INPLASY

Effects of cariprazine on cholesterol, glucose, and weight in patients with schizophrenia: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 October 2025 and was last updated on 7 October 2025.

INTRODUCTION

Review question / Objective It is well accepted that cariprazine is an effective and established treatment for schizophrenia; however, to date, no meta-analysis that synthesized metabolic alterations focused only onof cariprazine treatment in this disorder has been done. Based on the hypothesis that antipsychotic treatment is often associated with metabolic alterations, including weight gain, dyslipidemia, and increased risk of type 2 diabetes, we performed a systematic review and meta-analysis with the overarching aim of synthesizing study results that describe the effect of cariprazine on glucose and lipid homeostasis as well as weight in persons living with schizophrenia.

Rationale Antipsychotic treatment is often associated with metabolic alterations, including weight gain, dyslipidemia, increased risk of type 2 diabetes, and cardiovascular disease. Pillinger et al. in a systematic review and meta-analysis showed that cariprazine does not demonstrate evidence of disruption to glucose-insulin homeostasis or limit homeostasis and weight gain in replicated preclinical or clinical data. However, it can occur at significantly lower rates than other antipsychotic agents, as well as other dopamine partial agonists. Zhu et al.14 in-depth analysis of cariprazine's adverse events (AE) reports, based on the FDA's FAERS, demonstrated distinct characteristics of cariprazine AEs. Additionally, Masand et al.15 conducted a retrospective study using electronic health records to analyze the metabolic profiles of psychiatric patients during a 12-month period preceding cariprazine initiation (baseline) and for up to 12 months following initiation. Recently, Correll et al.16 in a large retrospective observational study on 612 psychiatric patients in treatment with cariprazine described that cariprazine was associated with estimated annual linear trajectories of+0.91 kg/year for weight, +0.31 kg/m2/year for BMI, – 2.38 mmHg/year for systolic blood pressure, and – 0.57 mmHg/year.

Condition being studied Schizophrenia is a chronic and severe mental disorder characterized by disturbances in thought, perception, emotion,

and behavior. Core symptoms include hallucinations, delusions, disorganized thinking, and cognitive impairment, often leading to significant functional disability.

Antipsychotic medications represent the cornerstone of treatment. They are effective in reducing positive symptoms (such as hallucinations and delusions) and, to a lesser extent, negative symptoms (such as social withdrawal and blunted affect). Antipsychotics are generally classified into first-generation (typical) and second-generation (atypical) agents, which differ in their receptor profiles and side effect patterns.

Despite their efficacy, antipsychotics are associated with various side effects. Typical antipsychotics often cause extrapyramidal symptoms (such as tremor, rigidity, and tardive dyskinesia), while atypical antipsychotics are more frequently linked to metabolic adverse effects, including weight gain, dyslipidemia, and impaired glucose regulation. Sedation, cardiovascular effects, and prolactin elevation may also occur. Careful monitoring and individualized treatment selection are therefore essential to balance efficacy and tolerability in long-term management.

METHODS

Search strategy Search Strategy
To ensure inclusivity, we systematically searched three major electronic databases of medical and social science research papers (PubMed/MEDLINE, PsycINFO, and Cochrane Central Register of Controlled Trials (CENTRAL)) for relevant titles and abstracts published between January 2014 and March 2025. The following terms were combined to search the databases in titles/abstracts (TAs): "Cariprazine" AND "Schizophrenia" OR "Psychosis" OR "Psych*" OR "Side effects" OR "Metabolic Effects" OR "Weight Gain" OR "Dyslpidemia" OR "Glucose" OR "Cholesterol".
"cariprazine" AND "schizophrenia" OR "psychosis" OR "side effects" OR "metabolic effects". Filters were used to limit the results to the English language. The search identified 752 papers. See Flow Chart for details of the study selection process.

Participant or population This review included original articles that explicitly discussed the presence of metabolic effects of the use of cariprazine in Schizophrenia. When the title or abstract indicated an eligible study, the full-text article was obtained and carefully examined to assess its relevance to the review's aims. Articles needed to meet the following eligibility criteria: (a) include the use of cariprazine and (b) include the presence of a Diagnosis Schizophrenia according to DSM-5 criteria; (c) include the presence of Side Effect, and parameters to value metabolic effect as laboratory value of Cholesterol total, HDL, and LDL, triglyceride, glucose and weight. In addition, (d) participants needed to be adults (aged 18 years and older), and (e) the study needed to be a quantitative research paper with case-control, cohort, or cross-sectional design or randomized controlled trials. The exclusion criteria were as follows: (a) studies published before 2014; (b) absence of side effects evaluation; (c) studies that did not investigate the efficacy and safety of cariprazine; (d) studies not published in peer-reviewed journals; (e) not published in English; (f) qualitative research, case studies, meta-analytical reviews, systematic reviews, narrative reviews, or book chapters.
Study Selection and Data Collection
The authors independently extracted and reviewed the studies using a two-step process: (1) screening and selecting based on the article's title and abstract, and (2) screening and selecting based on the full text. A data extraction spreadsheet was developed, adding the author(s), publication year, country, sample characteristics (population type and sample size), study design, outcome measures, and main results. Discussions among the senior authors, who also independently read all the articles, resolved potential disagreements regarding article inclusion and data collection. Furthermore, we managed screening, data extraction, and risk-of-bias assessment in Covidence (Veritas Health Innovation, Melbourne, Australia). All search results were exported to Covidence (Veritas Health Innovation, Melbourne, Australia) for record management. Covidence automatically removed duplicates prior to screening. Two reviewers independently screened titles/abstracts and then full texts against pre-specified eligibility criteria within Covidence; conflicts were resolved by consensus or, when necessary, a third reviewer. Reasons for full-text exclusion were logged in Covidence and are reported in the PRISMA 2020 flow diagram. Furthermore, the assessment of inter-rater reliability yielded an overall Cohen's kappa coefficient of 0.92, reflecting an almost perfect level of agreement between the two independent reviewers across all domains.

Intervention Electronic searches identified 755 publications. After excluding duplicates (n = 196), 559 abstracts and titles were screened for suitability. After non-RCT studies (n = 63), studies

not in English language (n = 20) and non-pertinent studies (n = 436) were removed (n = 519), 40 full-text titles were assessed for eligibility, with 28 records excluded because they did not align with the aims and inclusion criteria of our review (see Figure 1). Any disagreements regarding study eligibility were resolved following consensus discussions among the authors. Overall, 12 controlled studies were included in the present review. (For PRISMA checklist see supplementary materials).

Meta-analyses methods
Three meta-analyses focused on patients with schizophrenia, evaluating changes in weight, cholesterol, and glucose for both cariprazine 1.5 mg and 3 mg. Eggers' test and funnel plots were used to assess the presence of publication bias, while the homogeneity test was conducted to evaluate variability among the studies examined. The meta-analyses were performed using the difference between the mean values in the placebo group and the mean values in the cariprazine 1.5 mg/3 mg groups as the effect size. We did not evaluate other doses of cariprazine in the meta-analysis process due to the paucity of randomized controlled trials. In all the aforementioned analyses, an alpha significance level of 0.05 was used. IBM SPSS Statistics software version 29 was used for the statistical analysis.

Comparator All the studies in the metaanalysis compare Cariprazine to placebo.

Study designs to be included RCT for the metaanalysis, metaanalysi, open label, pooled analysis for the revision part.

Eligibility criteria This review included original articles that explicitly discussed the presence of metabolic effects of the use of cariprazine in Schizophrenia. When the title or abstract indicated an eligible study, the full-text article was obtained and carefully examined to assess its relevance to the review's aims. Articles needed to meet the following eligibility criteria: (a) include the use of cariprazine and (b) include the presence of a Diagnosis Schizophrenia according to DSM-5 criteria; (c) include the presence of Side Effect, and parameters to value metabolic effect as laboratory value of Cholesterol total, HDL, and LDL, triglyceride, glucose and weight. In addition, (d) participants needed to be adults (aged 18 years and older), and (e) the study needed to be a quantitative research paper with case-control, cohort, or cross-sectional design or randomized controlled trials. The exclusion criteria were as follows: (a) studies published before 2014; (b) absence of side effects evaluation; (c) studies that did not investigate the efficacy and safety of cariprazine; (d) studies not published in peer-reviewed journals; (e) not published in English; (f) qualitative research, case studies, meta-analytical reviews, systematic reviews, narrative reviews, or book chapters.

Information sources The authors independently extracted and reviewed the studies using a two-step process: (1) screening and selecting based on the article's title and abstract, and (2) screening and selecting based on the full text. A data extraction spreadsheet was developed, adding the author(s), publication year, country, sample characteristics (population type and sample size), study design, outcome measures, and main results. Discussions among the senior authors, who also independently read all the articles, resolved potential disagreements regarding article inclusion and data collection. Furthermore, we managed screening, data extraction, and risk-of-bias assessment in Covidence (Veritas Health Innovation, Melbourne, Australia). All search results were exported to Covidence (Veritas Health Innovation, Melbourne, Australia) for record management. Covidence automatically removed duplicates prior to screening. Two reviewers independently screened titles/abstracts and then full texts against pre-specified eligibility criteria within Covidence; conflicts were resolved by consensus or, when necessary, a third reviewer. Reasons for full-text exclusion were logged in Covidence and are reported in the PRISMA 2020 flow diagram. Furthermore, the assessment of inter-rater reliability yielded an overall Cohen's kappa coefficient of 0.92, reflecting an almost perfect level of agreement between the two independent reviewers across all domains.
To ensure inclusivity, we systematically searched three major electronic databases of medical and social science research papers (PubMed/MEDLINE, PsycINFO, and Cochrane Central Register of Controlled Trials (CENTRAL)) for relevant titles and abstracts published between January 2014 and March 2025. The following terms were combined to search the databases in titles/abstracts (TAs): "Cariprazine" AND "Schizophrenia" OR "Psychosis" OR "Psych*" OR "Side effects" OR "Metabolic Effects" OR "Weight Gain" OR "Dyslpidemia" OR "Glucose" OR "Cholesterol".
"cariprazine" AND "schizophrenia" OR "psychosis" OR "side effects" OR "metabolic effects". Filters were used to limit the results to the English language.

Main outcome(s) Based on the hypothesis that antipsychotic treatment is often associated with metabolic alterations, including weight gain, dyslipidemia, and increased risk of type 2 diabetes, we performed a systematic review and meta-analysis with the overarching aim of synthesizing study results that describe the effect of cariprazine on glucose and lipid homeostasis as well as weight in persons living with schizophrenia.

Additional outcome(s) Efficacy of Cariprazine on schizophrenia symptoms.

Data management We managed screening, data extraction, and risk-of-bias assessment in Covidence (Veritas Health Innovation, Melbourne, Australia). All search results were exported to Covidence (Veritas Health Innovation, Melbourne, Australia) for record management. Covidence automatically removed duplicates prior to screening. Two reviewers independently screened titles/abstracts and then full texts against pre-specified eligibility criteria within Covidence; conflicts were resolved by consensus or, when necessary, a third reviewer. Reasons for full-text exclusion were logged in Covidence and are reported in the PRISMA 2020 flow diagram. Furthermore, the assessment of inter-rater reliability yielded an overall Cohen's kappa coefficient of 0.92, reflecting an almost perfect level of agreement between the two independent reviewers across all domains.

Quality assessment / Risk of bias analysis We managed screening, data extraction, and risk-of-bias assessment in Covidence (Veritas Health Innovation, Melbourne, Australia). All search results were exported to Covidence (Veritas Health Innovation, Melbourne, Australia) for record management. Covidence automatically removed duplicates prior to screening. Two reviewers independently screened titles/abstracts and then full texts against pre-specified eligibility criteria within Covidence; conflicts were resolved by consensus or, when necessary, a third reviewer. Reasons for full-text exclusion were logged in Covidence and are reported in the PRISMA 2020 flow diagram. Furthermore, the assessment of inter-rater reliability yielded an overall Cohen's kappa coefficient of 0.92, reflecting an almost perfect level of agreement between the two independent reviewers across all domains.

Strategy of data synthesis Three meta-analyses focused on patients with schizophrenia, evaluating changes in weight, cholesterol, and glucose for both cariprazine 1.5 mg and 3 mg. Eggers' test and funnel plots were used to assess the presence of publication bias, while the homogeneity test was conducted to evaluate variability among the studies examined. The meta-analyses were performed using the difference between the mean values in the placebo group and the mean values in the cariprazine 1.5 mg/3 mg groups as the effect size. We did not evaluate other doses of cariprazine in the meta-analysis process due to the paucity of randomized controlled trials. In all the aforementioned analyses, an alpha significance level of 0.05 was used. IBM SPSS Statistics software version 29 was used for the statistical analysis.

Subgroup analysis The meta-analyses were performed using the difference between the mean values in the placebo group and the mean values in the cariprazine 1.5 mg/3 mg groups as the effect size. We did not evaluate other doses of cariprazine in the meta-analysis process due to the paucity of randomized controlled trials. In all the aforementioned analyses, an alpha significance level of 0.05 was used. IBM SPSS Statistics software version 29 was used for the statistical analysis.

Sensitivity analysis Initially, Egger's test and the funnel plot were utilized to assess the presence of publication bias. Egger's test indicated no evidence of publication bias consequently, the analysis proceeded to consider all four of the initial articles.

Language restriction English.

Country(ies) involved Italy.

Keywords cariprazine, antipsychotics, schizophrenia, metabolic alterations, weight gain, metabolic syndrome, diabetes.

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