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Effect of Cariprazine on Metabolic Parameters in Patients with Affective Disorders: 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 13 October 2025 and was last updated on 13 October 2025.

INTRODUCTION

Review question / Objective We performed a systematic review and metanalysis to evaluate the role of cariprazine on glucose and lipid homeostasis as well as weight in persons living with BDbipolar disorder and MDDdepression by including more recently published studies with this agent at a range of variable dosages.

Condition being studied Mood disorders—including major depressive disorder and bipolar disorder—are common, recurrent conditions characterised by disturbances in mood, energy, sleep, cognition, and functioning. They are major contributors to disability and premature mortality worldwide, partly due to elevated suicide risk and cardiometabolic comorbidity. Course is often episodic with residual symptoms between episodes; early onset, comorbid anxiety/substance use, and psychosocial stressors worsen prognosis. Optimal care is multimodal: evidence-based pharmacotherapy (e.g., antidepressants, mood stabilisers, selected antipsychotics), structured psychotherapies, lifestyle interventions, and proactive monitoring of physical health. Person-centred, measurement-based, and collaborative approaches improve outcomes and support recovery.

METHODS

Search strategy To be inclusive, 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 “Depress*” OR “Bipolar Disorder” OR “Affective disorders*” OR “Side effects” OR “metabolic effects”. Filters were used to limit the results to the

English language. The search identified 650 papers. See Flow Chart for details of the study selection process.

Participant or population People living with schizophrenia experience a heterogeneous illness course marked by positive symptoms (hallucinations, delusions), negative symptoms (amotivation, anhedonia, social withdrawal), and cognitive impairment that can substantially affect education, employment, and relationships. Comorbidities are common—including depression, substance use, and cardiometabolic risk—and contribute to excess morbidity and premature mortality. Stigma and social disadvantage often limit access to timely diagnosis and high-quality care. Optimal management is multidisciplinary: evidence-based antipsychotic therapy, psychoeducation, cognitive-behavioural and family-based interventions, supported employment/education, and proactive physical-health monitoring. Recovery is possible; person-centred, trauma-informed care that emphasises autonomy, social inclusion, and shared decision-making improves outcomes and quality of life.

Intervention We evaluated metabolic collateral effect of Cariprazina 1,5 mg and 3 mg in patients affected by affective disorders.

Comparator The comparator of RCT inclused in the revision is 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 major depression and bipolar disorder. 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 of major depressive disorder or bipolar disorder 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 required to be a quantitative research paper with a case-control, cohort, or cross-sectional design. 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 To be inclusive, 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 "Depress*" OR "Bipolar Disorder" OR "Affective disorders*" OR "Side effects" OR "metabolic effects". Filters were used to limit the results to the English language. The search identified 650 papers. See Flow Chart for details of the study selection process.

Main outcome(s) This review included original articles that explicitly discussed the presence of metabolic effects of the use of cariprazine in major depression and bipolar disorder. 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 of major depressive disorder or bipolar disorder 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 required to be a quantitative research paper with a case-control, cohort, or cross-sectional design. 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.

Quality assessment / Risk of bias analysis 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. Only the 1.5 mg and 3 mg doses of cariprazine were included in the meta-analysis, as these were the only fixed-dose regimens consistently investigated across randomized controlled trials in both BD and MDD populations. Higher or flexible-dose regimens (e.g., 3–12 mg/day) were excluded, since they were reported predominantly in open-label or post hoc analyses, which were not suitable for quantitative synthesis. 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 (IB, AVM) 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 The PRISMA flowchart of the study selection process is presented in Figure 1. Electronic searches identified 650 publications. After excluding duplicates (n = 63), 587 abstracts and titles were screened for suitability. After non-RCT studies (n = 343), not in English (n=12) and non-pertinent studies (n = 195) were removed (n = 550), 37 full-text titles were assessed for eligibility, with 18 records excluded because they were not in line with the aims and inclusion criteria of our review (see Flow Chart for detailed reasons). Any disagreements regarding study eligibility were resolved following consensus discussions among the authors. Overall, 19 controlled studies were included in the present review. Of these, 11 studies were on BP and eight on MDD.

Subgroup analysis Six meta-analyses were performed for patients diagnosed with BD, assessing changes in body weight, total cholesterol levels, and fasting glucose levels for both cariprazine 1.5 mg and 3 mg. Another six meta-analyses were conducted for patients with major depression, considering the same metabolic outcomes and dosages. We did not evaluate other doses of cariprazine in the meta-analysis process due to the paucity of randomized controlled trials. 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. 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 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.

Country(ies) involved Italy.

Keywords cariprazine, antipsychotics, affective disorders, metabolic alterations, weight gain, metabolic syndrome, diabetes.

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