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Metabolic effects of long-term Aripiprazole use in patients with schizophrenia and first-episode psychosis: A systematic review

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Metabolic effects of long-term aripiprazole use in patients with schizophrenia and first-episode psychosis: A systematic review

Running title: Long-Term Metabolic Effects of aripiprazole

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Abstract

Objective: Schizophrenia and first-episode psychosis often require long-term antipsychotic treatment, making metabolic adverse effects an important clinical concern. This study evaluated the long-term metabolic effects of aripiprazole compared with other antipsychotics.

Methods: This systematic review analyzed randomized controlled trials with at least one year of follow-up and was conducted in accordance with the Cochrane

Handbook for Systematic Reviews of Interventions and the PRISMA guidelines. The protocol was prospectively registered in PROSPERO (CRD4202563245). Two authors independently conducted a systematic search in MEDLINE/PubMed, Embase, and Cochrane databases from inception to December 2024. Adult patients with schizophrenia spectrum disorders or first-episode psychosis were included. Primary outcomes were weight, body mass index, and cholesterol. Two authors independently assessed the risk of bias in the included randomized clinical trials using the Cochrane Risk of Bias 2 tool, with any discrepancies resolved by a third reviewer.

Results: Long-term aripiprazole treatment was associated with comparable metabolic changes, including increases in body weight, BMI, and lipid parameters. However, head-to-head comparisons did not demonstrate a consistent pattern of greater metabolic worsening with aripiprazole relative to other antipsychotics. Some studies reported no statistically significant between-group differences in weight, BMI, or cholesterol, while others described numerically lower frequencies of selected metabolic adverse events with aripiprazole. Nevertheless, statistical testing and reporting of confidence intervals were inconsistent across studies, limiting firm comparative conclusions

Conclusions: These findings suggest that aripiprazole may have a comparably favorable metabolic profile for selected outcomes during chronic treatment; however, increases in weight, BMI, and lipid parameters were observed in some studies. Further long-term studies with standardized metabolic outcome reporting are warranted to clarify its comparative effects across broader clinical populations.

Keywords: Aripiprazole; schizophrenia; psychotic disorders; weight gain

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1. Introduction

Schizophrenia is a long-term mental illness that severely impacts patients as it presents through positive symptoms such as delusions and hallucinations, and negative symptoms, such as social withdrawal and apathy, as well as cognitive impairments[1]. A first psychotic episode is a critical moment at which immediate treatment of newly appearing symptoms prevents functional decline and enhances

long-term outcomes[2]. Studies in the neurobiology of psychosis have demonstrated that dysfunctions in dopaminergic and glutamatergic systems are key elements in disease pathophysiology and possible mechanisms involved in treatment response[3].

Current psychiatric treatments to manage psychotic disorders involve mainly second-generation antipsychotics. Long-term use of these medications frequently leads to negative metabolic outcomes, including weight gain, dyslipidemia, and insulin resistance, all of which contribute to greater cardiovascular risk and may negatively impact treatment adherence[4]. Although some antipsychotics such as Olanzapine and Quetiapine have a strong association with metabolic side effects, short-term studies have shown aripiprazole as having a potentially lower risk for metabolic and cardiovascular adverse outcomes[5,6].

For patients diagnosed with schizophrenia or other psychotic disorders that demand treatment for longer periods, long-term medication use may lead to increasing metabolic risks, which in turn can impact treatment. Although aripiprazole appears to have a better metabolic profile, evidence regarding its long-term effects remains limited. The majority of primary studies focus on short-term follow-ups or do not conduct longitudinal assessments, which creates barriers to estimating the metabolic risks from long-term use of aripiprazole, as well as from other second-generation antipsychotics[7].

This study aims to clarify whether aripiprazole maintains its benign metabolic profile in long-term use. Conducting a systematic review will provide additional evidence that may help clinicians optimize therapeutic strategies when choosing antipsychotic medications, especially for long-term treatment.

2. Methods

2.1. Study design and protocol

We performed a systematic review following the Cochrane Handbook for Systematic Reviews of Interventions and structured it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations[8]. The study protocol was prospectively registered (PROSPERO ID: CRD4202563245). No ethics committee approval was required.

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2.2. Search strategy and study selection

Two authors independently conducted a systematic search in MEDLINE/PubMed, Embase, and Cochrane databases from inception to December 2024. The search strategy was the following: (aripiprazole OR Abilify) AND (Acepromazine OR Acetophenazine OR Benperidol OR Bromperidol OR Butaperazine OR Carpipramine OR Chlorproethazine OR Chlorpromazine OR Chlorprothixene OR Clopentixol OR Cyamemazine OR Cyamepromazine OR Dixyrazine OR Droperidol OR Fluanisone OR Flupenthixol OR Fluphenazine OR Fluspirilen OR Haloperidol OR Levomepromazine OR Mepazine OR Mesoridazine OR Methotrimeprazine OR Molindone OR Moperone OR Oxypertine OR Penfluridol OR Perazine OR Periciazine OR Perphenazine OR Pimozide OR Pipamperone OR Pipotiazine OR Prochlorperazine OR Promazine OR Promethazine OR Prothipendyl OR Thiopropazate OR Thioproperazine OR Thioridazine OR Thiothixene OR Trifluoperazine OR Trifluperidol OR Triflupromazine OR Zuclopenthixol OR Amisulpride OR Asenapine OR Blonanserin OR Clozapine OR Iloperidone OR Levosulpiride OR Loxapine OR Lurasidone OR Melperone OR Mosapramine OR Olanzapine OR Paliperidone OR Perospirone OR Quetiapine OR Seroquel OR Risperidone OR Risperda OR Sertindole OR Sulpiride OR Tiapride OR Zotepine OR Ziprasidone OR placebo) AND (Schizophrenia OR "Schizophrenic Disorders" OR Schizophrenic OR "Schizophrenic Disorder" OR "Psychotic Disorders" OR “first-episode psychosis” OR FEP) AND ("randomized controlled trials" OR "randomized controlled trial[pt]" OR "clinical trial" OR "controlled clinical trial [pt]" OR randomized[tiab] OR placebo[tiab] OR "drug therapy" [sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("systematic reviews" OR "meta-analysis" OR review OR cohort OR "case study" OR "retrospective cohort" OR protocol OR "prospective cohort" OR guidelines OR "retrospective study" OR "observational study" OR protocol).

The identified records were imported into Zotero software (Corporation for Digital Scholarship, George Mason University). After removing duplicates, titles, and abstracts were screened based on predefined eligibility criteria. Subsequently, the full texts of the remaining articles were assessed for inclusion. Additional studies were identified by reviewing the reference lists of included articles, prior meta-analyses, and relevant reviews. Any disagreements were resolved by a third author (PD).

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2.3. Eligibility criteria

The inclusion criteria specified in advance were randomized clinical trials (RCTs) involving patients diagnosed with schizophrenia or first-episode psychosis based on the Diagnostic and Statistical Manual of Mental Disorders DSM (IV, IV-Text Revision, 5, or 5- Text Revision) or the International Classification of Diseases ICD (Tenth or Eleventh Revision) with at least one year of follow-up. We excluded persecutory delusional disorder and schizoaffective disorder because this review aimed to assess the long-term metabolic effects of aripiprazole through randomized controlled trials with at least one year of follow-up. For both conditions, there is a scarcity of long-term RCTs evaluating metabolic outcomes, particularly compared with the more consistent evidence available for schizophrenia and first-episode psychosis. In addition, studies on schizoaffective disorder frequently involve concomitant treatments, such as mood stabilizers and antidepressants, which may confound metabolic findings. Therefore, inclusion was restricted to improve methodological consistency and comparability across studies. As long-term placebo-controlled RCTs in patients with schizophrenia or first-episode psychosis are restricted by ethical considerations, all eligible studies compared aripiprazole with other active medications. Therefore, all included studies compare aripiprazole with comparator antipsychotics. There were no restrictions regarding publication date, geographic location, or language. Studies were excluded if they were observational, lacked relevant outcome data, did not have a follow-up of at least 1 year, or were non-RCTs. The quality of the included studies was evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool[8].

2.4. Outcomes

The primary outcome was total weight gain. Secondary outcomes included: (i) a change in Body Mass Index (BMI) and (ii) an increase in cholesterol levels among the participants. Two reviewers (GV and MB) independently extracted data using Excel spreadsheets, with a third reviewer (PD) verifying the accuracy of the extracted data. The extracted data encompassed study characteristics (population, publication year, number of participants, trial duration, geographical location, and time of follow-up), patient demographics (mean age, gender distribution, mean weight, race), intervention characteristics (medication name and dosage), control group characteristics (medication name and dosage), and outcomes (weight gain,

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cholesterol level, and BMI). Whenever available, absolute and relative changes in weight, BMI, cholesterol, and other metabolic parameters, as well as risk ratios (RR), odds ratios (OR), hazard ratios (HR), 95% confidence intervals (95% CI), and p values, were extracted from the included studies.

2.5. Risk of Bias Assessment

Two authors independently assessed the risk of bias in the included randomized clinical trials using the Cochrane Risk of Bias 2 (RoB 2) tool, with any discrepancies resolved by a third reviewer. Publication bias assessment via funnel plot was not performed due to an insufficient number of studies. Instead, we applied the case-by-case method.

3.0. Results

The initial search found 5.749 documents on December 4th, 2024. After removing duplicate results and applying the eligibility criteria, 74 records were selected for full-text review (Figure 1). Six studies [10,11,12,13,14,15] were included in this systematic review, comprising 2.666 patients, of whom 1.440 (54%) were randomized to receive aripiprazole and 1.585 (59.4%) were male. The mean age of patients ranged from 25.2 to 46.5 years. aripiprazole was compared to paliperidone, ziprasidone, haloperidol, blonanserin, risperidone, quetiapine and ziprasidone. Individual study characteristics are displayed in
Table 1.

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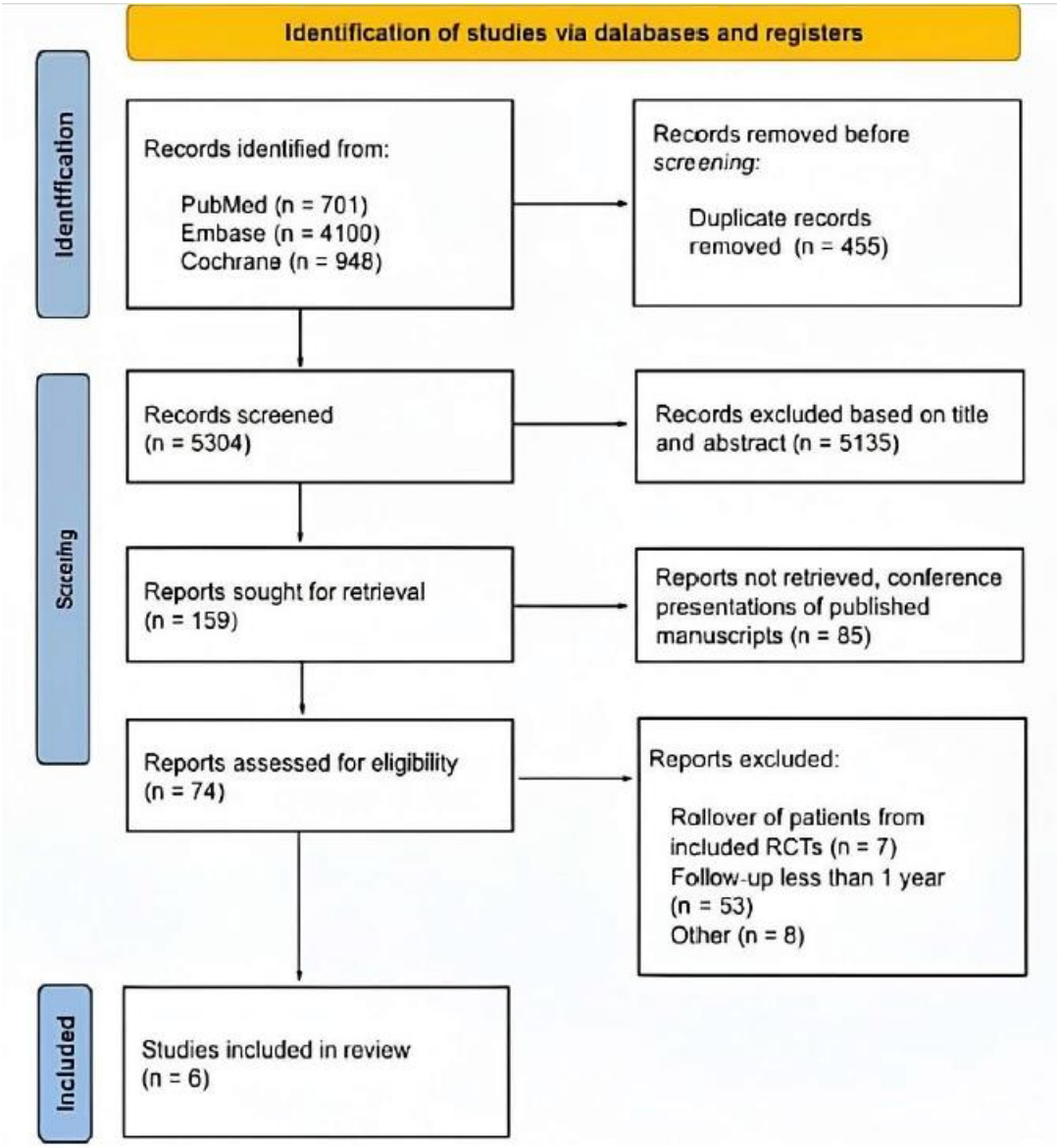


Figure 1. **PRISMA flow diagram illustrating the study screening process**. The flow diagram includes the identification, screening, eligibility, and inclusion of studies for the systematic review. RCT = Randomized controlled trial

Table 1. Baseline characteristics of clinical trials comparing aripiprazole with other antipsychotics

Study	Country	Patients	Male gender (%)	Mean age (sd), years	Mean weight (sd), kg	Intervention group	Control group	Follow-up, years	Population
Kasper 2003	U.S.A and worldwide	1294	758 (59)	37.1 (10.79)	74 (0.5)	Aripiprazole	Haloperidol	1	SCZ

Zhang 2012	China	254	124 (48.8)	26.4 (7.5)	N/A	Aripiprazole	Paliperidone and Ziprasidone	1	FEP
Kane 2020	U.S.A	489	368 (75.3)	25.2 (4.2)	N/A	Aripiprazole once-monthly	FDA-approved antipsychotics	2	SCZ
Vázquez-Bourgon 2022	Spain	180	98 (54.44)	32.26 (10,42)	64.46 (14.91)	Aripiprazole	Risperidone	1	FEP
Ishigooka 2024	Japan	251	133 (53)	46.5 (13.3)	67.7 (14.9)	Aripiprazole	Blonanserin and Paliperidone	2	SCZ
Vázquez-Bourgon 2018	Spain	198	104 (52.5)	32.1 (10.4)	65.8 (15.6)	Aripiprazole	Quetiapine and Ziprasidone	1	FEP

SCZ = schizophrenia.

3.1. Main outcomes

The studies included in this systematic review evaluated the long-term metabolic effects of aripiprazole compared to other antipsychotic agents, primarily second-generation antipsychotics, in patients with schizophrenia and first-episode psychosis[11,12,13,14,15,16]. Evidence derived from randomized controlled trials, pragmatic clinical trials, and naturalistic studies consistently indicates that antipsychotic treatment is associated with a progressive worsening of metabolic parameters over time, irrespective of the specific agent used[11,12,16]. These findings suggest that metabolic burden is largely related to sustained antipsychotic exposure rather than to substantial pharmacological differences between individual antipsychotics.

In the 52-week randomized study by Zhang et al. (2012), no significant between-group differences were observed in weight or BMI. Mean weight was 54.3 kg (SD = 7.2) in the aripiprazole group, 53.4 kg (SD = 6.3) in the paliperidone group, and 54.7 kg (SD = 6.8) in the ziprasidone group, with no significant difference among groups (F = 0.38; p = 0.645). Similarly, mean BMI values were 22.4 kg/m² (SD = 3.7), 21.5 kg/m² (SD = 3.2), and 21.9 kg/m² (SD = 3.4), respectively, also without significant between-group variation (F = 0.97; p = 0.322).

In the study by Vázquez-Bourgon et al. (2022), which compared aripiprazole and risperidone in patients with first-episode psychosis, both groups showed significant increases in weight and BMI after one year of treatment, but no significant differences were observed between treatments. Mean body weight reached 74.38 kg

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(SD = 14.83) in the aripiprazole group, corresponding to a 9.208 kg increase, and 74.07 kg (SD = 18.00) in the risperidone group, corresponding to a 10.502 kg increase, with no significant between-group difference (p = 0.824). BMI also increased significantly within both groups, reaching 25.60 kg/m² (SD = 4.02) with aripiprazole and 26.18 kg/m² (SD = 5.22) with risperidone, corresponding to increases of 3.2 kg/m² and 3.7 kg/m², respectively, without significant between-group differences (p = 0.576).

Similarly, in the trial by Vázquez-Bourgon et al. (2018), one year of treatment was associated with weight and metabolic increases across antipsychotic groups, but without statistically significant differences between them. Adjusted mean weight gain was 8.3 ± 1.0 kg with aripiprazole, 6.1 ± 1.1 kg with quetiapine, and 6.0 ± 1.2 kg with ziprasidone (F = 1.499; df = 144/2; p = 0.227). BMI increased by 2.9 ± 0.3 kg/m², 2.2 ± 0.4 kg/m², and 2.0 ± 0.4 kg/m², respectively, also without significant between-group variation (F = 1.705; df = 144/2; p = 0.185). Total cholesterol increased by 17.1 ± 4.4 mg/dL in the aripiprazole group, 20.0 ± 5.2 mg/dL in the quetiapine group, and 8.9 ± 4.9 mg/dL in the ziprasidone group, again with no significant differences among treatments (F = 1.301; df = 143/2; p = 0.275). In the overall sample, mean body weight increased by 7.0 kg, from 66.1 ± 13.4 kg at baseline to 73.1 ± 15.3 kg after one year (t = −10.85; p < 0.001), while BMI increased from 23.3 ± 3.7 kg/m² to 25.8 ± 4.1 kg/m² (t = −11.38; p < 0.001). Total cholesterol also rose significantly, from 175.1 ± 35.8 mg/dL to 190.6 ± 42.0 mg/dL (t = −5.37; p < 0.001). Kasper et al. (2003) also found no significant difference in weight change between aripiprazole and haloperidol, with mean increases of 1.05 kg (SE = 0.20) and 0.39 kg (SE = 0.28), respectively. Head-to-head comparisons between aripiprazole and other antipsychotics such as risperidone, quetiapine, ziprasidone, paliperidone, and haloperidol generally did not demonstrate clinically meaningful differences in long-term weight outcomes[11,13,16].

Although some studies suggested a more favorable metabolic profile for aripiprazole during early treatment phases, these differences were not consistently maintained at longer follow-up intervals. Kane et al. (2020) reported fewer metabolic adverse events with long-acting injectable aripiprazole once monthly (AOM) than with clinician's choice treatment, including lower rates of weight gain (14.4% vs. 19.5%; RR = 0.74) and elevated cholesterol (6.8% vs. 10.0%; RR = 0.68), although confidence intervals and p values were not provided for these outcomes. Consistent

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with these findings, Ishigooka et al. (2024) observed a low incidence of metabolic adverse events during long-term aripiprazole treatment, with only 2 of 82 patients (2.4%) reporting weight gain.

A similar pattern was observed for lipid parameters. Increases in cholesterol and triglyceride levels were commonly reported across treatment groups, including those receiving aripiprazole, with no consistent evidence of long-term metabolic superiority compared with other second-generation antipsychotics[13,16]. In the study by Vázquez-Bourgon et al. (2022), total cholesterol increased significantly after treatment in both groups, with no significant difference between aripiprazole and risperidone ($p = 0.658$). In the aripiprazole group, mean total cholesterol was 190.81 mg/dL (SD = 46.16), corresponding to an increase of 23.376 mg/dL ($t = 5.253$; $p < 0.001$). Similarly, the risperidone group showed a mean total cholesterol level of 190.23 mg/dL (SD = 36.86), with an increase of 17.545 mg/dL ($t = 5.200$; $p < 0.001$). Overall, long-term and naturalistic studies indicate that aripiprazole presents a metabolic profile broadly comparable to that of other second-generation antipsychotics when evaluated beyond the acute treatment phase[11,12]. While minor differences may be detected in specific metabolic parameters, these distinctions tend to diminish with prolonged exposure.

3.2. Quality assessment and publication bias

Two authors independently evaluated the risk of bias using the Cochrane risk-of-bias tool for randomized trials (RoB-2) tool. Any discrepancies were resolved through review and consensus with a third author. The overall risk of bias was moderate, with some concerns mostly related to missing outcome data and deviations from intended interventions. A summary of bias distribution in each study is presented in Table 2.

Table 2. Risk of Bias Assessment Using RoB2 Tool

Study	Bias from randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcomes	Bias in selection of the reported result	Overall risk of bias
Zhang 2012	Low	Some concerns	Low	Some concerns	Low	Some concerns

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Ishigooka 2024	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Kane 2020	Low	Low	Some concerns	Low	Low	Some concerns
Vázquez-Bourgon 2022	Low	Low	Low	Low	Low	Low
Kasper 2003	Low	Low	Low	Low	Low	Low
Vázquez-Bourgon 2018	Low	Some concerns	Low	Some concerns	Low	Some concerns

Risk of Bias Assessment Using RoB2 Tool showed an overall moderate risk of bias, with some concerns mostly related to missing outcome data and deviations from intended interventions. The assessment covered domains such as randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain is categorized as low risk, some concerns, or high risk of bias.

To assess publication bias, we employed the case-by-case method. Zhang et al. (2012)[15] presented some concerns regarding bias due to deviations from intended interventions and selection of reported results, indicating a moderate risk of publication bias. Ishigooka et al. (2024)[12] also raised concerns about deviations from intended interventions, missing outcome data, and selection of reported results, suggesting potential selective reporting. The study by Kane et al. (2020) [10] exhibited certain concerns about missing outcome data while maintaining a low risk of bias in other domains, indicating a relatively low risk of publication bias. Vázquez-Bourgon et al. (2022) [13] demonstrated low risk of bias across all domains, minimizing concerns about selective reporting. In contrast, Vázquez-Bourgon et al. (2018) [16] were rated as having some concerns, mainly due to the lack of blinding and medication changes that could have influenced adherence; nonetheless, they maintained methodological rigor, with transparent reporting and robust analysis. Finally, Kasper et al. (2003)[11] was assessed as having a low risk of bias across all evaluated domains, including the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. The study demonstrated consistent methodological quality and transparent reporting, with no major concerns regarding selective reporting or other sources of publication bias.

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4.0. Discussion

This review synthesized data from six RCTs aimed to evaluate the long-term metabolic effects of aripiprazole in patients diagnosed with schizophrenia or FEP. Across these trials, the analysis specifically focused on clinically relevant metabolic parameters, including total weight gain, BMI, and cholesterol levels. Long-term studies evaluating aripiprazole reported heterogeneous metabolic findings across body weight, BMI, lipid parameters, and adverse events. Some studies[11,13,14,15] reported no statistically significant differences in metabolic outcomes between the groups. However, other studies showed that aripiprazole was associated with metabolic worsening during prolonged treatment, such as increases in weight and BMI[13, 15]

Previous research has consistently highlighted that antipsychotic medications can induce metabolic complications, including significant weight gain, dyslipidemia, and insulin resistance, all of which contribute to elevated cardiovascular risk prediction factors and may negatively influence treatment adherence[4,16,17,18]. Within this context, aripiprazole has been recognized for its relatively favorable metabolic profile, showing minimal impact on weight and lipid parameters in both short- and long-term studies[5,6,19,20,21]. Nonetheless, some longitudinal studies have reported that, despite its comparatively benign metabolic effects, patients treated with aripiprazole may still experience modest but clinically relevant weight gain over longer periods of treatment[14,15,22], underscoring the importance of continued monitoring in clinical practice.

Several limitations should be considered when interpreting the results of this review. First, substantial heterogeneity was observed across the included studies, which may reflect differences in the comparator drugs, as each antipsychotic possesses its own unique metabolic risk profile. Second, the study populations included both patients with FEP and those with chronic schizophrenia, which differ in terms of baseline metabolic risk, prior exposure to antipsychotics, and sensitivity to metabolic side effects. Third, variations in dosing regimens and follow-up durations, ranging from just over one year to longer-term periods, may have influenced the observed outcomes. Finally, ethical considerations precluded the inclusion of placebo-controlled RCTs in this patient population, meaning that all included trials compared aripiprazole to other active antipsychotics. Fourth, a meta-analysis could not be performed due to the high heterogeneity of the included data. This

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heterogeneity encompassed differences in study populations, comparator antipsychotics, follow-up durations, and outcome definitions, including variability in outcome reporting formats. Such methodological heterogeneity precluded the statistical pooling of results and the construction of forest plots, requiring a narrative synthesis of the findings instead.

Despite these limitations, this review has notable strengths. The inclusion of exclusively RCTs enhances the internal validity of the findings, minimizing biases commonly observed in observational studies. Moreover, this was the first review to systematically investigate the long-term metabolic effects of aripiprazole in schizophrenia and patients with FEP.

Long-term treatment with aripiprazole was associated with metabolic changes, including increases in weight, BMI, and lipid parameters in several studies. Therefore, aripiprazole should not be considered metabolically comparable during prolonged use. However, the available comparative evidence did not demonstrate a consistent or robust pattern of greater metabolic worsening with aripiprazole relative to other antipsychotics. This information is particularly valuable for clinicians seeking to balance therapeutic efficacy with the minimization of adverse metabolic effects.

Furthermore, the evidence highlights that while metabolic monitoring remains essential for all patients receiving antipsychotic therapy, aripiprazole may represent a favorable option for individuals who are especially vulnerable to metabolic complications, such as those with preexisting risk factors for obesity, dyslipidemia, or diabetes. Its comparatively mild impact on metabolic parameters, combined with established efficacy in symptom control, supports its role as a suitable and sustainable treatment choice in long-term management strategies. Collectively, these findings contribute to a more nuanced understanding of the metabolic safety profile of aripiprazole and underscore its clinical relevance in optimizing both psychiatric and physical health outcomes for patients with psychotic disorders.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data supporting the findings of this study are included in this published article or available from the corresponding author upon reasonable request.

Author Contributions (CRediT taxonomy):

Conceptualization: Gustavo and Andrea. **Data curation:** Gustavo and Milena. **Formal analysis:** Mateus, Mahmood, Vitória, Milena, and Gustavo. **Funding acquisition:** not applicable. **Investigation:** Gustavo and Milena. **Methodology:** Gustavo. **Project administration:** Gustavo. **Resources:** not applicable. **Software:** Gustavo. **Supervision:** Andrea. **Validation:** Paulo, Andrea, Anna, and Mateus. **Visualization:** Gustavo. **Writing – original draft:** Gustavo, Milena, and Izidione. **Writing – review and editing:** Paulo, Andrea, Anna, Mateus, and Milena. All authors have read and approved the final version submitted and take public responsibility for all aspects of the work.

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