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 adherence[3]
- Identifying the treatments most strongly linked to these outcomes is critical for informing clinical decisions and mitigating patient risk

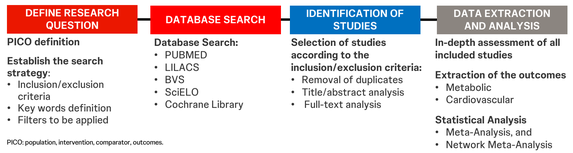
Objective

- 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 Handbook[4] and PRISMA[5] 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



PICO: population, intervention, comparator, outcomes.

FIGURE 2: PICO acronym to express the research question

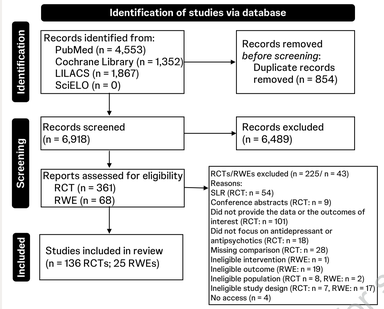
Component	Data to collect
Population	Patients with MDD
Intervention	Antidepressant and antipsychotic treatments
Comparator	N/A
Outcomes	Cardiometabolic outcomes: • *Primary outcomes:* BMI changes(continuous variable – mean, SD), weight changes (continuous variable – mean, SD), % of weight increase or 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, triacylglycerols, 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.

RCT FINDINGS - ANTIPSYCHOTICS

Weight gain

- Aripiprazole, brexpiprazole, and quetiapine XR—commonly used atypical antipsychotics—were consistently among the least favorable treatments regarding weight gain risk in patients with major depressive disorder.
- Aripiprazole showed the highest risk for weight gain, with brexpiprazole and quetiapine XR also significantly increasing weight compared to placebo and most other treatments, making them less suitable for patients concerned about weight neutrality.

Ranking based on P-score and SUCRA methods

Treatment	P-score	SUCRA
Placebo	0.9117	0.9057
Cariprazine	0.8930	0.8838
Quetiapine XR	0.7010	0.6968
Brexpiprazole [1–3 mg]	0.6017	0.6093
Brexpiprazole [1 mg]	0.4973	0.4964
Brexpiprazole [2 mg]	0.4611	0.4680
Aripiprazole [3 mg]	0.3071	0.3072
Bupropion + Aripiprazole	0.2654	0.2396
Aripiprazole [3–15 mg]	0.1948	0.2222
Aripiprazole	0.1671	0.1710

Note. Unless otherwise noted, studies did not report dose-dependent treatment effects.

Weight Change

- Aripiprazole, brexpiprazole [2 mg], and cariprazine are all linked to significant weight gain when compared to placebo.
- Quetiapine XR was associated with more weight gain than placebo, brexpiprazole [2 mg] had an even greater effect—causing significantly more weight gain than both placebo and quetiapine XR.
- Brexpiprazole [2 mg] stands out as having the least favorable profile in terms of weight change in this comparison.

League table comparing the weight change between treatments: mean differences

Note. Unless otherwise noted, studies did not report dose-dependent treatment effects.

Abbreviations: AE, adverse event; BMI, body mass index; FGAs, first-generation antipsychotics; NDRIs, norepinephrine-dopamine reuptake inhibitors; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomized control trial; RWE, real-world evidence; SGAs, second-generation antipsychotics; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; TeCAs, tetracyclic antidepressants

RCT FINDINGS - ANTIDEPRESSANTS

- **BMI increase, mean:** Paroxetine was the most effective antidepressant for minimizing increases in BMI, while amitriptyline was most likely to raise BMI.
- **Risk of weight gain:** Sertraline, fluoxetine, and venlafaxine had the lowest risk of weight gain, whereas mirtazapine, amitriptyline, and nortriptyline posed the highest risk.
- **Risk of weight loss:** No antidepressant consistently promoted weight loss.
- **Blood pressure**
  - **Systolic:** Paroxetine and placebo caused minimal changes in systolic blood pressure, while higher doses of duloxetine, especially 120 mg, increased the risk of elevated systolic blood pressure.
  - **Diastolic:** Paroxetine had the most favorable effect, with minimal impact on diastolic blood pressure, whereas duloxetine 120 mg was associated with the greatest increase.
- **Risk of cardiometabolic event (AE related to weight, weight, blood pressure, dyslipidemia, diabetes, and similar outcomes):** Fluoxetine showed the best safety profile for cardiometabolic events, while imipramine had the least favorable profile.
- **Absolute weight change, mean:** Paroxetine IR, desvenlafaxine (50 mg), fluoxetine, and citalopram were most weight-neutral, while amitriptyline, mirtazapine, and imipramine were linked to greater weight gain.

Summary findings regarding the effect of antidepressants on cardiometabolic outcomes

Outcome	Most favorable*	Unfavorable†
BMI increase, mean	Paroxetine	Amitriptyline
Risk of weight gain	Sertraline, fluoxetine, and venlafaxine	Desvenlafaxine [50mg]
Risk of weight loss	Nortriptyline and amitriptyline	Venlafaxine and fluoxetine
Systolic blood pressure increase	Paroxetine	Duloxetine [120mg]
Diastolic blood pressure increase	Paroxetine	Duloxetine [120mg]
Risk of cardiometabolic event	Fluoxetine	Imipramine
Absolute weight increase, mean	Paroxetine IR	Mirtazapine and amitriptyline

*Most favorable = least likely to cause the outcome
†Unfavorable = more likely to cause the outcome

Note. Unless otherwise noted, studies did not report dose-dependent treatment effects.

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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