequently, the imperative to develop a drug that effectively reduces the symptoms of the disease while minimizing side effects is underscored by its high occurrence and severity.

Regrettably, the antipsychotic drugs that are usually used in treatment can cause weight gain by disrupting the management of glucose. This disruption leads to an increased production of glucose by the liver (HGP) and decreased insulin secretion [2, 3]. Furthermore, these drugs enhance the orexigenic stimulation of the hypothalamus, activating the "hunger center", resulting in a rise in hunger and an increase in calorie consumption [4]. This mechanism plays a significant role in the development of obesity and related cardiovascular diseases [5].

The presence of obesity significantly elevates the risk of morbidity and mortality, primarily associated with certain types of cancer, notably breast cancer, endometrial cancer, and colorectal cancer. Moreover, obesity contributes to a higher incidence of various health conditions, including but not limited to type 2 diabetes, hypertension, hyperuricemia, lipid metabolism disorders, polycystic ovary syndrome, sleep apnea syndrome, gout, ischemic heart disease, and kidney stones [6, 7].

In the context of individuals diagnosed with schizophrenia, it is worth noting that a significant proportion,

ranging from 22.2% to 29.3%, experience issues related to obesity, while 53.5% to 63.6% are affected by overweight and obesity [8]. Regrettably, this weight gain can result in an increased mortality rate and a reduced life expectancy, typically averaging 15-20 years less than the general population [9]. Multiple factors contribute to the challenges faced by these patients, encompassing an unhealthy lifestyle, socioeconomic disparities, and genetic predispositions [10]. Therefore, mitigating weight gain resulting from pharmacological treatment becomes an imperative consideration.

This article explores the potential of utilizing samidorphan in combination with olanzapine as a strategy to mitigate weight gain in individuals with schizophrenia, a crucial concern associated with antipsychotic medications like olanzapine. It delves into the mechanisms of opioids, particularly samidorphan, and their potential for counteracting the weight gain and metabolic disturbances induced by antipsychotic drugs. Additionally, it examines the impact of this combination therapy on psychiatric symptoms, cardiovascular risk factors, and potential drug interactions. In essence, this article offers valuable insights into addressing the pressing issue of weight gain in schizophrenia patients through the use of samidorphan alongside olanzapine, with a focus on potential benefits and considerations for side effects and drug interactions, ultimately contributing to the development of more effective and safer treatment options.

OLANZAPINE IN TREATING SCHIZOPHRENIA

In the management of schizophrenia the primary therapeutic agents are antipsychotic medications, categorized into two main groups: first-generation (FGAs) and second-generation antipsychotics (SGAs). First-generation antipsychotics primarily target dopamine D_2 receptors in the striatum, requiring around 65% striatal D_2 receptor occupancy for clinical improvement [11]. However, they often lead to extrapyramidal side effects (EPS) due to their blocking of nigrostriatal D_2 receptors and hyperprolactinemia by affecting tuberoinfundibular D_2 receptors [12, 13]. In contrast, second-generation antipsychotics (SGAs), such as clozapine and quetiapine, are equally effective but have a lower risk of EPS and hyperprolactinemia. PET imaging has shown that SGAs can be effective with less than 60% striatal D_2 receptor occupancy, challenging the idea that antipsychotic efficacy depends directly on D_2 receptor occupancy [14, 15]. The antagonism of serotonin 5-HT_2A receptors by SGAs is thought to contribute to their efficacy and lower D_2 receptor occupancy requirements, reducing side effects [16]. However, some FGAs also have significant 5-HT_2A receptor affinity, complicating this hypothesis [17].

Olanzapine is an atypical antipsychotic drug used to treat not only schizophrenia but also bipolar disorder. This substance affects dopamine (D_2) and serotonin ($5HT_2A$) receptors, which helps to decrease both the positive and negative symptoms of psychotic disorders [18].

Several studies have demonstrated that olanzapine is more effective than other antipsychotic medications at alleviating symptoms of the disease [19-21] is better tolerated by patients, and results in a lower rate of treatment discontinuation [21]. Olanzapine is also characterized by a reduced percentage of hospitalizations, including rehospitalizations for all reasons, which increases the patient's comfort and reduces the total cost of treatment [22].

In the context of extensive comparative studies such as CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and EUFEST (European First Episode in Schizophrenia Trial), it is noteworthy that despite its propensity to induce weight gain and metabolic issues, olanzapine exhibited a lower withdrawal rate compared to alternative antipsychotic agents [20, 23, 24]. In both of these studies olanzapine consistently demonstrated enhanced efficacy, particularly in terms of the duration of treatment continuation, when contrasted with risperidone, quetiapine, ziprasidone, haloperidol, and amisulpride. This pattern persisted even among patients who transitioned due to inadequate therapeutic effects, with olanzapine surpassing quetiapine and ziprasidone in CATIE [23]. However, there were no statistically significant variances in discontinuations due to intolerability. Overall, the robust therapeutic efficacy associated with olanzapine appeared to outweigh its associated side effects, culminating in a lower withdrawal rate.

As with any medication, olanzapine has potential side effects, and weight gain is a common occurrence, affecting approximately 51% of treated patients. Therefore, it is important for healthcare providers to consider the risk of weight gain when prescribing olanzapine and to monitor patients closely for any adverse effects. In addition, there is a heightened risk of developing metabolic diseases, particularly insulin resistance. It is important to note that the use of second-generation antipsychotics may increase the likelihood of experiencing akathisia, extrapyramidal symptoms, tardive dyskinesia, and neuroleptic malignant syndrome. However, it is worth noting that the risk of these adverse effects is lower than that associated with the use of first-generation antipsychotics [18].

PREVIOUS ATTEMPTS TO MITIGATE WEIGHT GAIN CAUSED BY ANTIPSYCHOTIC MEDICATIONS

Efforts have been made to minimize weight gain associated with the use of antipsychotic drugs by exploring combination therapy involving atypical drugs and other medications, such as antidiabetic drugs, topiramate, or orlistat.

Metformin is an oral medication used to treat diabetes by lowering blood glucose levels. It works by limiting the formation of free fatty acids in adipose tissue, which helps reduce insulin resistance [25]. Additionally, it enhances the body's ability to use glucose and reduces appetite, positively affecting weight control [26].

Although metformin is not included in the guidelines for preventing weight gain during the treatment with antipsychotic drugs of schizophrenia, studies have demonstrated its positive effects. Significant body weight and BMI changes has been observed in adults and children during treatment. However, metformin may be less effective for patients already experiencing weight gain complications due to the metabolic changes caused by long-term antipsychotic drug therapy [26].

Topiramate is a drug that has been extensively researched for its ability to counteract weight gain resulting from the use of second-generation antipsychotics, following metformin. It is a fructopyranose derivative that exhibits anticonvulsant properties. While one of its notable side effects is weight loss, it differs from metformin in that it functions centrally rather than peripherally. However, it is important to note that topiramate has the potential to interact with multiple medications, poses higher risks, and could potentially impact the efficacy of schizophrenia treatment [27].

Orlistat is another drug that has been tested as an auxiliary in antipsychotic therapy. It is a long-acting inhibitor of lipases produced in the digestive tract and is commonly used to treat obesity in both adults and children [28]. Orlistat works by reducing the absorption of fats and calories in the body. In overweight or obese patients on long-term clozapine or olanzapine treatment, taking orlistat without diet or behavioral changes resulted in moderate weight loss, only in men. Some metabolic improvements were also observed, regardless of weight changes [29].

GLP-1 is a versatile hormone with effects on blood glucose control, neuroprotection, cognitive improvement, cardiac protection, and weight regulation, which is particularly vital in managing type-2 diabetes [30]. Limited research explores the use of GLP-1 agonists to counteract weight gain in individuals on antipsychotic medications. These studies emphasize the potential benefits of GLP-1 receptor agonists such as semaglutide, liraglutide, and exenatide for managing weight and blood sugar in schizophrenia patients. However, individual effectiveness varies, calling for further research to optimize their use in this specific population [31-34].

Reboxetine, a selective norepinephrine reuptake inhibitor, has been safely added to conventional antipsychotics in individuals with schizophrenia. There is a hypothesis that reboxetine's stimulation of adrenergic activity might reduce olanzapine-induced weight gain [35]. The olanzapine/reboxetine combination demonstrated reduced weight gain, decreased appetite, and good tolerability compared to olanzapine/placebo [36]. Another trial suggested that olanzapine/reboxetine + betahistine had a weight-attenuating effect twice as potent as reboxetine alone [37].

Sibutramine is a medication that helps with weight loss in obesity by inhibiting the reuptake of norepinephrine, serotonin, and dopamine, leading to reduced appetite and increased feelings of satiety [38]. Sibutramine studies have shown mixed results, with some indicating weight loss benefits when combined with behavior modification [39, 40], while others found no significant effects [41]. More extensive and longer-term research is needed to clarify sibutramine's role in managing antipsychotic-induced weight gain.

MECHANISM OF ACTION OF OPIOIDS IN REDUCING THE RISK OF WEIGHT GAIN

The three types of opioid receptors – mu-receptor (MOR), kappa-receptor (KOR), delta-receptor (DOR) – are distributed throughout the central and peripheral nervous system and play a crucial role in various body functions [42]. These receptors modulate mood, pain processing, reward response, and physiological mechanisms such as the endocrine and immune systems and respiration [43-45].

Furthermore, opioid receptors exhibit diverse roles in the regulation of metabolic physiology. DOR deficiency may impact energy metabolism and thermogenesis, influencing weight gain and fat accumulation [46], as well as salt appetite regulation, possibly through interactions with the angiotensinergic system [47]. MOR's involvement extends to body weight regulation through insulin secretion, with potential implications for diabetes therapies, particularly in specific populations like African Americans [48, 49]. KOR, when genetically deleted in mice, leads to altered metabolic responses, including lower body weight and fat mass, reduced liver triglyceride synthesis, and increased hepatic β-oxidation in response to high-energy diets [50]. Additionally, KOR appears to be involved in the modulation of salt intake under certain physiological conditions [51].

These findings underscore the intricate role of opioid receptors in the regulation of metabolic processes. Consequently, drugs targeting these receptors may hold promise for addressing conditions such as obesity and diabetes, offering potential avenues for therapeutic interventions in these health concerns.

Additionally, opiate antagonists are being explored as potential treatments for binge eating disorder (BED) and abnormal eating behaviors due to the complex relationship between the opioid system and eating habits. Combining pharmacotherapy and psychotherapy seems to enhance the management of EDs, with the involvement of families or support groups potentially improving treatment adherence and outcomes [52].

SAMIDORPHAN

Samidorphan is an opioid antagonist that acts on MOR, DOR, and KOR receptors. Its mechanism of action involves blocking these receptors, leading to various effects [53]. In terms of reward pathways, the activation of MOR enhances the reward value of flavors, while KOR activation reduces preference for previously experienced flavors [44]. Samidorphan can modulate these pathways by blocking the receptors. It also regulates energy metabolism by counteracting the metabolic damage caused by high-fat diets [46, 47]. In terms of feeding behavior, opioid receptors in certain brain regions affect food intake, and samidorphan can modulate this by blocking opioid-induced feeding [44]. Additionally, the mu-opioid system is implicated in cognitive function, and samidorphan's antagonistic effects may help reduce craving, impulsive behaviors, and depressive symptoms associated with addiction and mood disorders [45]. Overall, samidorphan's mechanism of action involves blocking MOR, DOR, and KOR receptors, thereby affecting reward pathways, energy metabolism, feeding behavior, and cognitive function.

Numerous studies have evaluated the efficacy of samidorphan in treating various psychiatric disorders, including alcohol dependence, binge-eating disorder, schizophrenia, and weight gain associated with antipsychotic medication [54].

The main side effects reported by the subjects were drowsiness, gastrointestinal complaints in the form of nausea and constipation [55-57]. Other side effects include dizziness, tachycardia, dry mouth, headache, vomiting, orthostatic hypotension, weight gain and anxiety [58-60].

Samidorphan is currently unavailable in Poland; however, Alkermes, Inc. is actively conducting three research studies in recruitment phases, focusing on the safety, tolerance, and pharmacokinetics of OLZ/SAM [61, 62], along with assessing potential BMI and body weight changes in children with schizophrenia and bipolar I disorder, comparing OLZ/SAM with olanzapine [63]. Additionally, there is an ongoing study primarily taking place in the USA and Europe, examining the long-term safety, tolerance, and durability of ALKS 3831 treatment effects in patients with schizophrenia, schizophreniform disorder, and bipolar I disorder. It is noteworthy that Alkermes, Inc. is conducting research in Poland, with one investigational site located in Poznań [64].

METHODS

A literature search was conducted in the PubMed database using the keywords "weight mitigation", "olanzapine treatment", "samidorphan", and "opioid antagonists", as well as combination of these terms. We included meta-analyses, reviews and clinical studies regarding said topics, to identify the role of samidorphan and its potential for weight regulation.

RESULTS

Antipsychotic effects

Several clinical trials have demonstrated that the effectiveness of antipsychotic treatment with a combination of olanzapine and samidorphan (OLZ/SAM) is comparable to that of olanzapine monotherapy. The efficacy was evaluated by measuring the change in the overall score of Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions–Severity of Illness Scale (CGI-S) (Table 1).

In a randomized double-blind phase 2 study [65] in patients with schizophrenia there were no differences in the PANSS score between the OLZ/SAM and olanzapine plus placebo groups. The PANSS score for OLZ/SAM changed from 62.0 (SD = 9.7) to a least square score of –2.2 (95% CI: –3.2, –1.3) for the olanzapine plus samidorphan group and from 62.0 (SD = 10.4) to –2.9 (95% CI: –4.5, –1.3) for the olanzapine plus placebo group. The average PANSS score stayed consistent between week 12, which was the beginning of the extension study, and week 24.

During a 4-week long phase 3 clinical trial (ENLIGHTEN-1 study) a statistically significant LS difference from placebo in the OLZ/SAM group was observed starting from the second week. The OLZ/SAM group showed a significant change from baseline at week 4 in a CGI-S score of -0.38 ± 0.12 ($p = 0.002$), while the olanzapine group had a greater change. The effectiveness of OLZ/SAM compared to a placebo, evaluated through the change in the PANSS total score from baseline at week 4, was found to be comparable to olanzapine versus placebo across all subgroups divided by age, gender, and race [36]. In the extension study, patients who had finished ENLIGHTEN-1 were given open-label OLZ/SAM at the same dose of olanzapine they had been taking at the end of the previous study. They were given doses of either 10/10 mg, 15/10 mg, or 20/10 mg over a period of 52 weeks, with study visits every other week. Although changes in dosage were allowed, they were not encouraged. At the end of the 52 weeks the mean change from baseline for the PANSS total score (95% CI) was –16.2 (–18.5 to –14.0) [66].

Effects on body weight

A proof-of-concept trial by Silverman *et al.* [55] was conducted to study the safety and weight effects of a combination of OLZ/SAM (10/5 mg) compared to olanzapine alone in healthy, male volunteers with normal weight. The study was conducted at multiple centers, was randomized, double-blind, placebo-controlled and lasted for

three weeks. The primary efficacy endpoint, mean (SD) body weight change from baseline to last assessment in the 3-week treatment period, was significantly less for OLZ/SAM vs. olanzapine-only subjects [+2.2 (1.4) kg vs. +3.1 (1.9) kg; respectively; $p = 0.02$]. In contrast, there was no significant difference in weight from baseline for either SAM or placebo [+0.1 (1.0) kg and +0.8 (1.4) kg, respectively; $p = 0.09$] [55].

In the treatment phase of another 12 week clinical trial [65], the OLZ/SAM group exhibited a 37% lower mean percent change in body weight, with a least square mean percent change from the baseline of 2.6% and an absolute change of 1.9 kg in contrast to the olanzapine plus placebo group, which displayed a 4.1% mean percent change and an absolute change of 2.9 kg. The difference in least square mean between the two groups was 21.5% (95% CI = 22.5, 20.4, $p = 0.006$) and 21.0 kg (95% CI = 21.8, 20.2, $p = 0.018$). Furthermore, patients who received olanzapine plus placebo had a higher chance of gaining > 10% of their baseline body weight compared to those who received OLZ/SAM (odds ratio = 2.73, $p = 0.023$). The difference in weight gain > 7% was not statistically significant (odds ratio = 1.56, $p = 0.227$).

In the ENLIGHTEN-1 Study the mean ±SD change in weight from baseline to week 4 in the placebo group was 0.24 ± 2.76 kg compared with 3.02 ± 3.56 kg for OLZ/SAM and 2.38 ± 3.65 kg in the olanzapine group [60].

Regarding the extension study (ENLIGHTEN-2 study), after 24 weeks the average weight change from the start of the study was 4.21% (SE = 0.68) for those in the OLZ/SAM group and 6.59% (SE = 0.67) for those in the OLZ group. The difference between the two groups was 22.38% (SE = 0.76). Patients who received a combination of olanzapine and samidorphan gained less weight than those who only received olanzapine. In the OLZ/SAM group, 17.8% had weight gain over 10%, while 29.8% in the olanzapine group did. Moreover, increases in waist circumference were smaller in the OLZ/SAM combination group compared with the olanzapine group [67].

Throughout the 52 weeks of treatment, the patients' weight remained stable with a mean (SD) change of –0.03 (6.22) kg from baseline to week 52. The weight change profile observed with OLZ/SAM treatment at week 52 was similar regardless of the treatment received in the previous ENLIGHTEN-2 study. During the study, 21.5% of patients experienced clinically significant weight gain of at least 7%, while 21.1% experienced clinically significant weight loss of at least 7%. Waist circumference also remained stable during treatment with a mean (SD) change of –0.35 (6.12) cm at week 52. The waist circumference change observed

Table 1. Summary of included studies

Authors (year)	Phase	Duration	Sample size	Demographic characteristics	BMI	Results OLZ vs. OLZ/SAM
Silverman *et al.* (2018)	1	3 weeks	106	Healthy adults (ages 18-40 years)	18-25 kg/m^2	Weight effects (kg): 3.1 vs. 2.2 GIR: –3.5 vs. –3.2 TG (mmol/l): 0.4 vs.0.2 TC (mmol/l): 0.3 vs. 0.05 Adverse events (%): 88.6 vs. 91.2
Toledo *et al.* (2022)	1	3 weeks	60	Healthy adults (ages 18-40 years)	18-25 kg/m^2	Weight effects (kg): 2.87 vs. 3.16 $AUC_{insulin}$(h · μU/ml): 223.71 vs. 208.13 HIR index (nIU/l/min): 4.89 vs. –0.52 Caloric intake (kcal): 201.6 vs. –297.6 Resting energy expenditure (kcal/day): 67.9 vs. 19.4 Adverse events (%): 79.2 vs. 87.5
Martin *et al.* (2019)	2	12 weeks	347	Adults (ages 18-50 years) with schizophrenia	–	Weight effects (kg): 2.9 vs. 1.9 Antipsychotic efficacy (PANSS): –2.9 vs. –2.2 Adverse events (%): 54.7 vs. 54.3
Potkin *et al.* (2020) (ENLIGHTEN-1)	3	4 weeks	401	Adults (ages 18-70 years) with schizophrenia	18-40 kg/m^2	Weight effects (kg): 3.02 vs. 2.38 Antipsychotic efficacy (PANSS): –3.4 ± 0.9 vs. –2.8 ± 0.9 Adverse events (%): 54.9 vs. 54.5
Correll *et al.* (2020) (ENLIGHTEN-2)	3	24 weeks	561	Adults (ages 18-55 years) with schizophrenia	18-30 kg/m^2	Weight effects (kg): 5.08 vs. 3.18 Waist circumference effects (cm): 4.47 vs. 2.36 TG mg/dl: 29.36 vs. 26.77 Antipsychotic efficacy (PANSS): –9.4 vs. –8.2 Adverse events (%): 82.2 vs. 74.1
Kahn *et al.* (2021) (ENLIGHTEN-2-EXT)	3	52 weeks	265	Adults (ages 18-55 years) with schizophrenia	18-30 kg/m^2	Weight effects (kg): -0.42* vs. 0.32 Waist circumference effects (cm): –1.26* vs. 0.48 Prolactine (ng/ml)**: –3.2 Antipsychotic efficacy (PANSS)**: –0.2 Adverse events (%)**: 60.8

GIR – glucose/insulin ratio, TG – triglycerides, TC – total cholesterol, HIR index – hepatic insulin resistance index
**Olanzapine was switched to olanzapine/samidorphan after the 24th week of the study.*
***The outcomes presented exclusively pertain to the OLZ/SAM treatment.*

at week 52 was similar regardless of the treatment received in the previous ENLIGHTEN-2 study [66].

In addition, after analysing different subgroups in ENLIGHTEN-2, researchers discovered that there were no significant differences between the treatment groups in terms of weight gain, despite the fact that females, patients under 30, non-black patients, and those with a BMI less than 27 kg/m^2 were less likely to gain at least 10% of their baseline body weight with OLZ/SAM compared to olanzapine treatment. This was indicated by the 95% CIs, which crossed 1 [68] (Table 1).

Changes in blood test results

A study conducted by Toledo *et al.* [68] aimed to investigate the metabolic profile of OLZ/SAM in healthy volunteers in order to gain a better understanding of the drug's mechanisms. The study revealed that olanzapine led to hyperinsulinemia and reduced insulin sensitivity during an OGTT on day 19. These changes were not observed with OLZ/SAM or placebo. All treatment groups experienced a decrease in insulin sensitivity, as measured by hyperinsulinemic-euglycemic clamp, compared to baseline. However, this effect was greatest with olanzapine and OLZ/SAM [69].

During a 24-week long phase 3 clinical trial (Correll *et al.* [66]) in the metabolic laboratory parameters for the two treatment groups there were only slight variations in glycaemic and lipid laboratory measurements from baseline to week 24, and a comparable outcome. The most significant differences were served in triglyceride levels, where the combined OLZ/SAM group and the olanzapine group reported least square mean increases of 26.77 mg/dl (SE = 5.78) and 29.36 mg/dl (SE = 5.69), respectively [67].

Throughout the ENLIGHTEN-2 long-term extension study, there were generally small changes in fasting lipid and glycaemic parameters, with no significant fluctuations. Patients maintained stable levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, and insulin from baseline to study completion and at other time points during treatment. Additionally, HbA_{1c} values remained consistent over 52 weeks [66].

Effect on reducing the risk of cardiovascular events

Treatment with olanzapine is linked to an increased risk of deterioration in cardiometabolic risk factors associated with obesity, hypertension, and metabolism. However, multiple studies indicate that treatment with OLZ/SAM can decrease this risk.

In the ENLIGHTEN-2 study, after 24 weeks of treatment it was found that OLZ/SAM resulted in smaller changes from baseline in systolic and diastolic blood pressure, as well as BMI, when compared to olanzapine. The differences in least-squares mean were –2.63 mm Hg for systolic blood pressure, –0.75 mm Hg for diastolic blood pressure, and –0.65 kg/m^2 for BMI. Additionally, patients who received OLZ/SAM treatment had a reduced risk of developing hypertension, obesity, and metabolic syndrome compared to those who were treated with olanzapine [70].

Additionally, according to a study conducted by Sun *et al.* [71], it was found that OLZ/SAM did not have a significant effect on ECG parameters, such as QT/QTc prolongation, in patients with stable schizophrenia. This was observed even at high doses and plasma concentrations.

Adverse events

Overall, the combination of OLZ/SAM was well tolerated across all doses. However, comparison of the studies showed that there were some common adverse events (AEs) reported in relation to the use of olanzapine alone, OLZ/SAM, and olanzapine plus placebo. Dizziness was the most frequently reported AE across all treatments, with rates of approximately 24.4% in the olanzapine group and 30.4% in the OLZ/SAM group. Nausea and sedation were more commonly reported in the OLZ/SAM group (15.2% and 10.9%, respectively) compared to the olanzapine group (4.4% and 2.2%, respectively), as reported by Sun *et al.* [72]. Similarly, somnolence, sedation, dizziness, and constipation were reported at a higher rate in the OLZ/SAM groups compared to the olanzapine plus placebo group, as stated by Martin *et al.* [65]. Potkin *et al.* [59] and Silverman *et al.* [55] found that AEs such as somnolence, weight gain, dry mouth, and headache occurred at a rate at least 2-fold greater in the OLZ/SAM group compared to the placebo group. Overall, while some specific AEs varied between the studies, somnolence, dizziness, and gastrointestinal-related symptoms were consistently reported as common AEs associated with the use of olanzapine and OLZ/SAM.

Interactions

Several studies investigated the pharmacokinetics and potential drug interactions of the combination of olanzapine and samidorphan (OLZ/SAM). The studies utilized physiologically based pharmacokinetic (PBPK) modeling and clinical trials to evaluate various aspects of the combination therapy.

One study by Sun *et al.* [72] focused on predicting drug-drug interactions (DDIs) between OLZ/SAM and CYP3A4 or CYP1A2 modulators using PBPK modeling. The model suggested that coadministration with strong CYP1A2 inhibitors may increase olanzapine exposure, while CYP1A2 induction (such as from smoking) may reduce olanzapine exposure. CYP3A4 inhibitors were predicted to have a weak effect on samidorphan exposure and negligible impact on olanzapine exposure. Converse-

ly, moderate-to-strong CYP3A4 inducers were expected to decrease samidorphan and olanzapine exposure.

In another study, Sun *et al.* [73] evaluated the impact of food on the pharmacokinetics (PK) of OLZ/SAM. The study involved healthy volunteers and found that the PK profiles of OLZ and SAM were similar in fed and fasted conditions. The results indicated that food had no clinically relevant impact on the PK of OLZ and SAM when administered as OLZ/SAM.

A study by Sun *et al.* [74] investigated the potential interactions between OLZ/SAM and lithium or valproate, commonly used in the treatment of bipolar disorder. The study found that coadministration of OLZ/SAM with lithium or valproate did not have a clinically significant effect on the pharmacokinetics of these medications. The safety profiles of the combination therapy were consistent with previous reports for OLZ/SAM and the individual medications [74].

The impact of rifampin, a potent CYP3A4 inducer, on the pharmacokinetics of OLZ/SAM was examined in a study by Sun *et al.* [75]. Coadministration with rifampin resulted in a decrease in the exposure of both olanzapine and samidorphan. However, OLZ/SAM 10/10 was generally well tolerated in the study.

Lastly, Sun *et al.* [76] investigated the effects of hepatic impairment on the pharmacokinetics of olanzapine and samidorphan in the OLZ/SAM combination. The study utilized PBPK modeling and found a modest increase in exposures of olanzapine and samidorphan in subjects with moderate hepatic impairment compared to those with normal hepatic function.

Overall, these studies provide valuable insights into the pharmacokinetics, potential drug interactions, food effect, and impact of hepatic impairment on OLZ/SAM combination therapy. The findings contribute to a better understanding of the safety and efficacy of OLZ/SAM and help guide clinical decision-making.

CONCLUSIONS

Recent studies indicate that the use of samidorphan alongside olanzapine can help to decrease weight gain in patients. In addition, combining an opioid receptor antagonist with olanzapine does not affect its ability to reduce psychotic symptoms in patients with schizophrenia, as it does not impact its pharmacokinetics or pharmacodynamics. The use of samidorphan not only decreases body weight gain but also reduces insulin resistance, blood pressure, and triglyceride levels. This positive effect helps in minimizing the risk of cardiovascular events. However, it is important to be aware of the potential for increased side effects, particularly those affecting the digestive system. In conclusion, according to research findings the utilization of SAM/OLZ therapy could potentially provide significant advantages in the treatment of obesity among patients with schizophrenia. This development represents an important breakthrough in the field of schizophrenia treatment.

Conflict of interest

Absent.

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