

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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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. [Table 1](#) PRISMA IPD Checklist
2. [Table 2](#) Clinical Trials Included in the Analysis
3. [Table 3](#) Risk-of-Bias Assessment of Included Studies Assessing the Weight Change Profile of OLZ/SAM Versus That of Olanzapine
4. [Figure 1](#) PRISMA IPD Flow Diagram
5. [Figure 2](#) Sensitivity Analyses, 2-Stage Approach
6. [References](#)

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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). 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.	13
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): <ul style="list-style-type: none"> • Use of a one-stage or two-stage approach. 	15-16

		<ul style="list-style-type: none"> • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analyzed together (where applicable). • 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

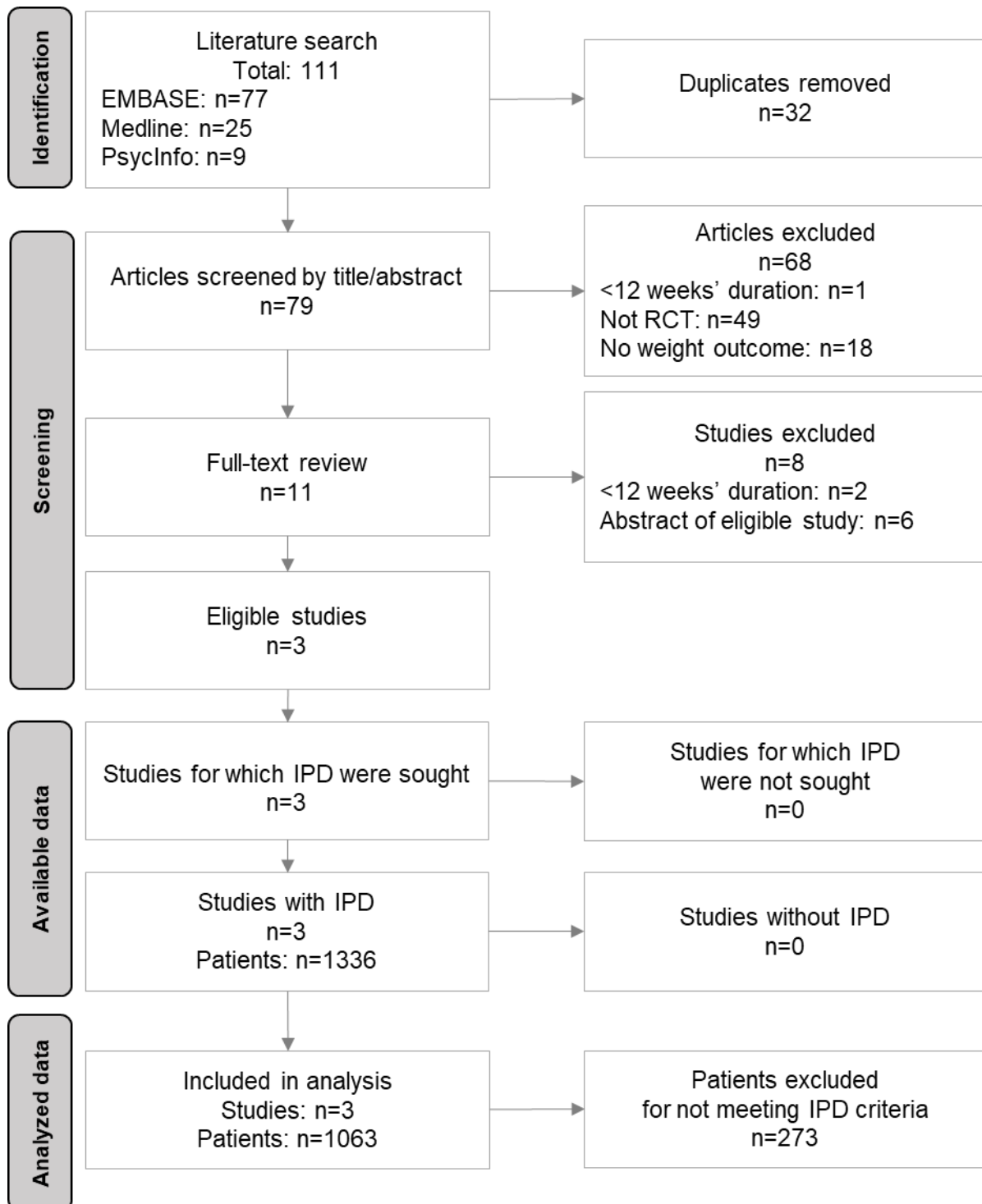
Abbreviations: AP, antipsychotic; BD-I, bipolar I disorder; BMI, body mass index; SZ, schizophrenia.

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

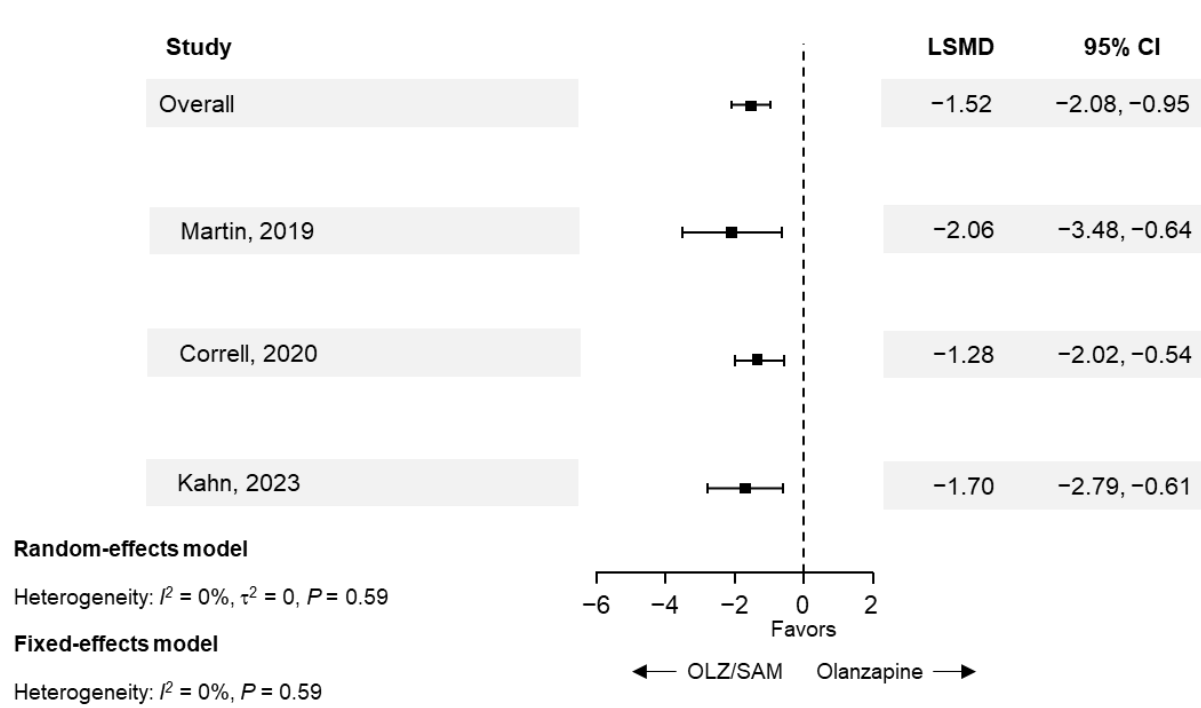
Abbreviation: OLZ/SAM, olanzapine combined with samidorphan.

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.

REFERENCES

1. Martin WF, Correll CU, Weiden PJ, et al. Mitigation of olanzapine-induced weight gain with samidorphan, an opioid antagonist: a randomized double-blind phase 2 study in patients with schizophrenia. *Am J Psychiatry*. 2019;176(6):457-467.
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.