

Cardiometabolic Effects of Pharmacologic Treatments for Major Depressive Disorder: A Systematic Review and Network Meta-Analysis of Antidepressants and Antipsychotics

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Background

- Pharmacologic treatments for Major Depressive Disorder (MDD), including antidepressants and adjunctive antipsychotics, are associated with varying degrees of cardiometabolic risk^{1,2}
- Adverse effects such as weight gain, increased body mass index (BMI), and elevated blood pressure may compromise long-term health and reduce treatment adherence³
- Identifying the treatments most strongly linked to these outcomes is critical for informing clinical decisions and mitigating patient risk

Objective

- To identify and compare pharmacologic treatments associated with the most adverse cardiometabolic outcomes in adults with MDD through a systematic review and network meta-analysis (NMA) of randomized controlled trials (RCTs) and real-world evidence (RWE) studies

Methods

- Systematic review adhering to Cochrane Handbook⁴ and PRISMA⁵ guidelines; registered with PROSPERO
- RCTs and RWE studies that reported outcomes related to weight, BMI, blood pressure, etc. (Fig. 2) among adults (≥ 18 years) diagnosed with MDD and prescribed an antidepressant or antipsychotic medication were included
 - no restrictions were made for diagnostic tools for MDD
 - antidepressants included NDRIs, SNRIs, SSRIs, TCAs, TeCAs, serotonin modulators; antipsychotics included FGAs and SGAs
- Random-effects NMA was performed in R; mean differences with 95% confidence intervals were reported, treatment rankings were based on P-score and surface under the cumulative ranking curve (SUCRA)

FIGURE 1: Summary of the methods

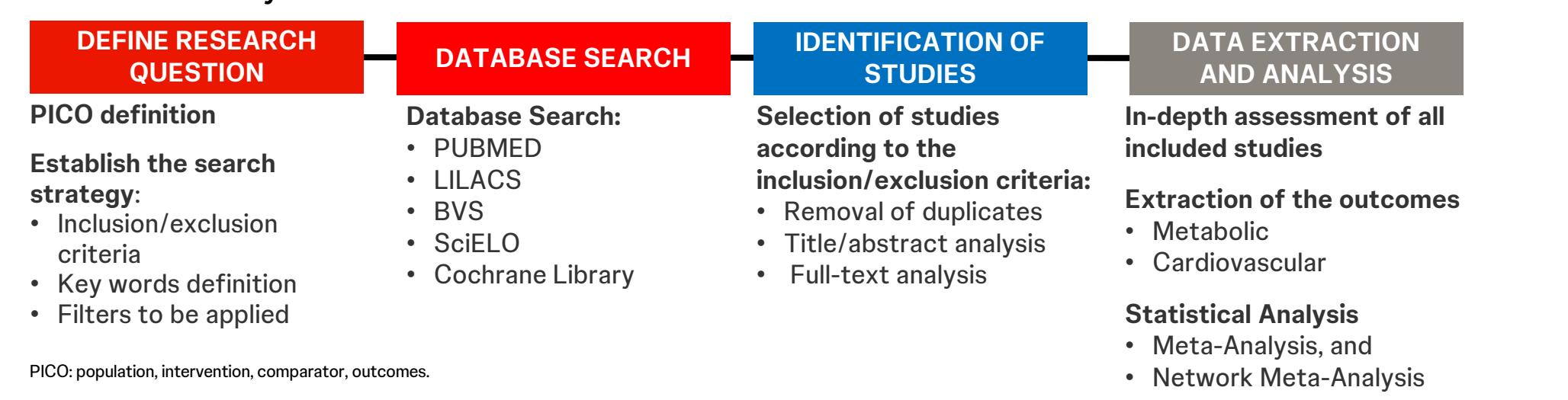


FIGURE 2: PICO acronym to express the research question

Component	Data to collect
PICO definition	Database Search: • PUBMED • LILACS • BVS • SciELO • Cochrane Library
Establish the search strategy:	Selection of studies according to the inclusion/exclusion criteria: • Removal of duplicates • Title/abstract analysis • Full-text analysis
• Inclusion/exclusion criteria	In-depth assessment of all included studies
• Key words definition	Extraction of the outcomes • Metabolic • Cardiovascular
• Filters to be applied	Statistical Analysis • Meta-Analysis, and • Network Meta-Analysis
PICO: population, intervention, comparator, outcomes.	

Cardiometabolic outcomes:

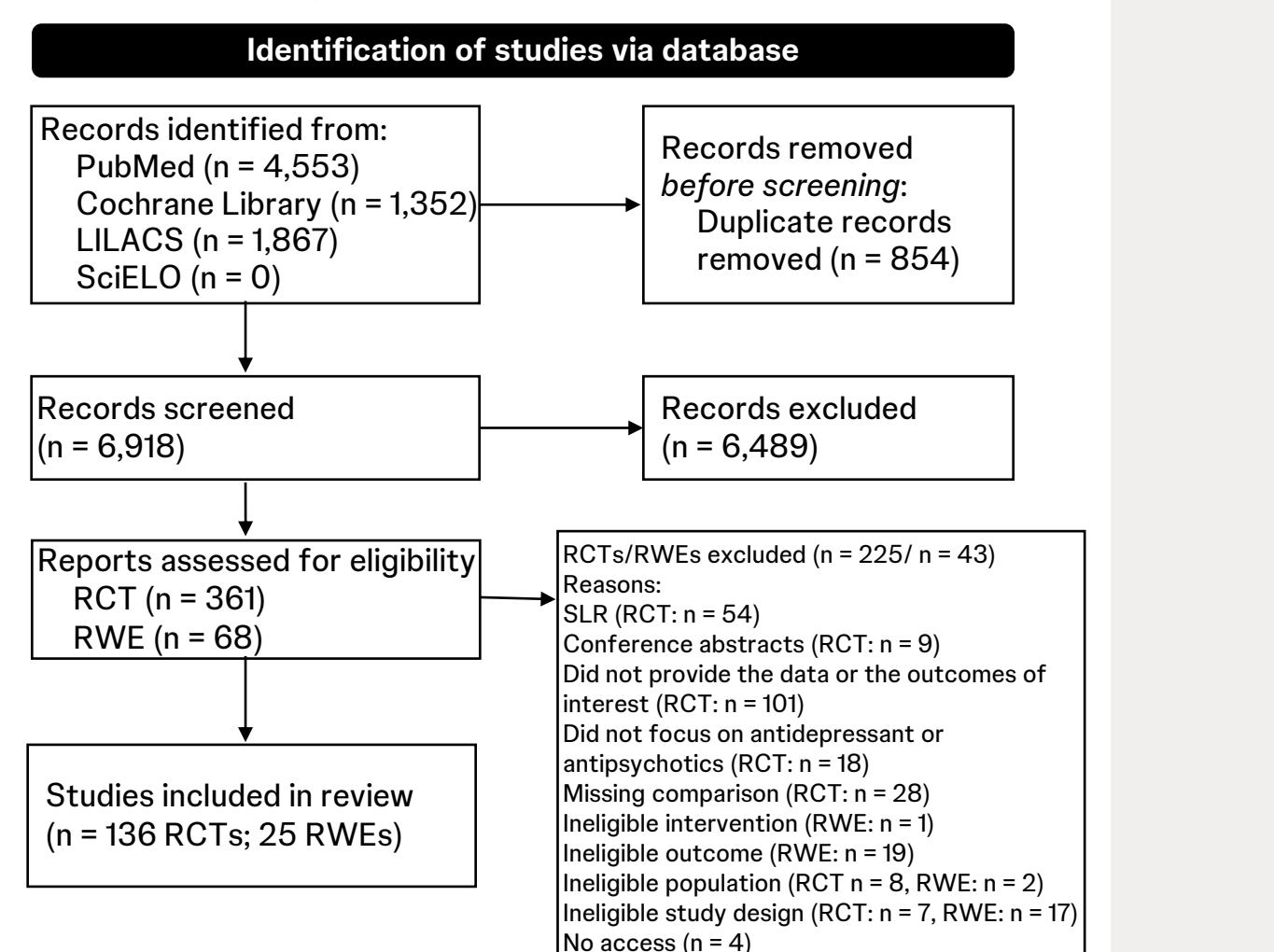
- Primary outcomes:** BMI changes (continuous variable – mean, SD), weight changes (continuous variable – mean, SD), % of weight increase or decrease (dichotomous variable – number of events), Glycemic changes (blood glucose levels, Hemoglobin A1C, insulin levels; continuous variable – mean, SD)
- Secondary outcomes:** Blood pressure changes (continuous variable – mean, SD), Lipid profile changes (alterations in cholesterol, triglycerides, and HDL cholesterol, and LDL cholesterol levels; continuous variable – mean, SD), Development of diabetes (dichotomous variable – number of events), Development of obesity (dichotomous variable – number of events), Waist circumference changes (continuous variable – mean, SD), HCRU and/or costs due to the cardiometabolic events, Follow-up measures: discontinuation, switching, monotherapy to adjunctive (combined therapies), augmentation doses (related to the cardiometabolic outcomes)

Results

OVERVIEW

- The systematic review yielded 6,918 studies after duplicates were removed (854 duplicates).
- We assessed the full text of 361 RCTs and 68 RWE studies to determine their relevance.
- We then extracted data from studies that reported outcomes aligned with our review objectives. This focused approach ensured that only studies addressing the cardiometabolic outcomes of interest were included in the final synthesis.
- Ultimately, 136 RCTs and 25 RWEs met all criteria and were included in the qualitative synthesis

Flowchart of the screening of the studies



RWE FINDINGS

Antipsychotics

- Weight gain:** Significant weight gain is observed with antipsychotic treatment – olanzapine, quetiapine, and aripiprazole – both in monotherapy and augmentation settings.
- Hyperlipidemia:** FGAs are associated with an increased risk of new-onset hyperlipidemia.
- Type 2 diabetes mellitus:** SGAs show no statistically significant association with type 2 diabetes risk overall.

Antidepressants

- Increased risk of adverse cardiometabolic outcomes; these risks are dose- and duration-dependent and may occur independently of depressive symptoms. The exposure was analyzed in broad pharmacological categories, limiting the ability to detect drug-specific effects.

References:

- Simon GE et al. *JAMA*. 2024;332(2):141-152. 2. Gafoor R et al. *BMJ*. 2018;361:k1951. 3. McIntyre RS et al. *Am J Psychiatry*. 2024;181(1):26-38. 4. Higgins JPT et al. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3. Cochrane; 2022. 5. Page MJ et al. *BMJ*. 2021;372:n160.

Key takeaway

In MDD, certain antipsychotics and antidepressants—particularly aripiprazole, brexpiprazole, amitriptyline, mirtazapine, and nortriptyline—are associated with higher risks of weight gain and metabolic side effects, while options like fluoxetine, sertraline, and venlafaxine, generally offer more favorable profiles for weight and cardiovascular health.

Conclusions

This study consistently found increased cardiometabolic risk associated with several antidepressants and antipsychotics included in this review, highlighting the need for MDD treatments that are both efficacious and that cause little-to-no cardiometabolic risk

While the cardiometabolic effects of antidepressants are well-documented and supported by a robust body of evidence, the data for antipsychotics remain limited and heterogeneous

- Current clinical trial data are insufficient to establish consistent or reliable rankings of antipsychotic-related cardiometabolic risk
- As a result, clinical decisions regarding antipsychotic use are often informed by expert consensus and clinical experience rather than high-quality comparative data
- These results emphasize the need for research utilizing other data sources (e.g., electronic medical records, claims) to better evaluate the risk of cardiometabolic events associated with all approved treatments for MDD

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Disclosures

N. Dwibedi and Z. Zhang are employees of Johnson & Johnson and own stock in Johnson & Johnson. R. Bartelli Grigolon and M. J. Cambron-Mellott are employees of Oracle Life Sciences, Oracle Corporation, which received funding from Johnson & Johnson to conduct and report on the study. M. J. Cambron-Mellott also holds stock in Oracle Corporation.

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