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Opioid antagonists to prevent olanzapine-induced weight gain: A systematic review

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Abstract

Introduction: Olanzapine (OLZ) is a second generation antipsychotic that is approved for the treatment of schizophrenia, bipolar disorder type 1 as monotherapy (acute manic or mixed episodes, maintenance), or as an add-on to lithium or valproate (manic or mixed episodes). It is one of the most effective antipsychotics for the treatment of schizophrenia, but concerns remain due to its significant metabolic adverse effects. Notably, OLZ has one of the highest rates of weight gain among all antipsychotic drugs. Previous studies report on potential mitigation of weight gain with opioid antagonists. A systematic review was conducted to summarize the impact of these agents on weight and BMI when used as adjuncts to OLZ.

Methods: A systematic review of randomized controlled trials was conducted with 3 searches between March 2, 2021 and March 27, 2022.

Results: Six studies met inclusion criteria, 5 of which assessed OLZ and samidorphan (SAM) and 1 of which assessed OLZ and naltrexone compared with OLZ monotherapy. A total of 1752 patients were included with 952 receiving SAM and 14 receiving naltrexone as an adjunct to OLZ. SAM was shown to mitigate OLZ-induced weight gain by 1.0 kg. Only 1 study assessed naltrexone with no statistically significant results for weight gain.

Discussion: SAM is effective at reducing OLZ-induced weight gain. Naltrexone did not reduce OLZ-induced increases in weight or BMI. However, there is a paucity of data on other opioid antagonists as adjuncts to OLZ treatment to prevent increases in weight or BMI.

Keywords: olanzapine, weight gain, body mass index, opioid antagonists

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Introduction

Olanzapine (OLZ) is a second generation antipsychotic with US FDA approval for the treatment of schizophrenia (SCZ), bipolar disorder type 1 as monotherapy (acute manic or

mixed episodes, maintenance), or as an add-on to lithium or valproate (manic or mixed episodes).[1] It is one of the most effective antipsychotics for the treatment of SCZ, but concerns remain due to its significant metabolic adverse effects.[2] Particularly, it causes some of the highest rates of weight gain among all antipsychotic drugs with average reported gains of 4.2 to 5.6 kg.[1,3-5]

Previous studies report on potential adjunctive pharmacological strategies to prevent or decrease weight gain secondary to antipsychotic treatment. The British Association for Psychopharmacology Guidelines on the Management of Weight Gain, Metabolic Disturbances and Cardiovascular Risk Associated with Psychosis and Antipsychotic Drug Treatment recommend metformin and aripiprazole as possible adjunct treatments. Amantadine, glucagon-like peptide-1 receptor agonists, melatonin, orlistat, reboxetine, topiramate, and zonisamide are not recommended for routine clinical practice due to insufficient evidence.[6]

A 2021 meta-analysis[7] supported the use of glucagon-like peptide-1 receptor agonists, metformin, topiramate, nizatidine, and zonisamide as adjuncts to antipsychotics to diminish their degree of weight gain and BMI increase. Topiramate stood out due to having more adverse events than the other four agents, notably somnolence, paresthesia, and memory difficulties. The authors did not recommend any of these four remaining drugs over another and suggested clinical decision making be guided by an assessment of each agent's efficacy and tolerability. However, appendix 3 of their study offers a ranking in terms of efficacy on body weight gain from most to least effective: topiramate, zonisamide, glucagon-like peptide-1 receptor agonists, metformin, and nizatidine, and BMI, from most to least effective: topiramate, nizatidine, zonisamide, metformin, and glucagon-like peptide-1 receptor agonists. A 2018 meta-analysis[8] assessed the impact of various agents on reducing antipsychotic-induced weight gain while taking into account treatment discontinuation due to adverse events over 6 to 26 weeks. Topiramate was found to have the greatest reduction in weight gain (3.1 kg, 95% confidence interval [CI] = –5.57, –0.48) along with metformin (2.5 kg, 95% CI = –3.21, –1.80), which was confirmed via a rank of effectiveness and a sensitivity analysis. Authors noted a low prevalence of discontinuation of agents due to adverse events with topiramate having the highest prevalence (relative risk 1.88, 95% CI = 0.44, 7.94), which was not statically significant. No studies evaluating which agents are most commonly used in clinical practice to mitigate antipsychotic-induced weight gain were found.

Agents that antagonize opioid receptors have been assessed as potential adjuncts to OLZ due to their impact on appetite. The endogenous opioid system has been implicated in the regulation of appetite and may, therefore, prove useful in reducing weight gain. In rat studies, mu opioid receptor agonism increased food intake and the hedonic impact of sweetness and fats in the nucleus accumbens and the amygdala, partially by suppressing satiety signals.[9] In contrast, administration of naloxone, an opioid antagonist, into the nucleus accumbens and amygdala decreased hunger and sweet-seeking behaviors.[10] Similarly, administration of naltrexone, another opioid antagonist, into the amygdala decreased fat-seeking behaviors.[11] Samidorphan (SAM; ALKS-33) is a novel agent with mu opioid receptor antagonism, 5 times that of naltrexone's, and kappa and delta receptor partial agonism.[12] A primate study[13] in 2011 revealed decreased weight gain associated with OLZ by adding SAM therapy for 28 days. In a rat and nonhuman primate study, adding SAM to OLZ led to a food-independent decrease in weight gain.[14] A combination product of OLZ and SAM was approved by the FDA in May 2021 for the treatment of SCZ, bipolar disorder type 1 as monotherapy (acute manic or mixed episodes, maintenance), or as an add-on to lithium or valproate (manic or mixed episodes) in adults.[15] The 10-mg dose of SAM was chosen for the combination product based on better efficacy than the 5-mg dose, comparable efficacy to that of the 20-mg dose but with fewer side effects than the latter (53.5% vs 63.2% for the 10- and 20-mg dose, respectively).[16]

Finding agents that are efficacious at mitigating OLZ-induced weight gain yet affordable and well-tolerated is important because OLZ is an effective therapy for SCZ and there are few available therapeutic options to reduce OLZ-induced weight gain. Given the availability of naltrexone and naloxone as generic monotherapy products and clinician familiarity with their use compared to SAM, it is worthwhile to assess if these options are also shown to mitigate OLZ-induced weight gain. This systematic review aimed to summarize available human data on the effect of opioid antagonists on weight or BMI as adjuncts to OLZ treatment.

Methods

A systematic review was performed following the 2020 update on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[17] The protocol was registered in the international database PROSPERO of the National Institute for Health and Research with the code CRD42020179851.

Studies were selected from BIOSIS, clinicaltrials.gov, Cochrane Central, Embase, Google Scholar, MEDLine, PsycINFO, PubMed, PubMed Central, and Web of Science. Two searches were completed between March 2 and November 16, 2021, using the search terms *olanzapine* AND (*narcotics* OR *opiates* OR *opioids*) AND (*weight gain* OR *obesity* OR *overweight* OR *weight increase* OR *body mass*

index). A third search was completed on March 27, 2022, using the search terms *olanzapine* AND (*opioid antagonists* OR *naltrexone* OR *naloxone* OR *samidorphan*) AND (*weight gain* OR *obesity* OR *overweight* OR *weight increase* OR *body mass index* OR *weight mitigation* OR *weight attenuation*). However, searches through BIOSIS, EMBASE, and Web of Science could not be carried out for this third search due to access limitations. References from articles, suggestions from databases, and high-frequency authors were also reviewed for inclusion.

Inclusion criteria were published randomized controlled trials on human adults with active OLZ and opioid antagonist treatment assessing changes in weight or BMI. No language or date restrictions were placed on any of the searches. Authors screened all reports, first reviewing titles and abstracts, then the full text of each article. To summarize relevant data, authors extracted the following variables from each study as applicable: number of participants, diagnoses, OLZ dose per day (mg), comparator dose per day (mg), duration of treatment (weeks), baseline weight and/or BMI, final weight and/or BMI, weight gain of more than 7% to 10%, reports of weight gain as an adverse effect, and relevant statistical results. Discrepancies were resolved through discussion among the authors until a consensus was reached.

Results

Search Results

The first stage of the search yielded 1261 results using the databases and search terms specified above (Figure). Records were then screened based on title and abstract, and any relevant studies were added, which resulted in 22 studies being further screened. Six studies[16,18-22] met inclusion criteria.

Study Characteristics

A total of 1752 patients who underwent randomization were included, 65% of whom were males and 9% for whom gender was not specified. Of the total population, 652 subjects received OLZ monotherapy, 966 subjects received OLZ and opioid antagonist combination therapy, and 134 subjects received OLZ and placebo. Two of the studies[16,18] allowed for a 1- to 4-week open-label period of OLZ monotherapy to assess tolerability prior to randomization. In all other studies, the adjunct opioid antagonist or placebo was initiated at the same time as OLZ. Opioid antagonists used were SAM in 5 studies and naltrexone in 1 of the studies. The average daily OLZ dose was 13.7 ± 3.04 mg when used as monotherapy and 13.7 ± 2.99 mg when used with opioid antagonists, the average daily SAM dose was 10 ± 4.63 mg, and the single daily naltrexone dose was 50 mg. Five studies assessed weight change outcomes, 4 evaluated percentage of reported weight gain as a side effect of treatment, 2 studies reported greater than 7% or 10% weight gain, and 1 study reported BMI changes. Five out of the 6 studies included patients with a diagnosis of SCZ, 1 study included patients with a diagnosis of schizoaffective disorder, 1 included patients with comorbid alcohol use disorder, and 1 study was conducted on healthy volunteers. The 6 studies had similar inclusion and exclusion criteria. Refer to Table 1 for a detailed summary of each study's criteria.

Outcomes

Baseline BMIs varied across studies with overweight BMIs in 4 of the studies, obese BMI in 1 study, and healthy BMI in 1 study.

Net weight gain with OLZ/SAM (1.5 to 3.2 kg) was significantly lower than with OLZ monotherapy (2.4 to 5.1 kg) across the 4 studies[16,19-21] that reported data analyses on this outcome with an average gain of 1 kg less with the combination product than with OLZ monotherapy. However, this seemed to vary slightly based on SAM dosing with a 0.9- to 1.9-kg reduction with the 5-mg combination product, a 1.4-kg reduction with the 10-mg combination products, and a 0.7-kg reduction with the 20-mg combination product. One study[20] found a 0.6-kg difference in weight gain with the 5-mg SAM and OLZ combination product compared with OLZ monotherapy with the combination product having the higher weight gain value. The studies[16,18-20,22] that included nonfixed doses of OLZ did not provide data analysis for how these differences in OLZ dosing could have affected overall weight gain outcomes.

Weight gain as a side effect was reported 12% to 36% of the time with OLZ monotherapy compared with 4% to 25% of the time with the combination product. This seemed to vary based on SAM dose with reports[18-20,23] of this adverse effect in 10% to 12% of patients with the 5-mg dose, 4% to 25% of patients with the 10-mg dose, and 6% to 9% of patients with the 20-mg dose. Two of the studies[18,20] noted higher rates of weight gain with 10 mg SAM combination therapy (14.3% and 18.7%) than with OLZ monotherapy (12.0% and 14.3%) with numbers needed to harm (NNH) of 22 and 43. One study[23] with an additional 12-week extension noted a higher rate of weight gain with 5 mg SAM combination therapy (11.5%) than the other doses of the combination product (4% to 6%). However, none of these studies was designed to assess weight gain as a primary outcome but, rather, to assess efficacy for acute SCZ exacerbations.

Greater than 7% weight gain was reported to occur 25% to 43% with OLZ monotherapy compared with 15% to 28%

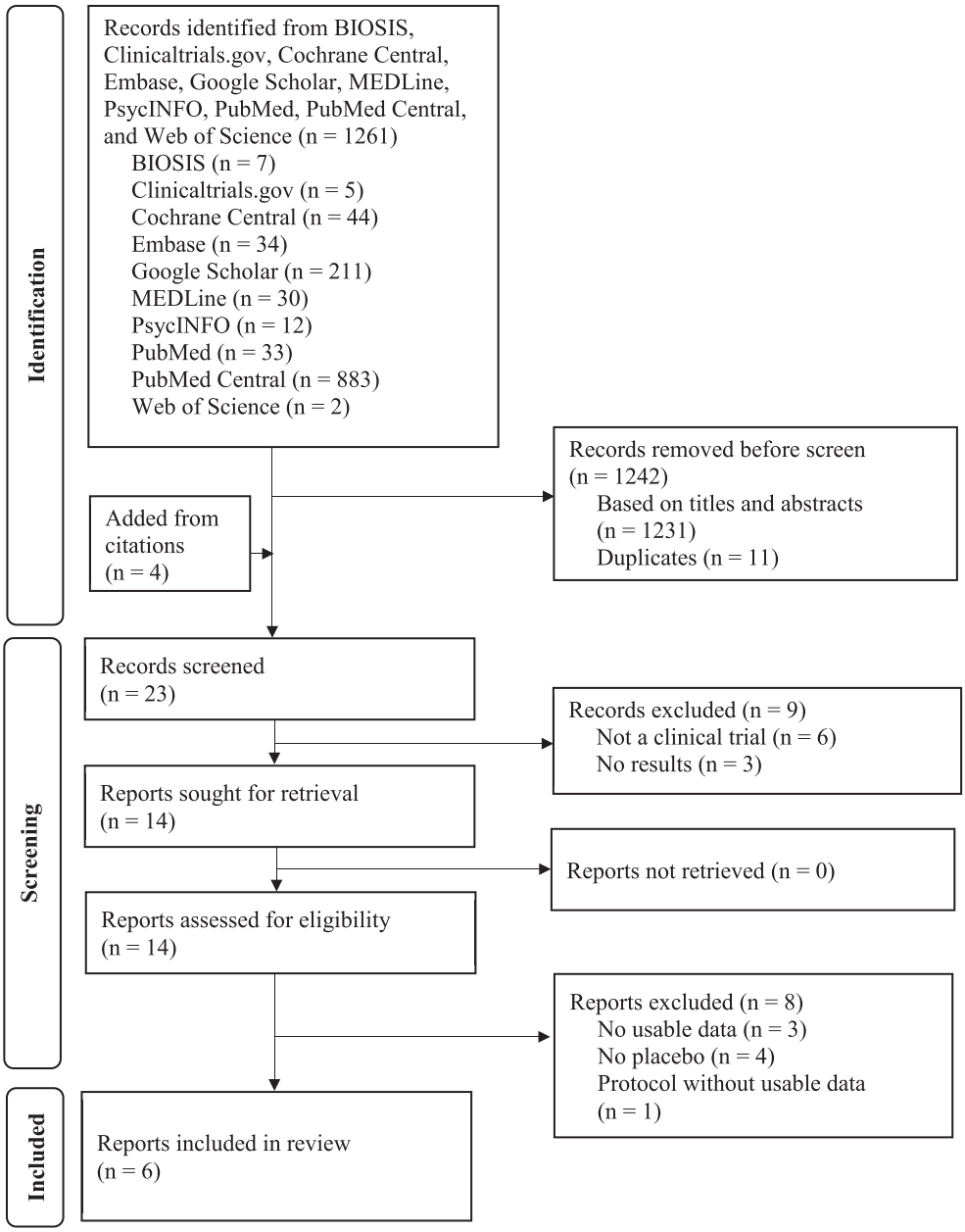

FIGURE: Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 flow diagram of search process

with the OLZ/SAM combination product in 2 of the studies.[16,19] One study[16] revealed an NNH of 35 with the 20-mg SAM dose, an NNH of 10 for both the 5- and 10-mg doses of SAM. The other one[19] had an NNH of 6 with a 10-mg SAM dose.

Greater than 10% weight gain was reported in 18% to 30% of participants with OLZ monotherapy compared with 6% to 18% of participants with the OLZ/SAM combination product in two studies.[16,19] One study[16] revealed an NNH of 8 with the 5-mg SAM dose, an NNH of 9 with the 10-mg SAM dose, and an NNH of 11 with the 20-mg SAM dose. The other one[19] had an NNH of 8 with a 10-mg SAM dose.

The addition of a 50-mg dose of naltrexone to OLZ afforded attenuation of weight gain by 0.2 kg ($P = .68$).[22] There were no changes in BMI in the naltrexone study. Surprisingly, all groups in this study lost weight or had a decrease in their BMI even with OLZ monotherapy. Refer to Table 2 for a more detailed summary of all outcomes.

Discussion

Weight gain caused by OLZ is a concern with its use despite its efficacy as an antipsychotic agent, and there have been only a few well-tolerated medications shown to mitigate this

TABLE 1: Characteristics of studies included in the systematic review

Study Information	Population and Sample Size	Inclusion Criteria	Exclusion Criteria
Correll (2020) ENLIGHTEN-2 24 wk total; participants were titrated to goal doses over 4 wk after randomization	SCZ OLZ: 276 OLZ/SAM: 274	Ages 18 to 55; BMI 18 to 30 kg/m^2; ≤5% weight change for 3 mo	• Treatment-resistant SCZ • <1 y since initial onset of symptoms • Naïve to antipsychotics • Use of OLZ within 60 d of screening • Active AUD or SUD (excluding cannabis) • Opioid agonist use within 14 d of screening • Opioid antagonist use within 60 d of screening • Anticipated need for opioid treatment during study • Clinically significant unstable medical condition
Brunette (2020) 36 to 60 wk total; OLZ monotherapy for 4 wk then OLZ/SAM combination for 2 wk to ensure tolerability before randomization	SCZ and AUD OLZ: 117 OLZ/SAM: 112	Ages 18 to 65; ≥10 drinking and ≥2 heavy-drinking d in the past month; AUD exacerbation ≤6 mo	• Intolerance to OLZ • Positive opioid test • SUD other than AUD
Potkin (2020) ENLIGHTEN-1 4 wk total; participants were titrated to goal doses over 3 d after randomization	SCZ (acute) OLZ: 133 OLZ/SAM: 134 Placebo: 134	Ages 18 to 70; PANSS ≥80 with ≥4 on at least 3 items: 1, 2, 3, or 6; CGI-S ≥4 at baseline and screening; BMI 18 to 40 kg/m^2; abide by contraception methods	• Exposure to OLZ, clozapine, mesoridazine, chlorpromazine, thioridazine, or LAI antipsychotics within 6 mo of screening • Exposure to 3-mo paliperidone LAI in the past year • Opioid agonist use within 14 d of screening • Opioid antagonist use within 60 d of screening • Weight-loss drug or hypoglycemic agent use at screening • Statin use within 3 mo of screening • <1 y since initial onset of symptoms • Clinically significant unstable medical condition • Moderate-to-severe AUD within 3 mo of screening • Positive UDS for opioids, amphetamines, phencyclidine, or cocaine • At risk for suicide
Martin (2019) 12 to 25 wk total; OLZ monotherapy for 1 wk to detect early weight gain for subsequent stratification in randomization, to identify the early weight gain population, and to ensure tolerability before randomization	SCZ 12 wk OLZ: 75 OLZ/SAM: 234 25 wk OLZ/SAM: 164	Ages 18 to 50; PANSS ≤80; CGI-S ≤3; ≤5% weight change for 3 mo; BMI 17 to 30 kg/m^2	• Exposure to OLZ, clozapine, mesoridazine, chlorpromazine, or thioridazine >1 wk within 1 y of screening or any time within 3 mo of screening • Weight reduction agent, systemic steroid, or antipsychotic medication use within 2 mo of screening • <2 y since initial onset of symptoms • First antipsychotic treatment within past year

TABLE 1: Characteristics of studies included in the systematic review (continued)

Study Information	Population and Sample Size	Inclusion Criteria	Exclusion Criteria
Silverman (2018) 3 wk total; no report of titration or an open-label phase prior to randomization	Healthy volunteers OLZ: 35 OLZ/SAM: 34	Male; ages 18 to 40; BMI 18 to 25 kg/m^2; ≤5% weight change for 3 mo; ≤1 kg weight change between screening and randomization	• Current psychiatric condition • Prior use of any antipsychotic medication for a psychiatric condition • Diabetes or glucose intolerance • Systemic corticosteroid use within 1 y • Clinically significant unstable medical condition • SUD (except caffeine or nicotine) • Active or planned involvement in weight management program within 6 mo
Taveira (2014) 12 wk total; no report of titration or an open-label phase prior to randomization	SCZ, schizoaffective disorder OLZ: 16 OLZ/NTX: 14	Ages 21 to 55; stable OLZ dose ≥5 and ≤30 mg for at least 2 mo; BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with one symptom of metabolic syndrome	• Dementia • Bipolar disorder • MDD • SUD • Eating disorder • Pregnancy or plans to become pregnant • Potentially confounding neurological condition • Potentially confounding medical condition

AUD = alcohol use disorder; CGI-S = Clinical Global Impressions-Severity of Illness Scale; LAI = long-acting injectable; NTX = naltrexone; OLZ = olanzapine; PANSS = Positive and Negative Syndrome Scale; SAM = samidorphan; SCZ = schizophrenia; UDS = urine drug screen.

side effect. This systematic review found that SAM is the most studied opioid antagonist to mitigate weight gain caused by OLZ. Assessment of the impact of other opioid antagonists and agents with other mechanisms of action on this outcome is of great interest given OLZ's efficacy in the treatment of SCZ.

The average OLZ dose used in the 6 studies, 13.7 mg, was lower than the average clinical dose of 20 mg used for the treatment of SCZ in adults based on the Clinical Antipsychotic Trials of Intervention Effectiveness trial.[2] A 2005 Cochrane review[24] determined that greater clinical responses in SCZ were seen with 15 mg of OLZ with smaller clinical effects seen with doses of 10 mg and none with 5 mg although the latter was based on a single study. A 2020 dose-response meta-analysis[25] in acute SCZ corroborated that an OLZ dose of at least 15.2 mg was needed for a clinical response. Both of these analyses were based on total score reductions on the Positive and Negative Syndrome Scale or the Brief Psychiatric Rating Scale. Thus, this reduces the generalizability of the studies included in this review. Future studies should assess the efficacy of SAM at diminishing OLZ-caused weight gain at OLZ doses between 15 and 20 mg.

Most of the weight gain associated with OLZ and general antipsychotic therapy is seen within the first 3 months of treatment; thus, a 3-month time frame for studies assessing this outcome was adequate.[26] However, weight gain secondary to antipsychotic treatment can continue after this time period as seen in the 25-week trial discussed above.[4,23] The 52-week extension to the ENLIGHTEN-1 trial used an average OLZ dose of 15.4 mg/d.[27] Patients who received OLZ/SAM or OLZ monotherapy during ENLIGHTEN-1 had higher baseline weights than those who received placebo. However, they experienced less weight gain at the end of the 52-week assessment period compared with those who received placebo during ENLIGHTEN-1. No data values or statistics for weight change were included in the main article or its supplements. A study assessed adverse events with the OLZ/SAM combination product with no comparator over 52 weeks as an extension to the ENLIGHTEN-2 trial.[28] Out of this population, 167 participants completed all 52 weeks of follow-up, 23 (9%) of them experienced weight loss (0.03 ± 6.2 kg), and 16 (6%) of them experienced weight increase (no average and standard deviations were reported for this). This may suggest the effects of SAM as an adjunct to OLZ for mitigating weight gain can be maintained for at least 1 year but that its efficacy may decrease with time, particularly after the first 3 months of treatment. It is unclear why weight gain mitigation does not increase as SAM doses increase. Thus, this is another area into which future studies could look.

Due to the paucity of data evaluating opioid antagonists other than SAM, it is unclear whether other mu opioid antagonists lead to similar outcomes in weight gain

TABLE 2: Outcomes of studies included in the systematic review

Study	Average Doses (mg)	Weight Gained			Weight Gain as a Reported Side Effect, n (%)
		Total (kg)	>7% From Baseline, n (%)	>10% From Baseline, n (%)	
Correll (2020)					
ENLIGHTEN-2	OLZ 16.9 ± 3.6	5.1	118 (42.7)	81 (29.8)	100 (36.2)
	OLZ / SAM 16.8 ± 3.9 / 10	3.2	76 (27.5)	47 (17.8)	68 (24.8)
	P value	.003[a]	.001[a]	.003[a]	–
Brunette (2020)	OLZ 14 ± 6.6				14 (12.0)
	OLZ / SAM 15 ± 6.8 / 10				16 (14.3)
	P value				–
Potkin (2020)					
ENLIGHTEN-1	OLZ 18.4	2.4 ± 3.7			19 (14.3)
	OLZ / SAM 19 / 10	3.0 ± 3.6			25 (18.7)
	Placebo	0.2 ± 2.8			4 (3.0)
	P value	–			–
Martin (2019)					
12 wk	OLZ 11.8	2.9 ± 3.1	14 (25.0)	10 (17.9)	9 (12.0)
	OLZ / SAM 11.1 / 5	2.1 ± 3.1	8 (15.4)	3 (5.8)	8 (10.0)
	OLZ / SAM 10.9 / 10	1.5 ± 3.0	9 (15.3)	4 (6.8)	7 (8.1)
	OLZ / SAM 12.1 / 20	2.2 ± 2.9	12 (22.2)	5 (9.3)	6 (8.8)
	P value	.018[a]	–	–	–
25 wk	OLZ / SAM 11.1 / 5				6 (11.5)
	OLZ / SAM 10.9 / 10				2 (3.5)
	OLZ / SAM 12.1 / 20				3 (5.5)
	P value				–
Silverman (2018)	OLZ 10	3.4 ± 1.8			
	OLZ / SAM 10 / 5	2.5 ± 1.4			
	P value	.009[a]			
Taveira (2014)	OLZ 11.3 ± 7.0	0.9			
	OLZ / NTX 14.8 ± 9.3 / 50	1.1			
	P value	.68			

NTX = naltrexone; OLZ = olanzapine; SAM = samidorphan; – = not provided.

[a]Statistically significant.

mitigation or if SAM's unique kappa- and delta-partial agonist activity is required. Additionally, it was noted that 10 mg SAM led to better mitigation of OLZ-induced weight gain compared with 20 mg SAM. This may suggest pharmacological activity at some receptors changes based on dosing, which should be taken into consideration for future studies looking at other opioid agonists. A 2014 study[29] tested the hypothesis that naltrexone would mitigate weight gain compared with placebo in 21 overweight females receiving antipsychotic treatment. They found that the naltrexone group had a mean weight loss of 3.4 kg compared with a mean weight gain of 1.4 kg in the placebo group, which was statistically significant ($P = .001$). However, the study did not break down outcomes based on which antipsychotic was used. Therefore, the effect of other concomitant opioid antagonists on weight gain attenuation secondary to OLZ may be a good topic for future studies because weight gain continues to be a barrier to this antipsychotic's use.

SAM's average decrease of 1.0 kg in weight gain from OLZ is lower or comparable to that of other agents for antipsychotic-induced weight gain such as metformin or topiramate. Total weight gained secondary to antipsychotics has been decreased on average by 2 to 3 kg with metformin and by 5 kg with topiramate.[7,8] Yet there are currently no studies assessing how SAM, metformin, and topiramate compare with one another as adjuncts to OLZ. Future studies could also compare SAM to other agents used to mitigate antipsychotic-induced weight gain in regard to other important metabolic parameters (fasting blood glucose, hemoglobin A1c, waist circumference, etc). Because

the OLZ/SAM combination product is currently only available as a brand name, it is crucial to take cost into account. On average, a 1-month supply of metformin ER 2000 mg daily and topiramate 200 mg daily would cost $27 to $50 and $21 to $250, respectively. A 1-month supply of the OLZ/SAM product would cost $1000 regardless of which dose of OLZ the product contains. These costs were calculated by using 60% of the average wholesale price found in Micromedex Red Book (as recommended by the International Society for Pharmacoeconomics and Outcomes Research).[30,31] Based on this review, OLZ/SAM may be a good option as an adjunct for patients with SCZ who have experienced clinically significant or bothersome weight gain with OLZ or who have other risk factors for weight gain (unhealthy diet, sedentary lifestyle, residence in a nonmetropolitan area, active weight-inducing medications, hypothyroidism, Cushing syndrome, etc) who are not achieving desired outcomes with trials of metformin or topiramate alone, or who cannot tolerate them.[32] However, due to the cost of the OLZ/SAM combination product, it is reasonable to prioritize and emphasize the role of diet and exercise in weight loss to patients and their families.

This systematic review has several limitations. First, although this review summarized available data on opioid agonists for OLZ-induced weight gain, it did not pool and analyze data from the studies that met inclusion criteria. Second, most of the studies summarized had primary outcomes assessing efficacy, not safety or adverse effects. Thus, these outcomes could be susceptible to type II errors. Third, study quality was not assessed, and thus, the risk of bias in each one was not evaluated as part of the discussion. The FDA evaluated the ENLIGHTEN-1 and ENLIGHTEN-2 studies (A305 and A303, respectively) as part of the approval process for the OLZ/SAM combination product.[19,20] Both of these studies were funded by Alkermes, Inc, the manufacturer of the combination OLZ/SAM product, which could have led to sponsorship bias. Fourth, due to the nature of systematic reviews being retrospective, it is possible that they are subject to systematic and random errors as well as selection bias. Fifth, most of the studies that met inclusion criteria assessed 1 single agent, SAM. This systematic review also has strengths including early registration with PROSPERO, the large number of databases that were used for the initial search, the use of reference lists and high-frequency authors to expand the search, inclusion of studies that were not in English, and its use of 2 screeners.

Conclusion

Opioid antagonists have been evaluated for OLZ-induced weight gain. Most data available support the efficacy of SAM for this indication. The majority of the SAM studies assessed a 10-mg dose in addition to OLZ, which is the dose included in the combination product. Due to its cost compared with other agents also shown to mitigate weight gain associated with antipsychotics, this product may be considered in patients who are stable on OLZ and are unable to tolerate or are not achieving desired outcomes with metformin or topiramate only after efforts have been made to increase a healthy diet and exercise in patients. There is a paucity of data for naltrexone and no studies for naloxone for this indication. Given their availability as generic monotherapy products and their frequent use in other clinical settings, it would be worthwhile to assess their efficacy in mitigating OLZ-induced weight gain.

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