# Olanzapine/Samidorphan Effects on Weight Gain:

## An Individual Patient Data Meta-Analysis of Phase 2 and 3 Randomized Double-Blind Studies

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## Abstract

**Objective:** To evaluate weight change with a combination of olanzapine and samidorphan (OLZ/SAM) versus olanzapine by pooling data across clinical studies.

**Methods:** This study was an individual patient data (IPD) meta-analysis of clinical trial data.

**Data Sources and Study Selection:** EMBASE, MEDLINE, and PsycInfo were searched for randomized clinical trials (≥12 weeks) in adults with schizophrenia or bipolar I disorder in which weight change from baseline was the primary or secondary end point. Search results were reviewed for eligible studies.

**Participants:** Patients receiving daily OLZ/SAM (olanzapine 5–20 mg + samidorphan 10 mg) or olanzapine (5–20 mg) who underwent ≥1 postbaseline weight assessment by week 12 were included.

**Outcomes:** The primary outcome was percent change in body weight at week 12. Secondary outcomes were proportions of patients with ≥7% or ≥10% weight gain from baseline at week 12.

**Results:** Overall, 1063 patients from 3 studies conducted between June 2013 and December 2021 were analyzed. At week 12, OLZ/SAM treatment was associated with a lower least squares mean (LSM) percent change in body weight from baseline (3.68%) vs olanzapine (5.43%) (LSM [SE] difference = −1.75% [.41]; 95% CI, −2.55 to −0.94). Fewer patients treated with OLZ/SAM gained ≥7% (23.9% vs 34.6%; odds ratio [OR] = 0.58; 95% CI, 0.043–0.79) or ≥10% (13.7% vs 20.4%; OR = 0.60; 95% CI, 0.42–0.88) of their baseline body weight at week 12.

**Conclusion:** In this IPD meta-analysis, OLZ/SAM treatment was associated with less weight gain and reduced risk of reaching ≥7% or ≥10% gain in body weight versus olanzapine over 12 weeks.


*J Clin Psychiatry 2025;86(1):24m15526*

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Schizophrenia and bipolar I disorder (BD-I) are mental health conditions associated with severe symptoms, physical and psychiatric comorbidities, and functional impairments in daily living tasks.[1–5] Olanzapine is an antipsychotic medication that has established antipsychotic efficacy for the treatment of schizophrenia and BD-I.[6,7] In 2 previously conducted comparative antipsychotic effectiveness trials that enrolled patients with first-episode (12-month randomized open-label trial) or chronic (18-month randomized double-blind trial) schizophrenia, patients treated with olanzapine had the lowest rates of all-cause discontinuation.[8,9] In a 5-study meta-analysis[10] of patients with BD-I and acute mania, olanzapine treatment significantly reduced symptoms compared with placebo, with the largest effect size for patients with the most severe symptoms at baseline.

Despite its established efficacy in patients with schizophrenia or BD-I, olanzapine's associated weight gain and potential for causing metabolic abnormalities have thus far limited its clinical use.[9,11,12] In clinical studies, a significant proportion of patients treated with olanzapine monotherapy experience clinically significant weight gain (defined as >7% increase from baseline), with rates as high as 86% in those with first-episode psychosis and 30% in those with chronic schizophrenia.[8,9] The risk of weight gain with olanzapine is generally dose dependent, with higher doses often associated with a greater likelihood of weight gain.[13,14]

## Clinical Points

- Previous reports estimating the weight-mitigation effect of a combination of olanzapine and samidorphan (OLZ/SAM) have had methodological shortcomings.
- In this individual patient data meta-analysis, treatment with OLZ/SAM was associated with less weight gain after 12 weeks compared with olanzapine.
- Similar changes in patients' disease severity were observed between OLZ/SAM and olanzapine; changes in metabolic parameters were small and similar.

The combination of olanzapine and samidorphan (OLZ/SAM) is approved in the United States for the treatment of adults with schizophrenia or BD-I.[15] This combination product provides the well-known and established antipsychotic efficacy of olanzapine while mitigating olanzapine-associated weight gain with the addition of samidorphan. Samidorphan acts as a μ-opioid receptor antagonist and a partial δ- and κ-opioid receptor agonist.[16] In clinical trials, OLZ/SAM has been consistently associated with efficacy similar to that of olanzapine but with less weight gain.[17–19] However, previous attempts at estimating the weight-mitigation benefit of OLZ/SAM have been limited by methodological shortcomings.[20–22]

The objective of this analysis was to evaluate the weight change profile of OLZ/SAM versus olanzapine using individual patient data (IPD) and meta-analytic techniques. The IPD meta-analysis approach has several advantages over aggregate data meta-analysis, such as checking data in detail, standardizing outcomes across studies, and increasing statistical power to detect treatment effects.[23,24] The weight change profile of OLZ/SAM versus olanzapine was assessed in patients with schizophrenia or BD-I who participated in clinical trials of ≥12 weeks' duration in which weight change was measured as a primary or secondary study end point.

# METHODS

## Protocol and Registration

All procedures for this IPD meta-analysis were in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) guidelines for IPD.[25] The PRISMA checklist is included as Supplementary Table 1. All analytic methods, study objectives, end points, and patient inclusion criteria were prespecified and documented in a statistical analysis plan for the study. The plan was finalized in November 2022.

## Information Sources and Search Strategy

A systematic literature search was conducted through August 23, 2024, in the EMBASE, MEDLINE, and PsycInfo databases. The following search strategy was used for EMBASE and MEDLINE: (olanzapine) AND (samidorphan) AND (random* OR placebo) [all fields + text]. The search string for PsycInfo was (olanzapine AND samidorphan AND (random* OR placebo)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, MESH word]. The search was not restricted by language or publication date.

## Eligibility Criteria

Eligible studies for this IPD meta-analysis were randomized double-blind studies of OLZ/SAM vs olanzapine ≥12 weeks' duration in which weight change was measured as a primary or secondary study end point. Inclusion criteria were predetermined in the study plan.

## Study Selection

The systematic literature search and initial review for relevance were conducted by medical staff (Omar H. Cabrera and Noud van Helmond). Individual articles were screened by title and abstract for eligibility. M.J.D. and D.M. confirmed the potential eligibility of articles. Full-text articles were reviewed for potentially relevant studies to determine if the report met eligibility criteria.

## Risk of Bias in Individual Studies

Included studies were assessed for methodological quality by M.J.D. using the Cochrane Collaboration's RoB 2 tool for assessing the risk of bias.[26]

## Individual Patient Data

Patients aged ≥18 years and meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision,* or *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, criteria for schizophrenia or BD-I were eligible.[27,28] Only patients receiving daily OLZ/SAM (olanzapine 5–20 mg + samidorphan 10 mg, doses approved by the US Food and Drug Administration [FDA]) or olanzapine (5–20 mg) who underwent ≥1 postbaseline weight assessment by week 12 were included. Data from patients taking a non–FDA-approved fixed-dose OLZ/SAM combination containing 5 or 20 mg of samidorphan were excluded.

## Assessments

The primary outcome was the percent change from baseline body weight at week 12. Secondary outcomes included the proportions of patients with clinically significant weight gain of ≥7% or ≥10% from baseline at week 12. Percent change from baseline body weight and the clinically significant weight gain thresholds of ≥7% and ≥10% were chosen because they are common end points in studies of weight gain associated with antipsychotic treatment.[9,29–31]

Additional assessments at week 12 included the overall mean change in weight from baseline. Subgroup analyses assessed percent change from baseline body weight based on various demographic categories (eg, age <30 or ≥30 years, male or female sex, Black or non-Black race, body mass index [BMI] <25 or ≥25 kg/m$^2$, US or non-US region). Adverse event (AE) rates and metabolic parameter changes were evaluated also. Changes in disease severity were assessed by using the Clinical Global Impressions–Severity of Illness (CGI-S) score. All outcomes were prespecified and assessed at the IPD level.

### Statistical Analysis

The primary outcome was analyzed using a 1-stage IPD random-effects model and a mixed model for repeated measures (MMRM) approach with percent change from baseline as the dependent variable. Treatment, visit, and treatment-by-visit interaction were categorical fixed effects (considered constant across studies), and study was a random effect. Baseline weight was included as a covariate.

The random-effects model assumes heterogeneity of the treatment effect between studies and that the observed variance is the sum of within-study and between-study components. The 1-stage approach was chosen because it more accurately models the statistical distribution of IPD.[23] The analysis was performed on all observed postrandomization, on-treatment weight assessments, without imputation of missing data. Least squares mean (LSM) difference was calculated as the measure of effect size, along with 95% CIs.

The proportions of patients who experienced clinically significant weight gain were analyzed using a generalized linear mixed model using ≥7% or ≥10% weight gain as a dependent variable; treatment, visit, and treatment-by-visit interaction as categorical fixed effects; study as a random effect; and baseline weight as a covariate. Odds ratios (ORs) and 95% CIs were calculated.

For the subgroup analyses by age, sex, race, BMI, and region, treatment effects and 95% CIs were calculated. The numbers and percentages of all randomized patients who received ≥1 dose of study drug in the primary clinical trial and reported an AE during the double-blind treatment period (week 12/week 13), including those for AEs that led to treatment discontinuation, serious AEs, drug-related AEs, and deaths, are provided. Descriptive statistics and changes from baseline values at week 12 (with a ±10-day window) are presented by treatment group (OLZ/SAM or olanzapine) for glycosylated hemoglobin (HbA1c), fasting blood glucose, total, low-density, and high-density lipoprotein cholesterol, and triglyceride levels. CGI-S scores of treated patients who underwent ≥1 postbaseline weight assessment by week 12 were also assessed.

Data analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).

### Sensitivity Analyses

Prespecified sensitivity analyses were conducted using 1-stage and 2-stage IPD MMRM approaches to evaluate the consistency of the treatment effect. Therefore, study was a variable evaluated as both a random effect (assuming heterogeneity) and a fixed effect (assuming homogeneity). For the 1-stage approach, study was a fixed effect. For the 2-stage approach, 2 analyses were conducted: 1 with study as a random effect and 1 with study as a fixed effect. The 2-stage approach is similar to a standard meta-analysis on aggregate data. Thus, individual study estimates were calculated, plotted, and compared for similarities or differences. The estimates were then weighted and pooled using random or fixed effect methods. Between-study heterogeneity was evaluated in the 2-stage approach with $I^2$, $\tau^2$, and Cochran Q $P$ values.

## RESULTS

### Study Characteristics

A total of 111 records were retrieved across the 3 databases (EMBASE, n = 77; MEDLINE, n = 25; PsycInfo, n = 9; Supplementary Figure 1). After removing 32 duplicates, there were 79 unique articles. Following title and abstract review, 68 articles were excluded for not meeting the eligibility criteria. Eleven articles were potentially eligible and underwent full-text review. Of these publications, 8 were excluded because they reported studies <12 weeks' duration or were abstracts reporting on the results of a study that were later published in full.

After screening, the following 3 studies were eligible: a phase 2, 12-week efficacy and safety study in patients with schizophrenia (NCT01903837)[17]; a phase 3, 24-week pivotal weight study in patients with schizophrenia (NCT02694328)[17,18]; and a phase 3, 12-week study in patients with recent-onset schizophrenia, schizophreniform disorder, or BD-I (NCT03187769)[19] (Supplementary Table 2).

All 3 studies were conducted between 2013 and 2021. In each study, eligible patients were required to have a BMI of ≤30 kg/m$^2$. Patient data were maintained in internal databases belonging to Alkermes, Inc., and were checked for completeness.

### Population Characteristics

Of the 1336 patients randomized in the 3 studies, 1063 (80%) met inclusion criteria and underwent ≥1 postbaseline weight assessment by week 12 (NCT01903837, n = 161; NCT02694328, n = 538; NCT03187769, n = 364). The baseline mean (SD) age was 35.2 (10.7) years, 755 (71%) patients were male, 569 (54%) patients were Black, and the mean (SD) BMI was 24.8 (3.3) kg/m$^2$. Overall, 833 (78%) patients were from the United States (Table 1).

Table 1.
**Demographic and Baseline Characteristics**

| Parameters | OLZ/SAM (n = 532) | Olanzapine (n = 531) | All patients (N = 1,063) |
|---|---|---|---|
| **CGI-S score, mean (SD)** | 3.54 (0.7) | 3.61 (0.7) | 3.58 (0.7) |
| **Age, mean (SD), y** | 35.2 (10.6) | 35.2 (10.9) | 35.2 (10.7) |
| **Sex, n (%)** | | | |
| Male | 379 (71.2) | 376 (70.8) | 755 (71.0) |
| Female | 153 (28.8) | 155 (29.2) | 308 (29.0) |
| **Race, n (%)** | | | |
| Black | 287 (53.9) | 282 (53.1) | 569 (53.5) |
| White | 223 (41.9) | 217 (40.9) | 440 (41.4) |
| Asian | 8 (1.5) | 14 (2.6) | 22 (2.1) |
| American Indian or Alaska Native | 4 (0.8) | 3 (0.6) | 7 (0.7) |
| Native Hawaiian or other Pacific Islander | 1 (0.2) | 2 (0.4) | 3 (0.3) |
| Other | 3 (0.6) | 4 (0.8) | 7 (0.7) |
| Multiracial | 6 (1.1) | 9 (1.7) | 15 (1.4) |
| **BMI, mean (SD), kg/m$^2$** | 24.8 (3.3) | 24.9 (3.4) | 24.8 (3.3) |
| **Region, n (%)** | | | |
| US region | 416 (78.2) | 417 (78.5) | 833 (78.4) |
| Non-US region | 116 (21.8) | 114 (21.5) | 230 (21.6) |

Abbreviations: BMI = body mass index; CGI-S = Clinical Global Impressions–Severity of Illness; OLZ/SAM = olanzapine combined with samidorphan.

Patient characteristics were similar between the OLZ/SAM and olanzapine groups, with baseline mean (SD) ages of 35.2 (10.6) and 35.2 (10.9) years, respectively. Most patients in the OLZ/SAM and olanzapine cohorts were male (379 [71%] and 376 [71%], respectively) and Black (287 [54%] and 282 [53%], respectively). The baseline mean (SD) BMIs were 24.8 (3.3) kg/m$^2$ for the OLZ/SAM group and 24.9 (3.4) kg/m$^2$ for the olanzapine group. Overall, 416 (78%) patients in the OLZ/SAM group and 417 (79%) in the olanzapine group were from the United States.

## Risk-of-Bias Assessment

The overall risk of bias was low for all studies assessing the weight change profile of OLZ/SAM versus olanzapine. There were some concerns about bias due to missing outcome data for one study[17] because multiple imputation was not performed on the weight outcome. However, the overall risk of bias in this study was low, and it was included in the sensitivity analyses. The results of the risk-of-bias assessment are reported in Supplementary Table 3. No data integrity issues were identified in a review of the IPD.

## Weight Change From Baseline

At week 12, treatment with OLZ/SAM was associated with a lower LSM percent change from baseline in body weight (3.68%) compared with olanzapine treatment (5.43%) (LSM [SE] difference = −1.75% [0.41%]; 95% CI, −2.55 to −0.94) (Figure 1). The LSM (SE) change from baseline in weight at week 12 was 2.63 (0.22) kg for the OLZ/SAM group and 3.96 (0.22) kg for the olanzapine group (LSM [SE] difference = −1.33 [0.30] kg; 95% CI, −1.92 to −0.75).

Fewer patients treated with OLZ/SAM (23.9%) than those treated with olanzapine (34.6%) gained ≥7% of their respective baseline body weight at week 12. The OR (95% CI) for attaining a ≥7% increase in body weight from baseline with OLZ/SAM vs olanzapine was 0.58 (0.43–0.79) (Figure 1). Fewer patients treated with OLZ/SAM (13.7%) than those treated with olanzapine (20.4%) had gained ≥10% of their respective baseline body weight at week 12. The OR (95% CI) for attaining a ≥10% increase in body weight from baseline with OLZ/SAM vs olanzapine was 0.60 (0.42–0.88) (Figure 1).

## Subgroup Analyses

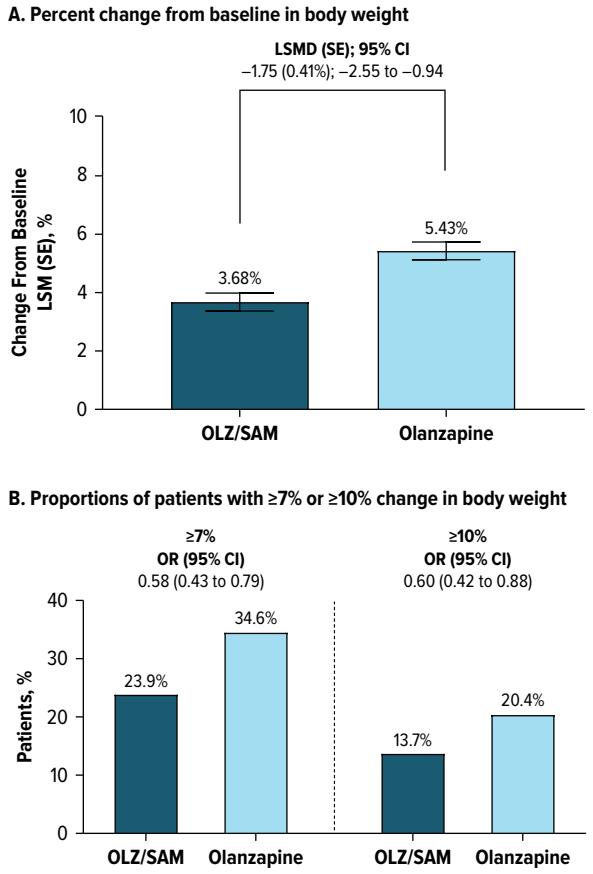
Numerically, OLZ/SAM resulted in a lower percent change in body weight across all subgroups examined, including by age, sex, race, BMI, and region (Figure 2).

## Safety

The proportions of patients with any AE(s) were similar between the OLZ/SAM and olanzapine groups, with 64% and 66%, respectively, experiencing at least 1 AE (Table 2). The most common AE was weight increase, which occurred in 19% of the patients receiving OLZ/SAM and 24% of those receiving olanzapine. Other AEs occurring in ≥5% of patients included somnolence, dry mouth, increased appetite, and waist circumference increase, which is consistent with the known AE profiles of olanzapine and OLZ/SAM.

Figure 1.

## Body Weight at Week 12




Abbreviations: LSMD = least squares mean difference; LSM = least squares mean; OLZ/SAM = olanzapine combined with samidorphan; OR = odds ratio.

## Metabolic Parameters

Changes in metabolic parameters were small and similar between the OLZ/SAM and olanzapine groups at week 12 (Table 3), despite the differential effects on weight that were observed. Mean (SD) blood glucose concentrations increased by 4.17 (21.3) mg/dL in the OLZ/SAM group and 1.93 (14.0) mg/dL in the olanzapine group at week 12. No relevant mean changes in HbA1c levels were observed. A mean (SD) increase in total cholesterol level was noted in both groups at week 12 (OLZ/SAM, 4.23 [29.5] mg/dL; olanzapine, 7.11 [29.6] mg/dL), with similar decreases in high-density lipoprotein cholesterol level and increases in low-density lipoprotein cholesterol level in both groups. Mean (SD) triglyceride levels increased by 15.38 (78.7) mg/dL in the OLZ/SAM group and 20.70 (70.8) mg/dL in the olanzapine group at week 12.

## Assessment of Disease Severity

Mean (SD) baseline CGI-S scores were 3.54 (0.7) for OLZ/SAM and 3.61 (0.7) for olanzapine, indicating mild-to-moderate illness severity. Mean (SD) changes from baseline at week 12 in CGI-S score were −0.41 (0.7) for OLZ/SAM and −0.42 (0.7) for olanzapine.

Table 2.

## Summary of Adverse Events Occurring in ≥5% of Patients in Any Treatment Group

| AE, n (%) | OLZ/SAM (n = 548) | Olanzapine (n = 544) |
|---|---|---|
| Any | 352 (64.2) | 360 (66.2) |
| Weight increase | 106 (19.3) | 133 (24.4) |
| Somnolence | 87 (15.9) | 68 (12.5) |
| Dry mouth | 45 (8.2) | 27 (5.0) |
| Appetite increase | 40 (7.3) | 49 (9.0) |
| Waist circumference increase | 23 (4.2) | 32 (5.9) |

Abbreviations: AE = adverse event; OLZ/SAM = olanzapine combined with samidorphan.

## Assessment of Sensitivity Analyses

The results of the sensitivity analysis using the 1-stage approach with study as a fixed effect were similar to those of the primary analysis. Treatment with OLZ/SAM was associated with a lower LSM percent change from baseline in body weight than treatment with olanzapine (LSM [SE] difference = −1.75% [0.41%]; 95% CI, −2.55 to −0.94). Similar results were obtained using the 2-stage approach with study as a random or fixed effect. Treatment with OLZ/SAM was associated with a lower LSM percent change from baseline than was treatment with olanzapine (LSM [SE] difference = −1.52% [0.29%]; 95% CI, −2.08 to −0.95) (Supplementary Figure 2). Measures of between-study heterogeneity suggested that the studies were similar enough in terms of design, population, and treatment effect to pool for meta-analysis.

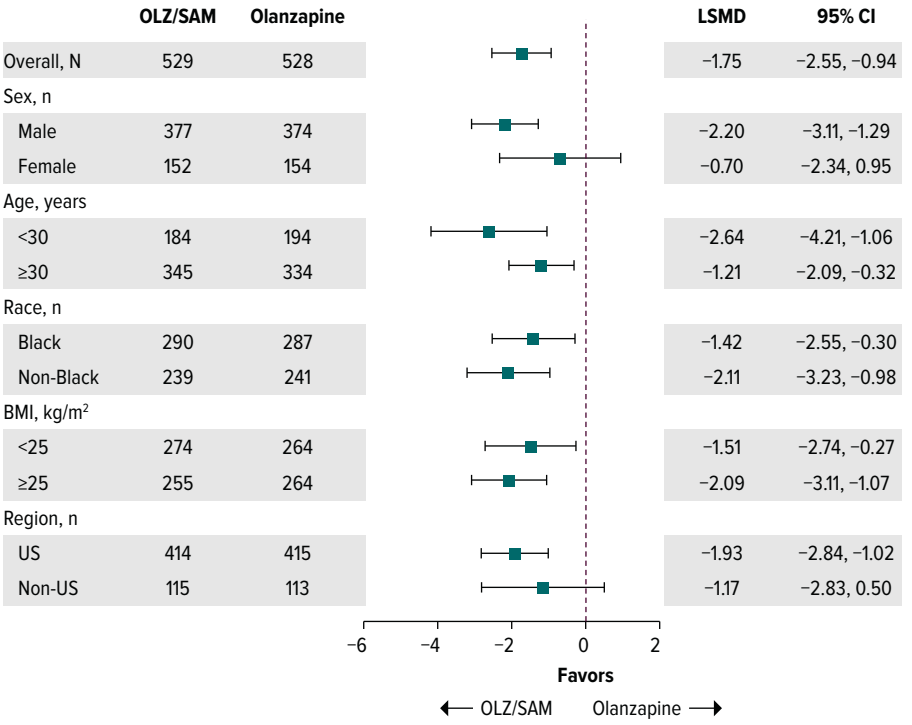
# DISCUSSION

In this IPD meta-analysis of 3 clinical trials, treatment with OLZ/SAM resulted in significantly less weight gain than treatment with olanzapine after 12 weeks. Results consistently favored OLZ/SAM for the outcome of percent change in weight and for the risk of experiencing clinically significant weight gain of ≥7% or ≥10%. In addition, OLZ/SAM resulted in lower mean changes in weight from baseline. On average, patients treated with OLZ/SAM gained about 3 pounds less over 3 months than those treated with olanzapine. Also, OLZ/SAM was associated with lower mean percent changes in body weight across all subgroups examined. These results suggest that OLZ/SAM may consistently mitigate olanzapine-associated weight gain across different patient populations.

This study was the first to generate estimates of the weight-mitigating benefit of OLZ/SAM across similarly

Figure 2.

## Subgroup Analysis of Percent Changes in Body Weight at Week 12




Abbreviations: BMI = body mass index; LSMD = least squares mean difference; OLZ/SAM = olanzapine combined with samidorphan.

Table 3.

## Changes From Baseline in Metabolic Parameters at Week 12

| Parameters | OLZ/SAM (n = 415), mean (SD) | Olanzapine (n = 425), mean (SD) |
|---|---|---|
| **Glucose,[a] mg/dL** | 4.2 (21.3) | 1.9 (14.0) |
| **HbA1c,[b] %** | 0 (0.4) | 0 (0.3) |
| **Total cholesterol, mg/dL** | 4.2 (29.5) | 7.1 (29.6) |
| **HDL cholesterol, mg/dL** | −3.5 (12.1) | −3.4 (12.2) |
| **LDL cholesterol, mg/dL** | 6.0 (26.6) | 7.2 (25.0) |
| **Triglycerides, mg/dL** | 15.4 (78.7) | 20.7 (70.8) |

[a]For change from baseline to week 12, n = 383 (OLZ/SAM) and n = 388 (olanzapine).
[b]For change from baseline to week 12, n = 411 (OLZ/SAM) and n = 418 (olanzapine).
Abbreviation: OLZ/SAM = olanzapine combined with samidorphan.

designed clinical trials and had several advantages over previous attempts.[20–22] Studies included in this analysis were of sufficient duration (≥12 weeks) to detect differences in weight gain between the OLZ/SAM and olanzapine groups.[18,19] In each study, the weight trajectories of patients taking OLZ/SAM and those taking olanzapine were similar for the first 4–6 weeks of treatment but diverged thereafter. Weight stabilized for patients on OLZ/SAM, while weight gain continued for patients on olanzapine.[18,19] Previous attempts to estimate the weight-mitigating effect of OLZ/SAM included studies that were only 3 or 4 weeks in duration, a time frame too short to determine the differential weight gain effect of OLZ/SAM versus olanzapine accurately.[32,33] Indeed, the "real-world" weight-mitigation benefit associated with OLZ/SAM may be even more pronounced over longer treatment durations given that weight gain plateaus within a few weeks after starting OLZ/SAM treatment but continues with olanzapine.[17–19] Another advantage of this study is that IPD were used to calculate weight estimates, whereas previous studies have relied on published, aggregated data.[20–22] Furthermore, only data from patients receiving an FDA-approved dose of OLZ/SAM (olanzapine 5–20 mg + samidorphan 10 mg) were assessed.[34] Other doses of OLZ/SAM are not relevant because they are not available for clinical use.[35] The adequacy of the IPD meta-analysis methodology enabled additional assessments of AEs, metabolic parameters, and the antipsychotic efficacy of OLZ/SAM across clinical trials.

The proportions of patients experiencing AEs were similar in the OLZ/SAM and olanzapine groups, and the most common AEs reported were consistent with the known profiles of olanzapine and OLZ/SAM. Both OLZ/SAM and olanzapine were associated with small

and similar changes in metabolic parameters across 12 weeks, despite the differences observed in weight gain. However, the 12-week duration of treatment in this analysis may have been too short to detect changes in metabolic risk factors associated with weight gain that develop over longer periods of olanzapine exposure.[36,37] Therefore, the observed results do not capture the longer-term health concerns, such as cardiometabolic changes, that may be associated with olanzapine use. In general, treatment with olanzapine has been associated with metabolic worsening and an increased risk of developing metabolic syndrome over time.[37,38] In a post hoc analysis of the 24-week pivotal weight study,[36] OLZ/SAM resulted in a significant reduction in the risks of metabolic syndrome and hypertension in patients free of those conditions at baseline. In addition, the small metabolic parameter changes observed in the 24-week study[18] remained stable over an additional 52 weeks of open-label OLZ/SAM treatment.[39] Furthermore, the weight-mitigation benefit observed with OLZ/SAM after 12 weeks of treatment appears to be durable, as changes in weight are small after OLZ/SAM treatment totaling up to 5.5 years.[18,39,40]

After 12 weeks of treatment, similar improvements in disease severity were observed in both the OLZ/SAM and olanzapine groups based on CGI-S scores. These results are consistent with those of another clinical trial in which OLZ/SAM treatment resulted in antipsychotic efficacy versus placebo that was comparable to that of olanzapine versus placebo.[33]

### Limitations

Several limitations of this post hoc analysis should be considered. This IPD meta-analysis assessed only short-term effects of OLZ/SAM versus those of olanzapine after 12 weeks of treatment. The analysis was not designed to make statistical comparisons between OLZ/SAM and olanzapine regarding AEs, metabolic parameter changes (other than weight gain), or antipsychotic efficacy. Because 2 of the 3 studies included only patients with schizophrenia, relatively few patients with BD-I were available for analysis. Given that patients in the analysis were enrolled in a randomized clinical trial with relevant exclusion criteria, the results may not be generalizable to the larger population of patients with schizophrenia or BD-I. The CGI-S was used to assess changes in disease severity; antipsychotic efficacy was not evaluated. Last, the numbers of patients in some subgroups were relatively small, thus limiting the conclusions that can be drawn from subgroup analyses. Despite these limitations, however, this study was the first IPD meta-analysis of the 3 available clinical trials of sufficient duration to assess the weight-mitigating effect of OLZ/SAM on olanzapine-associated weight gain.

## CONCLUSIONS

In this IPD meta-analysis of similarly designed studies that evaluated the effects of OLZ/SAM versus olanzapine on body weight as a primary or secondary study end point, treatment with OLZ/SAM was consistently associated with a lower percent weight gain, lower mean weight gain, and reduced risk of reaching the ≥7% or ≥10% threshold for clinically significant body weight gain versus treatment with olanzapine. In each study, weight mitigation with OLZ/SAM occurred after 4–6 weeks of treatment and body weight stabilized thereafter, whereas patients on olanzapine gained weight throughout the 12-week treatment window.

The reduction in percent weight gain with OLZ/SAM was observed across all subgroups examined, suggesting that OLZ/SAM provides weight-gain mitigation advantages across different patient populations. Metabolic changes were small and similar between patients taking OLZ/SAM and those taking olanzapine. Similar CGI-S score improvements observed between treatments further support the observation that the weight gain–mitigating effect of OLZ/SAM does not negatively affect the therapeutic efficacy of olanzapine. As a whole, these findings highlight the consistency with which OLZ/SAM mitigates olanzapine-associated weight gain, an effect that has been reported across multiple independent studies. By mitigating olanzapine-associated weight gain, OLZ/SAM provides a treatment option for patients with schizophrenia or BD-I with less weight gain and the established efficacy of olanzapine. Future studies may further explore OLZ/SAM's long-term benefits with respect to weight mitigation, disease improvement, and metabolic changes.

## Article Information

**Published Online:** January 2, 2025. https://doi.org/10.4088/JCP.24m15526


**Submitted:** July 18, 2024; accepted October 21, 2024.

**To Cite:** Correll CU, Doane MJ, McDonnell D, et al. Olanzapine/samidorphan effects on weight gain: an individual patient data meta-analysis of phase 2 and 3 randomized double-blind studies. *J Clin Psychiatry.* 2025;86(1):24m15526.

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**Author Contributions:** All authors had full access to the data and contributed to the drafting, critical review, and revision of the manuscript. All authors granted approval of the final manuscript for submission.

**Relevant Financial Relationships: Dr Correll** has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Adcock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, Intra-Cellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedinCell, Merck, MindPax, Mitsubishi Tanabe Pharma, Mylan, Neurelis, Neurocrine, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Takeda, Teva, Tolmar, Vertex, and Viatris; provided expert testimony for Janssen and Otsuka; served on a data safety monitoring board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva; received grant support from Janssen and Takeda; received royalties from UpToDate; and is a stock option holder of Cardio Diagnostics, Küleon Biosciences, LB Pharma, MindPax, and Quantic. **Dr Doane** is or was an employee of Alkermes, Inc., and may own stock/options in the company. **Dr McDonnell** is an employee of Alkermes Pharma Ireland Ltd. and may own stock/options in the company. **Dr Akerman** was an employee and shareholder of Alkermes, Inc., at the time this study was conducted. **Dr Saklad** was an employee of The University of Texas at Austin College of Pharmacy; was appointed to the Texas Health and Human Services Commission, San Antonio State Hospital, and is on the faculty of the UT Health San Antonio Long School of Medicine; has served as consultant for Alkermes, Genomind, Janssen, Karuna, and Otsuka; has participated on the speakers' bureau for Neurocrine, Otsuka PsychU, Teva, Texas Society of Health-System Pharmacists, and, on occasion, for several professional organizations; served on the Business Development Council for the American Association of Psychiatric Pharmacists; has served as expert witness on both defendant and plaintiff sides; and has no direct stock ownership in any pharmaceutical corporation.

**Funding/Support:** This study was sponsored by Alkermes, Inc., Waltham, MA.

**Role of the Sponsor:** This study was conducted by Alkermes, Inc., a pharmaceutical company that developed and markets OLZ/SAM, a combination of olanzapine and samidorphan for the treatment of adults with schizophrenia or bipolar I disorder, in the United States. Employees of Alkermes, Inc., were involved in the study design and data analyses. The authors interpreted the evidence and made the decision to submit the manuscript for publication.

**Previous Presentations:** Portions of this work were previously presented in a poster at American Society of Clinical Psychopharmacology Annual Meeting; May 30–June 2, 2023; Miami Beach, FL. Psych Congress 2023; September 6–10, 2023; Nashville, TN. 2023 Neuroscience Education Institute Congress; November 9–12, 2023; Colorado Springs, CO. American College of Neuropsychopharmacology Annual Meeting; December 3–6, 2023; Tampa, FL.

**Acknowledgments:** Medical writing and editorial support were provided by Rebecca Lane, PhD; Omar Cabrera, PhD; John H. Simmons, MD; and Noud van Helmond, MD, PhD, of Peloton Advantage, LLC, an OPEN Health company, and funded by Alkermes, Inc. The authors thank Meihua Wang, PhD, and Martin Dunbar, PhD, for their contributions to this study and data analysis, and Mark S. Todtenkopf, PhD, of Alkermes, Inc., who assisted in the preparation and proofreading of the manuscript.

**Data Sharing Statement:** The data collected in this study are proprietary to Alkermes, Inc. Alkermes, Inc. is committed to public sharing of data in accordance with applicable regulations and laws, and requests can be submitted to the corresponding author.

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**Supplementary Material:** Available at Psychiatrist.com.

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The Journal of Clinical Psychiatry

# Supplementary Material

**Article Title:** Olanzapine/Samidorphan Effects on Weight Gain: An Individual Patient Data Meta-analysis of Phase 2 and 3 Randomized Double-Blind Studies

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**DOI Number:** 10.4088/JCP.24m15526

## LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE



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# SUPPLEMENTARY MATERIAL

## Supplementary Table 1. PRISMA IPD Checklist

| PRISMA-IPD Section/Topic | Item No. | Checklist item | Reported on page(s) |
|---|---|---|---|
| **Title** | | | |
| Title | 1 | Identify the report as a systematic review and meta-analysis of IPD. | 1 |
| **Abstract** | | | |
| Structured summary | 2 | Provide a structured summary including as applicable: | 6-7 |
| | | **Background**: state research question and main objectives, with information on participants, interventions, comparators and outcomes. | |
| | | **Methods**: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias. | |
| | | **Results**: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice. | |
| | | **Discussion:** state main strengths and limitations of the evidence, general interpretation of the results and any important implications. | |
| | | **Other:** report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis. | |
| **Introduction** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 9-10 |
| Objectives | 4 | Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups. | 10-11 |
| **Methods** | | | |
| Protocol and registration | 5 | Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable. | 11 |
| Eligibility criteria | 6 | Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the | 12, 13-14 |

| | | | |
|---|---|---|---|
| | | review inclusion criteria. The rationale for criteria should be stated. | |
| Identifying studies - information sources | 7 | Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation. | 11-13 |
| Identifying studies - search | 8 | Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 11 |
| Study selection processes | 9 | State the process for determining which studies were eligible for inclusion. | 12 |
| Data collection processes | 10 | Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study). | 13 |
| | | If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators. | |
| Data items | 11 | Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardizing or translating variables within the IPD datasets to ensure common scales or measurements across studies. | 14 |
| IPD integrity | A1 | Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done. | 14 |
| Risk of bias assessment in individual studies. | 12 | Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis. | 13 |
| Specification of outcomes and effect measures | 13 | State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome. | 14-15 |
| Synthesis methods | 14 | Describe the meta-analysis methods used to synthesize IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to):<br>• Use of a one-stage or two-stage approach. | 15-16 |

| | | | |
|---|---|---|---|
| | | • How effect estimates were generated separately within each study and combined across studies (where applicable).<br>• Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for.<br>• Use of fixed or random effects models and any other model assumptions, such as proportional hazards.<br>• How (summary) survival curves were generated (where applicable).<br>• Methods for quantifying statistical heterogeneity (such as $I^2$ and $\tau^2$).<br>• How studies providing IPD and not providing IPD were analyzed together (where applicable).<br>• How missing data within the IPD were dealt with (where applicable). | |
| Exploration of variation in effects | A2 | If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analyzed as potential effect modifiers, and whether these were pre-specified. | 15 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables. | |
| Additional analyses | 16 | Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified. | 16-17 |
| **Results** | | | |
| Study selection and IPD obtained | 17 | Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram. | 17, Supplementary Figure 1 |
| Study characteristics | 18 | For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD. | Supplementary Table 2 |
| IPD integrity | A3 | Report any important issues identified in checking IPD or state that there were none. | 18 |
| Risk of bias within studies | 19 | Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions. | 18, Supplementary Table 3 |

| | | | |
|---|---|---|---|
| Results of individual studies | 20 | For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot. | 17-18, Figures 1 and 2 |
| Results of syntheses | 21 | Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based. | 18-20, Figures 1 and 2 |
| | | When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials. | |
| | | Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice. | |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables. | 18 |
| Additional analyses | 23 | Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarize the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available. | 18 |
| **Discussion** | | | |
| Summary of evidence | 24 | Summarize the main findings, including the strength of evidence for each main outcome. | 21 |
| Strengths and limitations | 25 | Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available. | 23 |
| Conclusions | 26 | Provide a general interpretation of the findings in the context of other evidence. | 24 |
| Implications | A4 | Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research. | 25 |
| **Funding** | | | |
| Funding | 27 | Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support. | 4 |

Abbreviations: IPD, individual patient data; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

## **Supplementary Table 2.** Clinical Trials Included in the Analysis

| Study Authors (Year; ClinicalTrials.gov Identifier) | Phase | Duration, Weeks | Population | Patients Randomized or Enrolled, n | Included | Excluded |
|---|---|---|---|---|---|---|
| Martin et al (2019; NCT01903837)[1] | 2 | 12 | Adults with SZ | 347 | Clinically stable patients with SZ, aged 18–50 years, and baseline BMI 17–30 kg/m$^2$ | Patients starting first AP treatment within previous 12 months and/or symptomatic <2 years |
| Correll et al (2020; NCT02694328)[2] | 3 | 24 | Adults with SZ | 561 | Patients with SZ, aged 18–55 years, and baseline BMI 18–30 kg/m$^2$ | Patients with history of treatment-resistant SZ, <1 year since symptom onset, AP naive, active alcohol/substance use disorder, and/or unstable medical illness |
| Kahn et al (2023; NCT03187769)[3] | 3 | 12 | Young adults with SZ, BD-I, or schizophreniform disorder who were early in the course of illness | 428 | Patients with SZ, BD-I, or schizophreniform disorder, aged 18–39 years (US sites, ≥16–39 years, baseline BMI <30 kg/m$^2$, <4 years since symptom onset, and <24 weeks' cumulative lifetime AP exposure | Patients with >14 days of olanzapine use in the 6 months before enrollment and/or >3 weeks' cumulative lifetime use |

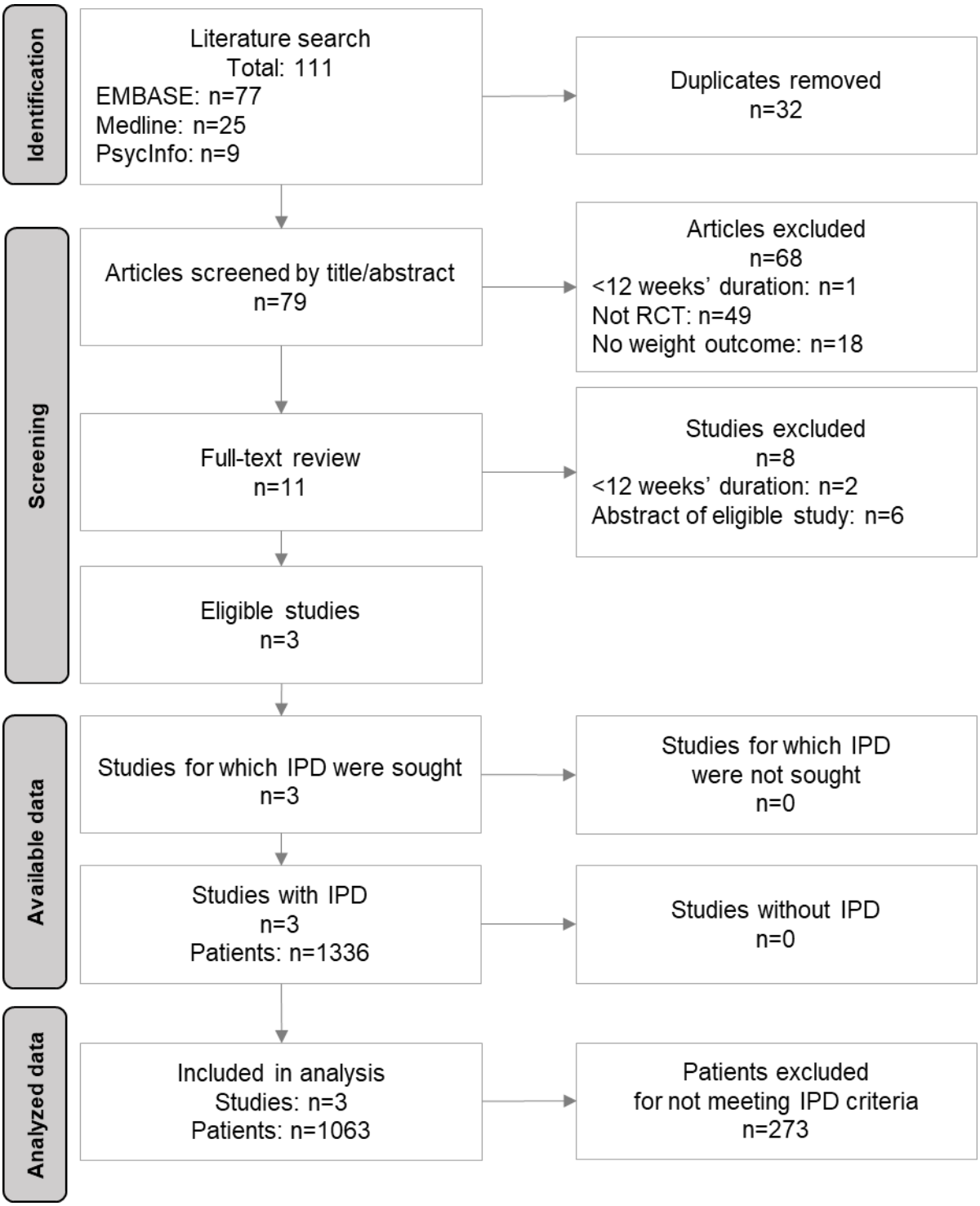
Abbreviations: AP, antipsychotic; BD-I, bipolar I disorder; BMI, body mass index; SZ, schizophrenia.

**Supplementary Table 3.** Risk-of-Bias Assessment of Included Studies Assessing the Weight Change Profile of OLZ/SAM Versus That of Olanzapine

| Author (year) | Bias arising from the randomization process | Bias due to deviations from intended interventions | Bias due to missing outcome data | Bias in measurement of the outcome | Bias in selection of the reported result | Overall risk of bias |
|---|---|---|---|---|---|---|
| Martin et al (2019)[1] | Low | Low | Some concerns | Low | Low | Low |
| Correll et al (2020)[2] | Low | Low | Low | Low | Low | Low |
| Kahn et al (2023)[3] | Low | Low | Low | Low | Low | Low |

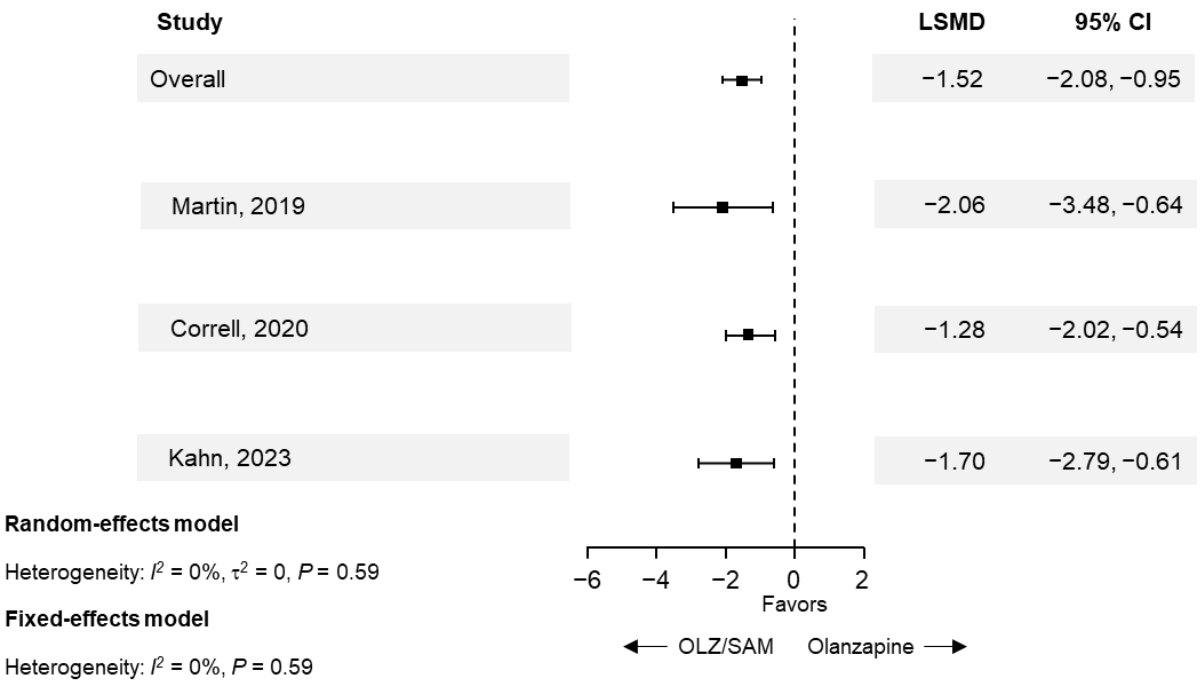
Abbreviation: OLZ/SAM, olanzapine combined with samidorphan.

## **Supplementary Figure 1.** PRISMA IPD Flow Diagram




Abbreviations: IPD, individual patient data; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled trial.

## **Supplementary Figure 2.** Sensitivity Analyses, 2-Stage Approach




Abbreviations: LSMD, least squares mean difference; OLZ/SAM, olanzapine combined with samidorphan.

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2. Correll CU, Newcomer JW, Silverman B, et al. Effects of olanzapine combined with samidorphan on weight gain in schizophrenia: a 24-week phase 3 study. *Am J Psychiatry*. 2020;177(12):1168-1178.
3. Kahn RS, Kane JM, Correll CU, et al. Olanzapine/samidorphan in young adults with schizophrenia, schizophreniform disorder, or bipolar I disorder who are early in their illness: results of the randomized, controlled ENLIGHTEN-Early study. *J Clin Psychiatry*. 2023;84(3):22m14674.