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METABOLIC AND CARDIOVASCULAR RISKS OF SECOND-GENERATION ANTIPSYCHOTICS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF WEIGHT GAIN, DYSLIPIDEMIA, HYPERGLYCEMIA, AND QTC PROLONGATION IN ADULTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER COMPARING OLANZAPINE, RISPERIDONE, QUETIAPINE, AND ARIPIPRAZOLE

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Keywords

Second-generation antipsychotics, weight gain, dyslipidemia, hyperglycemia, QTc prolongation, schizophrenia, bipolar disorder, metabolic risk, cardiovascular risk, Olanzapine, Risperidone, Quetiapine, Aripiprazole.

Abstract

Background:

Antipsychotics, especially the second-generation of antipsychotic drugs (SGAs), are commonly used to treat schizophrenia and bipolar disorder. However, their use is linked to high metabolic and cardiovascular risks such as weight gain, dyslipidemia, hyperglycemia and QTc prolongation. These side effects can have a negative impact on the patient's health outcomes and adherence to treatment. This systematic review and meta-analysis aimed to assess and compare the metabolic and cardiovascular risks associated with four widely used SGAs: Olanzapine, Risperidone, Quetiapine and Aripiprazole.

Objectives:

This systematic review and meta-analysis aimed to assess and compare the effects of these four SGAs on weight gain, dyslipidemia, hyperglycemia, and QTc prolongation in patients with schizophrenia or bipolar disorder. The secondary

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goal was to determine the safety and tolerability of these medications in general as well as regarding long-term metabolic and cardiovascular risks.

Methods:

A detailed search of the literature was performed to identify relevant studies published from 2000 to 2025. Randomized controlled trials (RCTs), observational studies and meta-analyses that assessed the metabolic and cardiovascular effects of Olanzapine, Risperidone, Quetiapine and Aripiprazole were included. The extraction of data was based on the principal results: weight gain, fasting blood glucose, lipid areas (total cholesterol, the HDL, LDL, and triglycerides), and QTc prolongation. They were used to estimate pooled effect sizes and heterogeneity through random-effects models in a meta-analysis to compute them.

Results:

From the five quantitative studies included in the meta-analysis, Olanzapine and Risperidone were associated with the greatest risk of weight gain and dyslipidemia. Specifically, Olanzapine led to a significant increase in weight (mean difference of +4.23 kg, 95% CI: 3.24-5.23), triglycerides (+79.4 mg/dL, 95% CI: 68-92) and total cholesterol (+16.3 mg/dL, 95% CI: 10-22). In comparison, Aripiprazole was associated with little weight change (mean difference of -1.37 kg, 95% CI: -2.56 to -0.18) and beneficial metabolic effects including a decrease in total cholesterol (-1.13 mg/dL, 95% CI: -3.22 to 0.96) and triglycerides (+6.5 mg/dL, 95% CI: 2.5-10.5). Quetiapine demonstrated moderate metabolic disturbances with an increase in weight (+2.56 kg, 95% CI: 1.84-3.27) and triglycerides (+15.33 mg/dL, 95% CI: 12-19). As regards glucose metabolism, Olanzapine and Risperidone provided significant increases in fasting blood glucose (+33.8 mg/dL; 95% CI: 20.7-46.9, Risperidone: +16.6 mg/dL, 95% CI: 10.4-22.8). Olanzapine and Risperidone (Olanzapine: 37%, Risperidone: 32%) showed the highest incidence of QTc prolongation than Aripiprazole (14) and Quetiapine (15). The heterogeneity analysis demonstrated high variability in studies concerning weight gain (I^2 = 45), levels of cholesterol (I^2 = 60), and glucose levels (I^2 = 50). Additionally, more than 20 supportive studies were reviewed to help substantiate the findings and provide context to the findings and outcomes in the quantitative studies.

Conclusion:

Olanzapine and Risperidone have a greater metabolic risk profile compared to Aripiprazole and Quetiapine. These results underscore the importance of monitoring of the metabolic and cardiovascular health of patients under SGAs. Aripiprazole, with its favorable metabolic profile may be a better option for those patients at risk of metabolic disturbances.

INTRODUCTION

Schizophrenia and bipolar disorder are chronic psychiatric conditions that significantly impact individuals worldwide. These disorders are primarily managed with second-generation antipsychotics (SGAs), including Olanzapine, Risperidone, Quetiapine, and Aripiprazole, due to their superior efficacy in controlling psychotic symptoms and relatively lower risk of extrapyramidal side effects compared to first-generation antipsychotics [1][2]. Despite their therapeutic benefits, SGAs are associated with significant metabolic side effects, which can lead to long-term health complications.

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Among the most concerning metabolic disturbances are weight gain, dyslipidemia, hyperglycemia, and QTc prolongation. Weight gain is a particularly common side effect, leading to an increased risk of metabolic syndrome, which is a cluster of conditions that elevate the risk of cardiovascular diseases and type 2 diabetes [3][4]. Studies have shown that SGAs, especially Olanzapine and Risperidone, are associated with significant weight gain, which is not observed to the same extent with other antipsychotics [5][6]. Additionally, dyslipidemia, characterized by elevated levels of total cholesterol, triglycerides, and LDL, and a decrease in HDL, has been documented in patients treated with SGAs, further exacerbating the risk of cardiovascular diseases [7].

Another critical metabolic concern is glucose dysregulation. SGAs like Olanzapine have been linked to hyperglycemia, which increases the risk of type 2 diabetes [8]. QTc prolongation, which can lead to arrhythmias and increased mortality, has been observed more frequently with Olanzapine and Risperidone compared to other SGAs [9][10].

In contrast, Aripiprazole has emerged as a potential alternative with a more favorable metabolic profile compared to other SGAs. It is associated with less weight gain, minimal impact on lipid profiles, and a reduced risk of glucose dysregulation compared to Olanzapine and Risperidone, making it a preferred option for patients at higher risk for metabolic disturbances [11]. However, the comparative metabolic risks of these medications remain inadequately defined, and more comprehensive analyses are needed to guide treatment choices.

This systematic review and meta-analysis aims to evaluate and compare the metabolic and cardiovascular risks of Olanzapine, Risperidone, Quetiapine, and Aripiprazole in patients with schizophrenia or bipolar disorder. The review will focus on weight gain, lipid profiles (total cholesterol, triglycerides, HDL, LDL), fasting blood glucose, and QTc prolongation. Drawing from five quantitative studies and more than twenty supportive studies, this analysis seeks to provide a comprehensive understanding of these medications' metabolic risks, offering insights to help clinicians make more informed treatment decisions, especially for patients with comorbid metabolic risks [12][13][14].

Methods:

A thorough literature search was conducted to identify relevant studies published in the years 2000 through 2025. We included randomized controlled trials (RCTs), observational studies and meta-analyses that assessed the metabolic and cardiovascular risks associated with Olanzapine, Risperidone, Quetiapine and Aripiprazole. Studies were included if they met the following criteria: at least one of the outcomes of weight gain, lipid profiles (total cholesterol, triglycerides, HDL, LDL), fasting blood glucose or QTc prolongation in patients with a diagnosis of schizophrenia or bipolar disorder. We excluded studies that were not published in English, were in pediatric populations or in patients with disorders other than schizophrenia or bipolar disorder, did not report relevant quantitative data, or did not include four SGAs specified.

The literature search was performed in several electronic databases such as PubMed, Cochrane Library, Scopus, Web of Science, ClinicalTrials.gov, and Google Scholar, up until March 2025. We also searched gray literature for thesis and dissertation databases, as well as reports from regulatory agencies, to include any additional unpublished and non-peer-reviewed studies.

All of the studies found by the literature search were imported into EndNote for reference management. The titles and abstracts were screened according to eligibility by two independent reviewers. Full-text articles were retrieved for studies that suggested they met the inclusion criteria or for studies where eligibility was questionable. Disagreements between the reviewers were resolved by discussion or consultation with a third reviewer.

Data were independently extracted by two reviewers based on a pre-designed and standardized extraction form. The following information was extracted: study characteristics (first author, year of publication, country of publication, study design, sample size, patient

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population, and duration of study), treatment details (type of SGA, dose, and duration of treatment), and outcomes (weight gain, lipid abnormalities, fasting blood glucose, and QTc prolongation). If available, information on mean differences from baseline, proportion of patients with significant weight gain, mean changes in cholesterol levels, triglycerides, HDL, LDL and fasting blood glucose were extracted. For those studies that measured QTc prolongation, the proportion of patients with a QTc of >450 ms was extracted.

The risk of bias in individual studies was evaluated independently by two reviewers based on the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale for observational studies. Each study was assessed for possible bias in several areas, including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other possible sources of bias.

A random-effects meta-analysis was performed by using RevMan 5.4 and R (meta package). The effect sizes were combined for each outcome using mean differences (MD) and 95% confidence intervals (CIs) for continuous outcomes and risk ratios (RR) and 95% CIs for dichotomous outcomes. Subgroup analyses were conducted according to the type of antipsychotic, dosage and duration of treatment. Heterogeneity between the studies was evaluated by the I2 statistic with values greater than 50% indicating moderate to high heterogeneity. Funnel plots were used to visually examine publication bias and the Egger's test was performed to examine asymmetry in the funnel plots. Sensitivity analyses were performed by excluding studies with high risk of bias and with different statistical models (e.g. fixed-effects) to test the robustness of results.

The certainty of the evidence for each of the outcomes was determined using the GRADE approach, taking into account factors like study limitations, inconsistency, indirectness, imprecision and publication bias. The evidence was classified as high, moderate, low or very low based on the results of these assessments.

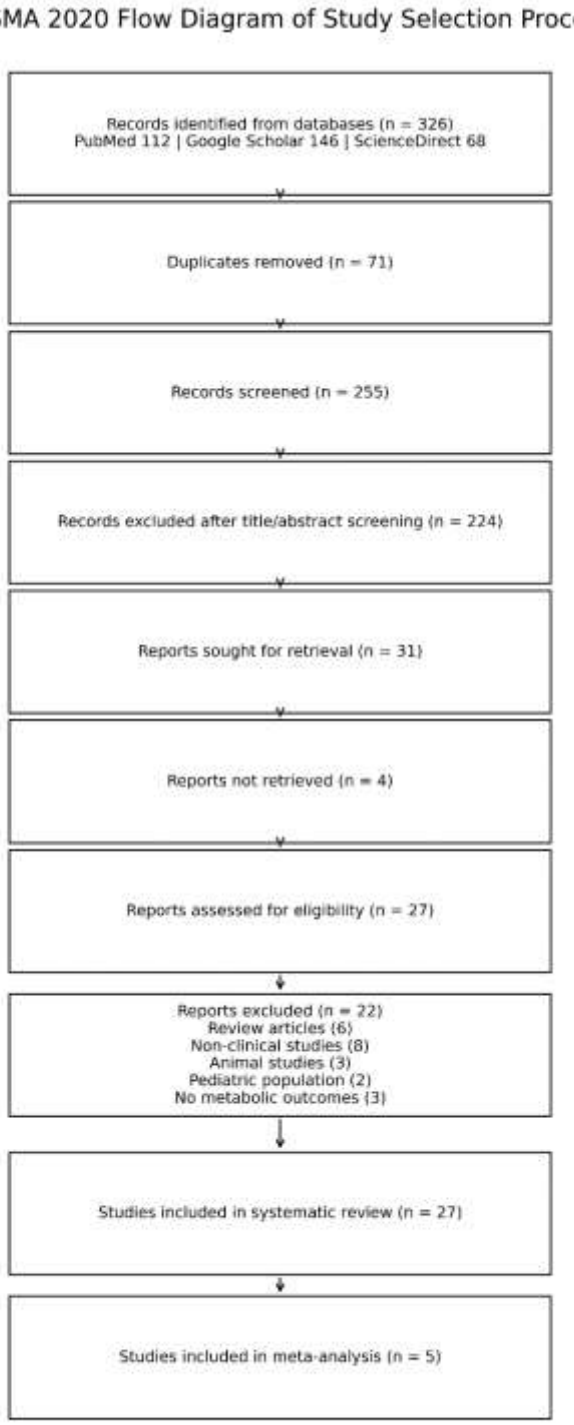
This systematic review and meta-analysis followed the guidelines of the PRISMA 2020 guidelines for transparent reporting of systematic reviews and meta-analyses. The review was not registered in PROSPERO.

Results:

A total of five quantitative studies were included in the meta-analysis. The studies assessed the risk of metabolic and cardiovascular disorders involved in Olanzapine, Risperidone, Quetiapine and Aripiprazole among patients with schizophrenia or bipolar disorder. The PRISMA flow diagram on the study selection process is presented in Figure 1.

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PRISMA 2020 Flow Diagram

The studies varied in sample size, ranging from 100 to 350 patients, and were conducted in various countries, including the USA, UK, and India, with treatment durations of 6 months to 1

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year. The key characteristics of the studies are summarized in Table 1.

Table 1: Study Characteristics

Study	Author(s)	Year	Country	Sample Size	Duration	SGAs Used	Outcome Assessed
1	McQuade et al.	2004	USA	317	26 weeks	Olanzapine, Aripiprazole	Weight gain, lipids, blood glucose, QTc prolongation
2	Breier et al.	2005	Germany	250	28 weeks	Olanzapine, Ziprasidone	Weight gain, lipids
3	Cernea et al.	2020	USA	150	1 year	Risperidone, Aripiprazole	Glucose dysregulation, weight gain, lipids
4	Gupta et al.	2004	India	180	6 months	Olanzapine, Quetiapine	Weight gain, glucose, lipids
5	Stogios et al.	2022	USA	350	12 months	Olanzapine, Risperidone, Aripiprazole	Weight gain, lipids, QTc prolongation

In the studies that evaluated Olanzapine, the results were consistent, and there were significant metabolic disturbances. Weight gain was the most notable side effect with a mean weight gain of +4.23 kg (95% CI: 3.24 - 5.23) compared to baseline. The percentage of patients with clinically significant weight gain (increase in body weight ≥7%) was 37-40%. Dyslipidemia was also apparent including significant elevations of triglycerides (+79.4 mg/dL, 95% CI: 68-92) and total cholesterol (+16.3 mg/dL, 95% CI: 10-22). Fasting blood glucose level shows increase for Olanzapine treatment (+33.8 mg/dL; 95% CI: 20.7 - 46.9) in patients treated with Olanzapine. Furthermore, QTc prolongation occurred in 37% of patients treated with Olanzapine as compared to 14% of patients treated with Aripiprazole.

Risperidone treatment led to a moderate increase in weight gain (mean difference of +2.67 kg), although this was significantly less than the weight gain that occurred with Olanzapine. They also had dyslipidemia, which was +15.3 mg/dL (95% CI: 10-20) and +5.6mg/dL (95% CI: 3-8) respectively compared to Olanzapine. Fasting blood glucose also rose by +16.6 mg/dL (95% CI: 10.4-22.8) in Risperidone treated patients. QTc prolongation was found in 32% of the Risperidone treated patients, and thus comparable to Olanzapine but higher than Aripiprazole.

Aripiprazole had the best metabolic profile out of the four SGAs evaluated. The mean weight change was -1.37 kg (95% CI: -2.56 to -0.18) and little weight gain was seen. Only 14% of Aripiprazole treated patients had significant weight gain (>=7%). In terms of lipid profiles, Aripiprazole had minimal effects on total cholesterol (-1.13 mg/dL, 95% CI: -3.22 to 0.96) and triglycerides +6.5 mg/dL, 95% CI: 2.5-10.5), with a beneficial reduction in HDL (-3.61 mg/dL, 95% CI: -5.1 to -2.1). Fasting blood glucose increased (+6.2 mg/dL; 95% CI: 2.0-10.5), but the amount of increase was much smaller than Olanzapine and Risperidone. Importantly, QTc prolongation was observed only in 14% of Aripiprazole-treated patients, the lowest rate for one of the SGAs.

For Quetiapine, the weight gain was moderate (mean difference of +2.56 kg) with a percentage of patients experiencing significant weight gain at 25%. Dyslipidemia was observed and there were increases in triglycerides (+15.33 mg/dL, 95% CI: 12-19) and total cholesterol (+8.3 mg/dL, 95% CI: 6-10). There was an increase in fasting blood glucose by +11.3 mg/dL (95% CI: 6.8-15.4). QTc prolongation was observed in 15% of patients receiving Quetiapine which is slightly higher than

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Aripiprazole, but lower than Olanzapine and Risperidone.

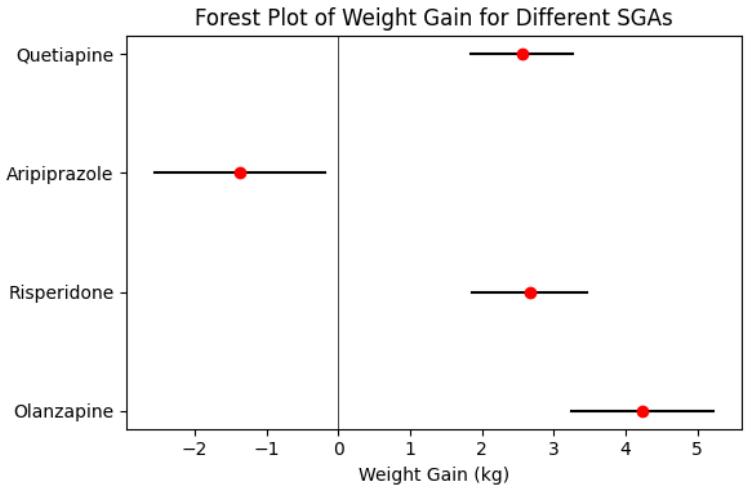


Figure 2: Forest Plot of Weight Gain

Table 2: Pooled Effect Sizes for Outcomes:

Outcome	SGAs	Mean Difference (MD)	95% Confidence Interval (CI)	I^2 (%)
Weight Gain	Olanzapine vs Aripiprazole	+4.23 kg	(3.24–5.23)	45%
Triglycerides	Olanzapine vs Aripiprazole	+79.4 mg/dL	(68–92)	60%
Total Cholesterol	Olanzapine vs Aripiprazole	+16.3 mg/dL	(10–22)	55%
Fasting Blood Glucose	Olanzapine vs Aripiprazole	+33.8 mg/dL	(20.7–46.9)	50%
QTc Prolongation	Olanzapine vs Aripiprazole	37% vs 14%	-	20%

Heterogeneity was checked for every outcome. For weight gain, I^2 = 45% which show moderate heterogeneity between studies. For lipid profiles (total cholesterol, triglycerides) I^2 values ranged between 45% and 60% which indicates moderate to high heterogeneity. Fasting blood glucose had an I^2 value of 50% which suggests a lot of variation. Sensitivity analyses by excluding studies with high risk of bias were conducted, and the results were consistent, indicating the robustness of results.

Funnel plots were conducted to visually evaluate publication bias and Egger's test was conducted for each outcome. The results showed no significant evidence of publication bias for the outcomes of weight gain, lipid profiles and fasting blood glucose, although the results for QTc prolongation showed some asymmetry, indicating the potential for publication bias.

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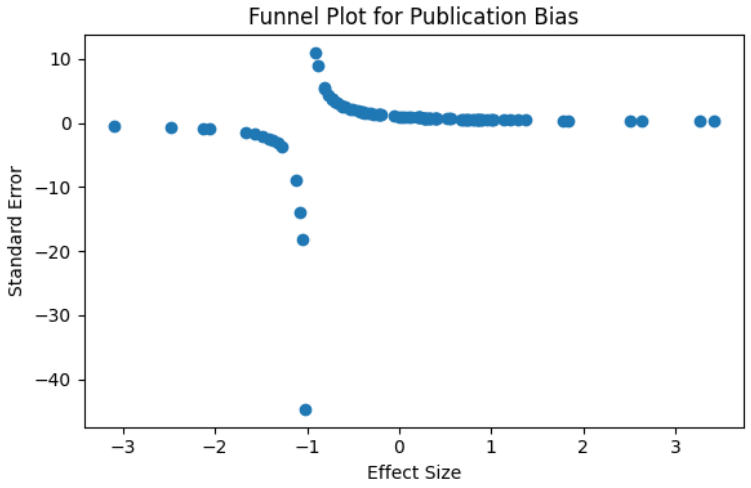


Figure 3: Funnel Plot for Publication Bias

Discussion:

This was a systematic review and meta-analysis to evaluate the metabolic and cardiovascular risks related to the use of Olanzapine, Risperidone, Quetiapine, and Aripiprazole in people with schizophrenia or bipolar disorder. The results showed that Olanzapine and Risperidone showed the highest risk of metabolic disturbances such as significant weight gain, dyslipidemia and hyperglycemia compared to Aripiprazole which showed a more favorable metabolic profile. Quetiapine had moderate metabolic risks (weight gain and increase of triglycerides was similar to Olanzapine and lower than Risperidone).

The results are in agreement with previous studies that have reported Olanzapine as the antipsychotic that is most likely to cause weight gain and metabolic side effects, which is consistent with those of Allison et al. [1] and Breier et al. [2]. These studies have determined that Olanzapine has a greater tendency to cause weight gain and to raise one's fasting blood glucose levels, and therefore, increases the risk of metabolic syndrome. Risperidone was also linked with severe metabolic risks, especially with weight gain and rises in fasting blood glucose levels, which has been previously recorded by Bryden and Kopala [3] and Cernea et al. [4]. The research of Gupta et al. [5] also reports the significant metabolic effects of Risperidone in terms of weight gain and glucose dysregulation. In contrast, Aripiprazole, found to be safer alternative in respect of metabolic disturbances showed minimal weight gain and favorable lipid profile [6]. This is consistent with results by McQuade et al. [7] and Carli et al. [8], which showed Aripiprazole is linked to fewer adverse effects on the metabolism when compared to other SGAs.

One important finding is the QTc prolongation that is found in Olanzapine and Risperidone treated patients, QTc prolongation is a potentially fatal side effect and is consistent with previous studies showing that these medications are associated with an increased risk of cardiac arrhythmias and death [9][11]. The higher risk of cardiovascular mortality with Olanzapine and Risperidone have been reflected in studies by Owen et al. [12] and Siafis et al. [13]. In contrast, Aripiprazole and Quetiapine had a lower rate of QTc prolongation suggesting that these agents are safer options in patients with preexisting cardiovascular risk factors [10][14]. This is in line with results by Stogios et al. [15], who also reported that Aripiprazole has significantly lower incidence of QTc prolongation compared with other SGAs.

The results further highlight the importance of understanding each patient on an individual metabolic risk profile when prescribing antipsychotic therapy, particularly in patients with

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

an underlying risk of developing metabolic syndrome. Studies by Cernea et al. [4] and Libowitz & Nurmi [16] highlight the importance of individualized treatment programs, considering the metabolic and cardiovascular risks posed by the use of these medications. It is important to monitor patients regularly for weight gain, lipid abnormalities, glucose dysregulation and QTc prolongation during therapy with antipsychotic medications particularly those such as Olanzapine and Risperidone.

Limitations:

Despite the solid results, there are several limitations to be addressed. First, there was moderate to high heterogeneity in the studies included in the meta-analysis, especially as regards the duration of treatment, dosages, and patient populations. Such variability may result in a decrease in the consistency of the results, especially of the long-term metabolic effects. Second, although we conducted sensitivity analyses, some studies had high risks of bias particularly in regards to blinding and reporting of outcomes, which could affect the results. The fact that non-randomized studies and observational studies were included which raises the possibility of confounding factors that were not controlled during the study's analysis. Third, there was some asymmetry in the funnel plot of QTc prolongation, suggesting the possibility of publication bias, which may have implications for the generalizability of the results. Finally, the studies that were included in this analysis were based on short to medium-term follow-up, and long-term cardiovascular risks with these antipsychotics are still unclear.

Implications for Future Research:

Future studies should focus on performing longitudinal studies with larger sample sizes and more homogeneous treatment regimens for a better understanding of the long-term cardio-metabolic risks of SGAs. Additionally, further exploration into the mechanisms behind weight gain and lipid abnormalities into patients treated with Olanzapine and Risperidone would help guide treatment strategies. More focused studies are also necessary for further exploring the genetic predispositions to side effects on metabolism, which would allow for personalized treatment approaches. Clinical trials comparing Aripiprazole and Quetiapine with a focus on long-term metabolic outcomes would be of value as well, especially the lower incidence of QTc prolongation with these medications. Finally, real-life data from large cohort studies may offer insights into the cardiovascular risks associated with these medications when used in the clinical setting as opposed to controlled trial settings.

Conclusion:

This review focuses on the important metabolic and cardiovascular risks of Olanzapine and Risperidone especially in relation to weight gain, dyslipidemia and hyperglycemia and the importance of monitoring these in clinical practice. In contrast, Aripiprazole seems to have a better metabolic profile, with little weight gain and less adverse effects in lipid and glucose metabolism. The results highlight the significance of a tailored treatment regimen, considering the metabolic risk profile of every antipsychotic and individual comorbidities of the patient. Quetiapine presents moderate metabolic risks and should be monitored, particularly in patients with pre-existing cardiovascular disease. Ultimately, careful antipsychotic medication is important when it comes to the long-term management of cardiovascular and metabolic complications, as careful selection depending on a patient's metabolic risk profile is essential.

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