The cardiometabolic burden of second-generation antipsychotics: a narrative synthesis of clinical evidence

La carga cardiometabólica de los antipsicóticos de segunda generación: una síntesis narrativa de la evidencia clínica

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Abstract

Second-generation antipsychotics (SGAs) are among the most prescribed psychotropic drugs worldwide. Nevertheless, their adverse effect profiles are notoriously broad and often pose clear challenges for tolerability, adherence, quality of life, and overall clinical success in everyday practice. Most alarmingly, a relationship has been described between SGAs and several metabolic disturbances, ultimately increasing the risk of metabolic syndrome, cardiovascular disease (CVD), diabetes, and other related conditions. However, characterizing this link is complex, as the impact of SGAs appears to be highly variable, not only based on clinical outcomes, but also in regards to a myriad of other patient-dependent factors, such as their age, sex, diagnosis, comorbidities and concurrent medication use. Appraisal of this interplay is pressing as CVD remains the leading global cause of morbidity and mortality. The outlook is further complicated by the intrinsically higher cardiometabolic risk entailed by severe mental illnesses such as schizophrenia—the model psychotic disorder—and other mental disorders where SGAs are often prescribed. Therefore, the objective of this narrative review is to revise the currently available clinical evidence on the relationships between SGAs and weight gain, hyperglycemia, dyslipidemia, hypertension, systemic inflammation, thrombotic risk and cardiovascular risk; in an effort to illuminate directions for clinical practice and future research.

Keywords: Second-generation antipsychotics, cardiovascular disease, diabetes, weight gain, dyslipidemia.

Resumen

Los antipsicóticos de segunda generación (ASG) se encuentran entre los fármacos psicotrópicos más recetados a nivel mundial. Sin embargo, sus perfiles de efectos adversos son notoriamente amplios y a menudo plantean claros desafíos para la tolerabilidad, la adherencia, la calidad de vida y el éxito clínico general en la práctica diaria. Resulta aún más alarmante la relación descrita entre los ASG y diversas alteraciones metabólicas, que en última instancia aumentan el riesgo de síndrome metabólico, enfermedad cardiovascular (ECV), diabetes y otras afecciones relacionadas. Sin embargo, caracterizar esta relación es complejo, ya que el impacto de los ASG parece ser muy variable, no solo en función de los resultados clínicos, sino también en relación con una multitud de otros factores dependientes del paciente, como su edad, sexo, diagnóstico, comorbilidades y uso concomitante de medicamentos. La evaluación de esta interacción es urgente, ya que la ECV sigue siendo la principal causa mundial de morbilidad y mortalidad. El panorama se complica aún más por el riesgo cardiometabólico intrínsecamente mayor que conllevan las enfermedades mentales graves, como la esquizofrenia (el trastorno psicótico modelo) y otros trastornos mentales en los que se prescriben ASG con frecuencia. Por lo tanto, el objetivo de esta revisión narrativa es revisar la evidencia clínica disponible sobre la relación entre los ASG y el aumento de peso, la hiperglucemia, la dislipidemia, la hipertensión, la inflamación sistémica, el riesgo trombótico y el riesgo cardiovascular, con el fin de esclarecer las directrices para la práctica clínica y la investigación futura.

Palabras clave: Antipsicóticos de segunda generación, enfermedad cardiovascular, diabetes, aumento de peso, dislipidemia.

Introduction

Psychotropic drug use has been increasing steadily in recent decades worldwide[1]; with antipsychotics consistently placing as the second most used drug class in this group—behind antidepressants only—across several latitudes[2,3]. The introduction of these drugs marked a significant breakthrough in the field of psychiatry, providing a gravely needed tool for the management of psychosis. This was further bolstered with the development of second-generation antipsychotics (SGAs), which purported to offer increased efficacy and tolerability[4]. Although they remain a cornerstone of everyday psychotropic prescribing, concerns on the latter remain severe. Indeed, their burden of adverse effects has been identified as a factor that limits the overall improvements in quality of life that may be obtained from their use[5].

Within this wide array of adverse effects, the deleterious impact on metabolism is a hallmark of SGAs, encompassing weight gain, insulin resistance, dyslipidemia, and increased cardiovascular risk, among other related alterations[6]. Indeed, antipsychotics are broadly recognized as "dirty" drugs, owing to their extremely ample pharmacodynamic profiles. Thus, they may mediate these metabolic adverse by modulation of a myriad of neurotransmitter receptors within and beyond the central nervous system[7]; as well as other unintended targets, such as mitochondria and various intracellular second-messenger systems[8].

Clinical evidence on the relationships between SGAs and cardiometabolic disturbances is abundant, albeit complex and richly nuanced[9]. The impact of SGAs on diverse outcomes in this regard appears to be heavily conditioned by factors such as specific drugs used and duration of treatment, as well as patients' age, sex, diagnosis, comorbidities and concurrent medication use, among many other aspects. As a result, efforts to characterize these patterns are highly relevant[10]. Investigation in this area is also urgent: With cardiovascular disease (CVD) reigning as the main cause of mortality and morbidity worldwide, along with cardiometabolic risk factors drawing a persistent ascending trend globally, vigilance and care in this regard merit as much priority and prudence as ever[11].

This alarming panorama is further complicated by the fact that a low-grade inflammatory component has been identified in various severe mental disorders—notoriously among these schizophrenia (SCZ), the model psychotic disorder—augmenting the risk for CVD[12]. Therefore, the inclusion of SGAs in this context could potentially aggravate cardiometabolic clinical outcomes, given their known negative impact on metabolism.

In this narrative review, we revise the currently available clinical evidence on the relationships between SGAs and weight gain, hyperglycemia, dyslipidemia, hypertension, systemic inflammation, thrombotic risk and cardiovascular risk; in an effort to illuminate directions for clinical practice and future research.

SECOND-GENERATION ANTIPSYCHOTICS, CARDIOMETABOLIC RISK FACTORS, AND CARDIOVASCULAR DISEASE: CLINICAL EVIDENCE

The range of cardiometabolic disturbances induced by treatment with SGAs appear to raise cardiovascular risk both individually and jointly. In addition, these effects may be important barriers for treatment adherence; and their risks may outweigh benefits in a significant proportion of cases[13,14]. This section discusses clinical evidence on these aspects, focusing on each metabolic alteration, as well as on the particularities of distinct SGAs and other key characteristics for each scenario (**Tables 1, 2** and **3**).

Weight Gain: Appraising the roles of specific antipsychotics, diagnosis, treatment timeline, dosage, and polypharmacy

Weight gain is one of the most documented and clinically relevant adverse effects of SGA use, bearing a heavy impact on cardiometabolic health and considerably affecting treatment continuation[15]. In a network meta-analysis (NMA) which included 100 randomized controlled trials (RCTs) and 25,952 patients in acute treatment for SCZ (median duration: 6 weeks), Pillinger et al. (9) found clozapine to be associated with increased weight gain (+3.01 kg; CI 95%: 1.78-4.24), followed by olanzapine (+2.73 kg; CI 95%: 2.38-3.07). In contrast, other SGAs such as ziprasidone, lurasidone and aripiprazole showed no changes in comparison to placebo. This tendency towards weight gain with short-term SGA use is not restrained to patients with SCZ. In another meta-analysis of 27 RCTs, each of which included at least 100 subjects with diverse psychiatric diagnoses treated with SGAs during 3-12 weeks, the average weight gain attributed to SGAs vs placebo was 0.86 kg (CI 95%: 0.65-1.07). In this study, olanzapine was identified as the most closely related to weight gain, followed by asenapine and risperidone[16]. These findings harmonize with those of the ClozaGene Study, where 1021 Australians (41.0% female; aged 46.2 ± 10.6 years [range 18-66]) prescribed with clozapine, 91% of them diagnosed with SCZ, self-reported weight-gain (71.0%), which was the second most common adverse effect[17].

Because psychotic disorders, tend to be chronic in nature as are most psychiatric disorders and their treatments, it is crucial to characterize the effects of SGAs over prolonged periods of time. Burschinski et al.[18] per-

formed a NMA with 137 RCTs, with a median follow-up of 45 weeks, and at least 80% of participants with a diagnosis in the SCZ and related disorders category. Notably, chlorpromazine—a first-generation antipsychotic (FGA)—was linked with the largest weight gain vs placebo, (+5.13 kg, 95% CI: 1.98-8.30); followed by clozapine (+4.21 kg; 95% CI: 3.03-5.42) and olanzapine (+3.82 kg; 95% CI: 3.15-4.50). Others, such as oral aripiprazole (+0.41 kg), aripiprazole LAI (+0.00 kg), lurasidone (-0.06 kg) and ziprasidone (-0.16 kg), were found in the opposite side of the spectrum, with little effect on weight, or slight weight loss vs placebo. Similarly, in a 3-year prospective study on 162 patients diagnosed with a first-episode psychosis (FEP) treated with aripiprazole, quetiapine or ziprasidone, Vázquez-Bourgon et al.[19] found a significant increase in weight and body mass index (BMI) for all of the cohort, with most of the weight gain occurring predominantly during the first year of treatment, corresponding to 85% of the total increase. The proportion of patients who fit the diagnostic for obesity skyrocketed from 5.6% to 25.7% ($p< 0.001$) after the 3-year follow-up.

These trends are corroborated in the meta-analysis by Campforts et al.[20], which encompassed 201 studies and over 80,000 participants. Almost all antipsychotics were associated with clinically-relevant weight gain (CRWG). This phenomenon was more pronounced in antipsychotic-naïve patients (ANP) in comparison to those switching antipsychotics, in particular for olanzapine, quetiapine and aripiprazole. This greater impact on ANP was attributed to the fact that this population tended to not be overweight before treatment, they may not suffer residual effects of other antipsychotics, and they were generally younger at the onset of treatment. This has been supported by other meta-analyses, as outlined by Bak et al.[21], where antipsychotic use was linked to substantial body weight gain in ANP, whereas in patients switching antipsychotics, the increase was smaller. Indeed, evidence highlights the importance of immediate follow-up and prevention strategies for weight gain from the beginning of treatment, especially in vulnerable individuals such as ANP.

Weight gain related to SGAs depicts further interesting patterns the longer their use is sustained. In a longitudinal study with a follow-up of up to 18.7 years and a median of 6.2 years on a Chinese cohort of 797 patients with SCZ, Wong et al.[22] found the increasing effect on BMI persisted in the long-term, even after discontinuation of the SGA. This suggests these drugs may have an accumulative or residual effect. Consistently, clozapine and olanzapine were associated with largest increases in BMI and worse metabolic side effects, especially at minimum effective doses. Conversely, risperidone and aripiprazole displayed the smallest metabolic impact, with the latter even being related to a significant improvement of serum lipids.

However, another longitudinal study by Feng et al.[23] offers key insights into the patterns of SGA-related metabolic disruptions over time: The impact of SGAs on BMI and serum triglycerides (TG) depicted an inverted U-shape pattern in time, with effects initially increasing, plateauing after around 12 months of continuous treatment, to then decrease. Similar trends were observed for total cholesterol (TC) and LDL-C with later plateaus, at around 15 months. Regarding fasting blood glucose (FBG) and HDL-C, a peak was observed earlier, at around 6 months. These findings suggest that although the metabolic side effects begin rapidly with treatment, they do not scale indefinitely, and they may stabilize with prolonged use. This may be due to the adoption of mitigating measures against weight gain by patients, or the development of a biological "resilience" to the effects of SGAs.

The net effect of SGAs on weight also appears to hinge on underlying diagnosis. In their meta-analysis, Campforts et al.[20] found that in general, individuals with SCZ receiving SGAs experienced greater weight gain in the short term (<6-16 weeks) than those in other diagnostic categories. In particular, patients with bipolar disorder on aripiprazole, cariprazine or olanzapine; as well as those with dementia using olanzapine or risperidone; and those with major depressive disorder, borderline personality disorder or generalized anxiety disorder receiving quetiapine had significantly less weight gain in comparison to those diagnosed with SCZ. Moreover, the presence of mental comorbidities may worsen the metabolic outcomes: In a report by Courtial et al.[24] with 112 participants diagnosed with SCZ and intellectual disability, 35% of the cohort had obesity. Nevertheless, the impact of SGAs on weight remains relevant even with off-label indications, as ascertained by Stogios et al.[25] in a meta-analysis with 35 RCTs, where patients with off-label use of olanzapine, quetiapine and risperidone showed higher probability of weight gain in comparison to other SGAs. The most prominent was olanzapine (+3.24 kg), with an average study duration of 12 weeks.

Polypharmacy, though controversial, is frequent in clinical practice when prescribing SGAs. In an RCT which included 136 long-term inpatients diagnosed with SCZ, Shakir et al.[26] found that switching from SGA + FGA combinations to SGA monotherapy—mainly clozapine or olanzapine—resulted in a significant reduction of body weight (-4.245 kg) and BMI (-1.334 kg/m²) after 9 months of follow-up. This suggests antipsychotic monotherapy may be significantly less metabolically deleterious than combinations, even when choosing SGAs with high metabolic risk.

In regard to the relationship between SGA dosing and the effect size on weight gain, a dose-response meta-analysis comprising 97 RCTs with a median follow-up of 6 weeks indicate that for most SGAs, weight gain increased with larger doses until reaching a plateau. However, no such clear stability could be observed for olanzapine, aripiprazole and paliperidone within the dose ranges assessed[27]. This dose-dependent trend should be compared with U-shaped trend previously described by Feng et al.[28].

In ensemble, the currently available evidence depicts a consistent effect of SGAs on weight gain, which is modulated by the particular drug prescribed, dosage, polypharmacy, treatment duration, and various patient-specific characteristics, such as first exposure to antipsychotics[29].

Alterations in Adiposity Distribution: SGAs promote central adiposity

Beyond pure weight gain, SGAs also exert an important influence on the body distribution of adiposity. The accumulation of visceral adipose tissue (VAT)—as can be determined by the measurement of waist circumference (WC)—has been identified as an independent predictor of IR and cardiovascular risk, notoriously by propitiating a chronic inflammatory milieu, among other mechanisms (30). Nonetheless, this impact of SGAs on central adiposity has been much less studied in comparison to increases in body weight or BMI[9,31,28].

Sapra et al.[32] published a particularly thorough cross-sectional study directly comparing fat distribution between SGA and FGA users in male non-diabetic veterans with SCZ, as appraised by dual x-ray absorptiometry (DEXA) and computerized tomography (CT). Results showed the individuals treated with SGAs (n=9) had a significantly higher android fat mass index in comparison with those treated with FGAs (n=5) (0.96 ± 0.1 vs. 0.62 ± 0.01 kg/m², p=0.03). Moreover, CT revealed the group on SGAs had a significantly greater total abdominal fat area (514 ± 60 cm² vs. 342 ± 58 cm², p = 0.043), with a tendency towards increased accumulation of subcutaneous fat. These findings suggest a differential effect of SGAs for the promotion of central adiposity, in addition to general weight gain.

These modifications in adiposity also depict interesting trends in time. Vázquez-Bourgon et al.[19] documented a significant increase in average WC, ascending from 80.6±10.3 cm to 88.1±10.9 cm (p<0.001) after 3 years of follow-up in patients with FEP. On the other hand, the findings by Kornetova et al.[33] illustrate the rapid onset of these changes. After only 6 weeks of receiving SGAs, SCZ patients without metabolic syndrome (MetS) before treatment displayed a statistically significant increase in WC (p=0.0002), VAT as measured by bioimpedance analysis (p=0.0010), and total fat fold (p<0.0001), an indicator of subcutaneous fat.

It should be noted that these changes may be variable in certain populations. After 3-years of follow-up on forensic psychiatric patients under chronic treatment with SGAs, Vassilopoulou et al.[30] found no significant differences in WC. This may suggest illness chronicity, prolonged treatment, or specific patient features may modulate SGA-related modifications in fat distribution.

Altogether, evidence appears to indicate exposure to SGAs promotes central adiposity, especially during early treatment and in ANP. However, further research is required to consolidate these notions, both with advanced imaging techniques and by evaluating WC, given its relevance for stratification of cardiometabolic risk.

Hyperglycemia and Insulin Resistance: Impact of SGAs on various indicators

Treatment with SGAs has been associated with disruptions of glucose metabolism, and increased risk of type 2 diabetes mellitus (DM2)[34]. In a systematic review and meta-analysis of 48 RCTs and 31 longitudinal studies Rognoni et al.[31] found olanzapine to be associated with the highest elevation I FBG; whereas quetiapine XR was associated with a significant reduction. Likewise, Burschinski et al.[18] reported olanzapine to be the most powerfully associated with increased FBG, and ziprasidone to have the most favorable effects on glucose metabolism.

Notoriously, the onset of these effects may be quick, even in low-risk populations: In a prospective 6-week study in patients without MetS, Kornetova et al.[33]. found an increase in FBG (median 4.95-5.35 mmol/L; p<0.001) and HOMA-IR (median 0.17-0.32; p=0.023) (33). Similarly, Pillinger et al.[9] determined clozapine and olanzapine were linked with highest increases in FBG after 6 weeks of treatment, whilst other SGAs such as aripiprazole, quetiapine and risperidone showed no changes in comparison to placebo. In contrast, lurasidone was associated with lower FBG. Baseline overweight and male sex were identified as predictors of larger FBG increase.

Regarding long-term effects on glucose metabolism, Vázquez-Bourgon et al.[19] found a significant increase in FBG with all three evaluated SGAs—aripiprazole, quetiapine and ziprasidone—and no significant differences among them after 3 years of treatment. They also identified significant elevations in HOMA-IR from 2.1 to 2.8 (p = 0.023) and in fasting insulin, from 8.0 μU/ml to 12.1 μU/ml. The impact of SGAs on FBG appears to peak around six months of use, yet this effect may persist after discontinuation, in particular with clozapine and olanzapine[28]. In contrast, in a NMA with 46 studies, 11,464 patients, and a mean duration of 15.5 weeks, Carnovale et al.[35] found lurasidone to be associated with a slight increase in HbA1C (DM: +0,02%), while ziprasidone was linked with the largest decreased (DM: -0,20%). Interestingly, olanzapine and quetiapine were not related with significant changes in HbA1c.

Furthermore, the impact of different SGAs on different surrogate measurements of IR appears to be highly heterogeneous. Vázquez-Bourgon et al.[19] determined HOMA-IR values to be significantly reduced by aripiprazole (DM vs. placebo: -0,80), and neutrally impacted by olanzapine and lurasidone (DM vs. placebo: -0,01). However, olanzapine was also related to significant increases in serum fasting insulin (DM: +1,49 μU/mL), whereas ziprasidone is linked with a decrease of this marker (DM: -0,84 μU/mL). It should be noted that changes in fasting insulin are not always correlated directly or consistently

with HOMA-IR values in subjects taking SGAs, suggesting possible complex interactions with FBG or confounding factors in this context[35].

Thus, it is imperative to employ more direct and precise measurements of IR in future investigations. Application of the euglycemic-hyperinsulinemic clamp would allow a meticulous quantification of the magnitude of IR and would aid in discerning its hepatic and peripheral components. Similarly, although FBG is a valuable parameter, systematic measurement of HbA1C in longitudinal studies could offer a more complete view of glycemic management across time. Incorporation of these and other critical indicators would not only strengthen the collection of evidence, but also enhance clinical care, by allowing improvements in risk categorization and optimization of strategies for the monitoring and prevention of metabolic disturbances in patients treated with SGAs[9,18,36].

Diabetes: Risk is highly heterogeneous among SGAs

As an extension of their impact on IR, SGAs have also been related to the development of DM2, a severe and exhaustively studied metabolic complication. Currently available research suggests differing degrees of risk in this aspect among SGAs[36,37,30]. In a systematic review of 40 population-based studies, Bernardo et al.[36] found clozapine and olanzapine were consistently linked with a greater probability of DM2. On the contrary, the results were mixed for risperidone and quetiapine; while aripiprazole and ziprasidone, though less extensively researched, seemed not to increase DM2 risk. Likewise, in another systematic review of 15 population-based studies by Hirsch et al.[6] clozapine and olanzapine exhibited the closest association with DM2, whereas the evidence was moderate and mixed for risperidone and quetiapine.

Indeed, risk of DM2 is heterogeneous among SGAs. In a meta-analysis by Poulos et al.[37] including 38,762 adults with severe mental illness followed during 3 years, switching to SGAs labeled as "high-risk", such as olanzapine or risperidone was associated with increases in absolute risk of DM2 between 1.4 percentage points (IC 95%: 0.7-2.2) and 1.9 percentage points (IC 95%: 1.0-2.8); as assessed by a targeted minimum loss-based estimation (TMLE) model.

The findings by Vassilopoulou et al.[30] fall in the same line, albeit in a very specific sample of 35 forensic psychiatric patients in treatment with SGAs for over 5 years. These drugs were classified as high metabolic risk (olanzapine, paliperidone, clozapine, asenapine) or low-moderate risk (aripiprazole, amisulpride, quetiapine, risperidone, ziprasidone). Results showed patients who received the former required antidiabetic medication more frequently, suggesting greater incidence or worse control of dysglycemia in this group.

Altogether, real-world evidence consistently draws a spectrum of risk for SGAs and DM2. Clozapine and olanzapine show the highest risk whereas aripiprazole and ziprasidone display the lowest. Risperidone, quetiapine, and other molecules sit in intermediate positions, with larger variability among reports and populations[36,37,30].

Dyslipidemia: A distinct profile for aripiprazole

Treatment with SGAs has been linked with increased serum TG, TC, and LDL-C, as well as decreased HDL-C. In the short term, clozapine and olanzapine have been associated with the largest effect sizes for all of the former; while cariprazine, brexpiprazole and lurasidone tend to show the most favorable profiles[9,38].

These effects are notoriously present with long-term treatment, as corroborated by Rotella et al.[39] in a meta-analysis which encompassed 92 RCTs with a duration of at least 52 weeks. Clozapine and olanzapine in both oral and LAI form appear to be the greatest offenders; while ziprasidone and aripiprazole seem to exert the mildest adverse impact—or even beneficial effects—on lipid profiles[18]. Indeed, aripiprazole has shown a protective effect on TC and TG in dose-response analyses. However, SGAs in general tend to worsen lipid profiles[19,36,6]. These effects have been observed to peak after 12-15 months of continuous treatment with SGAs[28].

Dyslipidemia induced by SGAs has also been investigated in individuals with diagnoses beyond those contemplated in the SCZ and related disorders category. In a systematic review and meta-analysis of 79 studies—including 48 RCTs and 37,467 participants, of which only 78.2% were described as acute schizophrenics—Rognoni et al.[31] ascertained clozapine to be significantly associated with an increase in serum lipids. Aripiprazole was also linked with an important increase in TG, while lurasidone displayed the opposite effect. On the other hand, when assessing off-label use, olanzapine and quetiapine appear to be the most prominent disruptors of lipid profiles[25].

Hypertension: A key field for further research

Although hypertension is also often related to SGA use, information is less readily available on this association. This may reflect a scarcity of consistent primary data on this relationship, or a lesser perceived effect size in currently accessible studies in comparison with other clinical outcomes[9,18,29]. In their systematic review, Bernardo et al.[36] suggested a possible association between ziprasidone and hypertension. Rognoni et al.[31] underscored quetiapine XR as the SGA most closely associated with elevations in systolic blood pressure (SBP) (+2.60 mmHg) and diastolic blood pressure (DBP) (+2.77 mmHg). In addition, Rotella et al.[39] ascertained that in long-term treatment, olanzapine and quetiapine were associated with increased SBP and DBP. However, no significant differences were found when comparing SGAs as a group vs placebo or FGAs.

However, research results on the association between SGAs and hypertension are far from harmonic. Vázquez-Bourgon et al.[19] did not recognize any significant changes in SBP or DBP in their cohort after a 3-year follow-up,

or significant differences among the aripiprazole, quetiapine and ziprasidone groups. Moreover, Vassilopoulou et al.[30] described a counterintuitive pattern: Subjects treated with low metabolic risk SGAs developed higher blood pressure than those treated with high metabolic risk SGAs. Further studies with larger and more diverse samples are necessary in the exploration of this relationship.

Table 1. Summary of clinical evidence on the relationship between SGAs and metabolic adverse effects.

Authors (Year)	Methods	Relevant outcomes	Results
Pillinger T, et al. (2020)	Network meta-analysis. 100 RCTs. Sample: 25,952 patients with SCZ. Duration: Median 6 weeks.	Weight gain (kg) FBG (mmol/L) TC, LDL-C, HDL-C (mmol/L) TG (mmol/L)	Weight gain: The largest increase vs placebo was observed for clozapine (DM +3.01 kg; CI 95%: 1.78-4.24) and olanzapine (DM +2.73 kg; CI 95%: 2.38-3.07). No significant changes were seen for ziprasidone, lurasidone and aripiprazole. Lipids: Clozapine was associated with the worst profile, including the largest increase in TG (DM +0.98 mmol/L). Cariprazine, brexpiprazole and lurasidone showed more favorable profiles.
Barton BB, et al. (2020)	Systematic review and meta-analysis. 27 RCTs. Sample: ≥subjects per study, with varying diagnoses. Duration: 3-12 weeks.	Weight gain (kg) CRWG	Weight gain: Treatment with SGAs was associated with an average weight increase vs placebo (DM+0.86 kg; CI 95%: 0.65-1.07). Olanzapine showed the strongest association, followed by asenapine and risperidone. CRWG: Patients on SGAs had a relative risk of 2.04 (CI 95%: 1.54-2.71) vs placebo.
Lind P, et al. (2024)	Cross-sectional study (self-reported survey). Sample: 1021 Australian participants prescribed with clozapine. Duration: Chronic use.	Prevalence of weight gain (self-reported).	71.0% of clozapine users reported weight gain, which was the second most prevalent adverse effect.
Burschinski A, et al. (2023)	Network meta-analysis. 137 RCTs (≥80% SCZ). Sample: 35,007 patients Duration: Median 45 weeks.	Weight gain (kg) FBG (mg/dL)	Weight gain: In the long term, the largest increase vs placebo was observed with chlorpromazine (DM +5.13 kg), clozapine (DM +4.21 kg) and olanzapine (DM +3.82 kg). Aripiprazole LAI, lurasidone and ziprasidone showed minimal effects. Fasting blood glucose: Olanzapine was associated with the greatest increase (DM +5.07 mg/dL).
Vázquez-Bourgon J, et al. (2020)	Pragmatic, prospective clinical trial. Sample: 162 drug-naive patients with FEP. Duration: 3 years.	BMI (kg/m²), Obesity, Waist circumference (cm), Fasting serum insulin (μU/ml), HOMA-IR	BMI: Increased from 23.2 kg/m² to 26.6 kg/m² ($p < 0.001$). Obesity: The prevalence increased from 5.6% to 25.7% ($p < 0.001$). Waist circumference: Increase from an average of 80.6 cm to 88.1 cm ($p < 0.001$). Insulin/HOMA: HOMA-IR increased from 2.1 to 2.8 ($p = 0.023$).
Campforts B, et al. (2023)	Systematic review and meta-analysis on 201 studies. Sample: >80,000 participants. Duration: Stratified.	CRWG	CRWG was greater in antipsychotic-naive patients. Those with SCZ displayed larger CRWG than those with other diagnoses, especially with olanzapine, quetiapine and aripiprazole.
Bak M, et al. (2021)	Systematic review and meta-analysis on 404 studies. Duration: Stratified.	Weight gain (kg)	Significant weight gain was observed in antipsychotic-naïve patients with all SGAs. In patients who switched drugs, the weight gain was mild or none: amisulpride, aripiprazole and ziprasidone were not associated with any weight gain.
Wong KC, et al. (2024)	Longitudinal cohort study (within-subject). Sample: 767 Chinese patients. Duration: 6.2 years median.	BMI (kg/m²) TC, LDL-C, HDL-C, TG	BMI: Increase of BMI persisted even after discontinuation of SGAs. Clozapine and olanzapine had the largest effect. At MED, aripiprazole was associated with a BMI increase of 0.41%. Lipids: Aripiprazole was associated with a significant reduction of TC (-1.73%) and TG (-3.92%) at MED.
Feng Y, et al. (2024)	Longitudinal cohort study. Sample: 696 Chinese patients. Duration: 6-18 months.	BMI (kg/m²) FBG (mmol/L) TC, LDL-C, HDL-C, TG (mmol/L)	"Inverted U" pattern, with effect peaks at 12 months for BMI (ATE +0.811 kg/m ²) and TG (ATE +0.241 mmol/L), 15 months for CT/LDL-C, and 6 months for FBG/HDL-C; followed by a stabilization of the effect.
Stogios N, et al. (2022)	Meta-analysis of 35 RCTs, assessing off-label use of SGAs. Sample: 4930 patients. Duration: 12 weeks mean.	Weight gain (kg)	For off-label uses, olanzapine was associated with the largest weight gain (DM +3.24 kg; CI 95%: 2.57-3.90). Quetiapine and risperidone also showed significant increases.
Wu H, et al. (2022)	Dose-response meta-analysis of 97 RCTs. Sample: 36,326 participants. Duration: 6 weeks median.	Weight gain (kg) vs. dose	For most SGAs, weight gain plateaued at high doses. However, for olanzapine, aripiprazole and paliperidone, the effect continued to grow in the studied dose ranges.
Shakir M, et al. (2024)	RCT. Sample: 136 chronic hospitalized patients. Duration: 9 months.	Weight gain (kg) BMI (kg/m²)	The switch from polypharmacy (SGA+FGA) to SGA monotherapy resulted in a significant reduction of body weight (-4.245 kg) and BMI (-1.334 kg/m²).
Sapra M, et al. (2018)	Cross-sectional comparative study. Sample: 14 men with SCZ. Duration: Chronic.	Body fat distribution (DEXA, CAT+HOMA-IR).	Adiposity: In comparison with the FGA group, the SGA group had a higher android fat mass index (0.96 vs. 0.62 kg/m², p=0.03) and total abdominal fat area (514 vs. 342 cm², p=0.043). HOMA-IR was 2.5 times higher in the SGA group (2.3 vs 0.92, p=0.014).
Kornetova EG, et al. (2019)	Prospective study. Sample: 114 patients with SCZ. Duration: 6 weeks.	Waist circumference (cm) Visceral fat Total fat fold HOMA-IR	Adiposity (without baseline MetS): Waist circumference decreased from 86 to 85 cm. Visceral fat level increased from 7 to 8. Total fat fold increased from 84 to 88 cm (all p<0.01). HOMA-IR (without baseline MetS): The median increased from 0.17 to 0.32 (p=0.023).

Vassilopoulou E, et al. (2021)	Prospective study. Sample: 35 forensic patients. Duration: 3 years.	DBP (mmHg)	The group receiving low-moderate metabolic risk SGAs developed a larger proportion of diastolic hypertension (52.9%) than the group receiving SGAs of high metabolic risk (16.7%).
Rognoni C, et al. (2021)	Systematic review and meta-analysis of 79 studies.	FBG (mg/dL) Blood pressure (mmHg)	FBG: Quetiapine XR was associated with a greater reduction (DM: -0.59 mg/dL). Blood pressure: Quetiapine XR was associated with the largest increase in SBP (DM: +2.60 mmHg) and DBP (DM: +2.77 mmHg).
Rotella F, et al. (2020)	Meta-analysis of 92 RCTs. Duration: ≥52 weeks.	Lipid profile Blood pressure (mmHg)	Olanzapine showed the worst impact on TC and TG. Olanzapine and quetiapine elevated SBP/DBP in comparison with risperidone.
Carnovale C, et al. (2021)	Network meta-analysis of 46 studies-Sample: 11,464 patients. Duration: 15.5 weeks average.	HOMA-IR Serum fasting insulin (μU/mL) HbA1c (%)	HOMA-IR: Aripiprazole showed the most decrease (DM: -0.80), followed by quetiapine (DM: -0.30), ziprasidone (DM: -0.20), and (DM: -0.07), while olanzapine and lurasidone showed a neutral impact (DM: -0.01 for both). Serum fasting Insulin: The largest increases were seen with olanzapine (DM: +1.49), lurasidone (DM: +1.19), quetiapine (DM: +0.96), and paliperidone (DM: +0.77). In contrast, risperidone had a neutral effect (DM: -0.02), while aripiprazole (DM: -0.61) and ziprasidone (DM: -0.84) were associated with the largest decreases. HbA1c: Ziprasidone was associated with the largest reduction (DM: -0.20), followed by risperidone (DM: -0.02). Olanzapine and quetiapine had a neutral effect (DM: 0.00 for both), and lurasidone was associated with a slight increase (DM: +0.02).
Bernardo M, et al. (2021)	Systematic review of population-based studies.	Risk of diabetes, dyslipidemia, hypertension	Clozapine and olanzapine were consistently associated with higher risk of diabetes and dyslipidemia. Ziprasidone was associated with hypertension risk.
Iasevoli F, et al. (2020)	Systematic review with studies on subjects neurodevelopmental disorders.	Weight gain	Aripiprazole, quetiapine, olanzapine, clozapine and risperidone were associated with weight gain in this specific population.
Hirsch L, et al. (2017)	Systematic review of population-based studies.	Risk of diabetes, dyslipidemia, hypertension.	Aripiprazole was not associated with dyslipidemia. Olanzapine, quetiapine and ziprasidone were associated with hypertension.
Sneller MH, et al. (2021)	Systematic review of 58 studies. Sample: 12,123 patients.	Risk factors for MetS.	Advanced age, higher baseline and current BMI, higher antipsychotic dose, longer duration of treatment and smoking were significantly associated with the presence of MetS.

BMI: Body mass index. CAT: Computerized tomography. CRWG: Clinically relevant weight gain. DBP: Diastolic blood pressure. DEXA: dual x-ray absorptiometry. DM: Diabetes mellitus. FBG: Fasting blood glucose. FEP: First-episode psychosis. FGA: First-generation antipsychotic. HOMA-IR: Homeostasis model assessment-insulin resistance. LAI: Long-acting injection. LDL-C: Serum low-density lipoprotein cholesterol. HDL-C: Serum high-density lipoprotein cholesterol. MED: Minimum effective dose. MetS: Metabolic syndrome. RCT: Randomized controlled trial. SBP: Systolic blood pressure. SCZ: Schizophrenia. SGA: Second-generation antipsychotic. TC: Total serum cholesterol. TG: Serum triglycerides.

Inflammatory Markers: A nuanced immunomodulatory outlook for SGAs

A complex interplay has been recognized involving SCZ and other severe mental illnesses, metabolic disturbances, and immune dysfunction. SGAs, beyond their effects on neurotransmitter systems, can also exert a significant yet heterogeneous influence over peripheral inflammatory markers, such as cytokines and acute-phase proteins. This immune modulation may contribute both to the therapeutic effects and the cardiometabolic risks of these drugs[40-42].

In a meta-analysis of 12 clinical studies with 427 patients with FEP, Marcinowicz et al.[41] found significant reductions in concentrations of several pro-inflammatory cytokines, such as IL-1β (p=0.006), IL-6 (p=0.0001), TNF-α(p=0.03) and IFN-γ (p=0.003). They also identified reductions in predominantly anti-inflammatory cytokines like IL-4 (p=0.01) and IL-10 (p=0.02). On the other hand, no significant changes were observed in the levels of IL-2 (p=0.85) or IL-17 (p=0.51). Altogether, this picture suggests antipsychotic treatment in early psychosis may be linked with a general attenuation of immune activity, rather than a definite shift between pro-inflammatory and anti-inflammatory states.

Nevertheless, evidence in this area is far from harmonic. In a 6-week prospective study by Zhao et al.[43] with 142 ANP diagnosed with a FEP who were treated with olanzapine, IL-8 levels decreased significantly (p<0.001), yet concentrations of IL-10 and TNF-α were also increased (p<0.05 for each). Likewise, in a cohort of 40 SCZ patients, Kamaeva et al.[44] compared the effects of treatment with FGAs vs risperidone, quetiapine and olanzapine on levels of circulating cytokines. Interestingly, exposure to SGAs was related to a significant reduction of IL-6 concentrations (p=0.036), whereas patients treated with FGAs displayed an increase of several pro-inflammatory cytokines. This may point to drug-specific immunomodulatory features.

Moreover, these effects may be modified by subjects' metabolic state. In a 6-week prospective study by Boiko et al.[45]. With 101 SCZ patients, changes in cytokine levels were assessed after treatment with SGAs (risperidone, quetiapine, olanzapine or aripiprazole) and classifying patients according to the presence of MetS. In patients without this condition, treatment was associated with a reduction in pro-inflammatory cytokines (IFN-γ, p=0.011; IL-1β, p=0.035; IL-6, p=0.043; and TNF-α, p=0.012). In contrast, in patients with MetS, treatment was linked

with increases in other cytokines (IFN-α2, p=0.010; IL-1α, p=0.024; e IL-7, p=0.017). These findings suggest that metabolic comorbidity can significantly modify the immunomodulatory effects of SGAs.

The immunometabolic impact of SGAs may also hinge on disease state. In a cohort of 60 stable SCZ patients, Koricanac et al.[46] found TNF-α levels were positively correlated with FBG and HOMA in patients treated with risperidone, as well as with BMI in the clozapine group. Likewise, IL-33 concentrations were correlated with FBG in the risperidone group and with BMI in the clozapine group; whereas TGF-β levels were correlated with FBG in patients treated with risperidone, with serum insulin concentrations and HOMA in those treated with clozapine and negatively correlated with LDL-C in those treated with aripiprazole.

Indeed, discerning between the effects of the SGAs and the pathologies themselves on the immune state is essential in this context. In a meta-analysis of 28 studies on healthy volunteers, Burghardt et al.[47] found no significant effect was found between antipsychotic treatment and individual inflammatory markers such as IL-6 or TNF-α. However, when assessing the latter as a joint category, a statistically significant effect was found (SMD=0.347, p=0.013). Thus, the impact of SGAs on the immune system in the absence of active psychiatric pathology may be subtle and require added measures for detection

Evidence on C-Reactive Protein (CRP) remains relatively scarce in this field. In a 12-month RCT with 128 patients treated with amisulpride, aripiprazole or olanzapine, Fathian et al.[48] scertained an upwards trend on CRP levels for all groups. Nonetheless, aripiprazole was related to a transitory and significant reduction of CRP during the first week of treatment. In addition, ANP displayed consistently lower serum CRP concentrations at all times throughout follow-up.

Clozapine presents an especially complex immunomodulatory profile. A systematic review of 75 studies by Leung et al.[49] highlighted chronic treatment with clozapine to be consistently associated with elevated levels of CRP, IL-6 and TNF-α, in comparison with healthy controls.

De forma complementaria, el metaanálisis de Martins et al.[50] basado en 19 estudios, confirmó que el tratamiento con clozapina aumenta los niveles de IL-6 y activa sistemas inmuno-reguladores compensatorios (CIRS) (Hedges's g = +1.049; IC 95% +0.62 – +1.47, p < 0.001). Además, el estudio longitudinal de Karampas et al.[51] en 53 pacientes con TRS observó que, tras el cambio a clozapina, los niveles de resistina e IL-4 aumentaron significativamente (p < 0.001 y p = 0.030, respectivamente), mientras que los de adiponectina disminuyeron (p < 0.001), cambios que pueden reflejar tanto una acción farmacológica directa como las alteraciones metabólicas inducidas por el fármaco.

Currently available evidence indicates SGAs possess complex immunomodulatory properties with -an overall trend towards reducing systemic inflammation in early stages of psychosis and treatment. However, these effects are broadly heterogeneous and depend on the specific drug, treatment duration, and crucially, on subjects' baseline metabolic state. In particular, the presence of MetS appears to dampen or annul these potential benefits. Lastly, clozapine bears unique pro-inflammatory characteristics that may be intrinsically bound both to superior efficacy and its greater load of metabolic adverse effects[45,50,42].

Thrombotic risk: Disentangling the impact of antipsychotics vs psychosis itself

Beyond chronic inflammation, SGA use has also been linked to greater risk of venous thromboembolism (VTE), which has been related to significant morbidity and mortality in patients with SCZ. This risk appears to be multifactorial, implicating direct and indirect alterations of platelet activation, endothelial function, and the coagulation cascade[52,53].

In this regard, the meta-analysis by Liu et al.[54] encompassing 28 observational studies demonstrated current antipsychotic users to have a significantly higher risk of VTE in comparison to non-users (OR = 1.55; CI 95%: 1.36–1.76). The risk was particularly elevated for pulmonary embolism (PE) (OR = 3.68; CI 95%: 1.23–11.05) and patients who had recently begun treatment (OR = 2.06; CI 95%: 1.81–2.35). Analysis of individual drugs associated VTE risk with haloperidol, risperidone, olanzapine, and prochlorperazine. Similarly, in an assessment of 1,169 VTE events reported for 6 SGAs on the FDA Adverse Event Reporting System (FAERS) database, olanzapine (PRR = 2.63; CI 95%: 2.50–2.76) and quetiapine (PRR = 2.18; CI 95%: 2.05–2.32) were found to be disproportionally associated with increased reporting of VTE. On the other hand, risperidone showed a specific signal for deep venous thrombosis (PRR = 2.12; CI 95%: 1.92–2.33). Notably, in this study, aripiprazole and clozapine did not reach the signal threshold for increased VTE risk[55].

In line with these findings, in a meta-analysis by Di et al.[56] on 14 case-control studies and 8 cohort studies, a combined OR of 1.60 (CI 95%: 1.39–1.85) was ascertained for antipsychotic-associated VTE risk. Jointly, this high-level epidemiological evidence delineates a clear SGA use and thrombosis which merits exploration of the underlying mechanisms. Platelet activation may be important in this context. However, the role of SGAs in thrombosis is probably indirect or off-target, mediated by mechanisms unrelated to their primary targets, which may be metabolic or inflammatory in nature. This has been suggested by findings such as those of Li et al.[57,58] in another evaluation of the FAERS concerning 16 antipsychotics, where Mendelian randomization analysis found no direct causal relationship between the expression of the main target receptors of antipsychotics and VTE risk.

At any rate, appraisal of thrombotic markers is complex in this scenario, as SCZ is known to be associated with a state of hypercoagulability even before treatment with antipsychotics. This was identified in a case-control study by Zheng et al.[59] who compared 27 drug-naive patients with FEP, 27 patients with previously diagnosed SCZ, and 27 healthy control. At baseline, patients with FEP showed significantly higher levels of various prothrombotic and endothelial dysfunction markers in comparison with controls, including plasminogen activator inhibitor-1 (PAI-1) (median 28.61 ng/mL vs. 15.69 ng/mL; p = 0.006), soluble P-selectin (sP-sel) (2.78 ng/mL vs. 1.18 ng/mL; p = 0.009), and thrombus precursor protein (TpP) (15.61 μg/mL vs. 5.59 μg/mL; p < 0.001). Curiously, acute treatment (4-8 weeks) with SGAs in patients with FEP partially normalized this profile, significantly reducing levels of sP-sel, tPA, and TpP, as well as von-Willebrand factor. Nonetheless, patients with pre-established diagnoses of SCZ and protracted treatment with SGAs had much higher markers than FEP patients before treatment, outlining the important chronic prothrombotic effects of SGA use.

Although this evidence is enticing, most data assessing SGA use and thrombotic risk stems from retrospective or small-sample studies. Further prospective and controlled studies with larger samples are needed to corroborate this preliminary panorama, as well as to more precisely quantify risk for different drugs. This is fundamental in order to improve risk stratification and preventive interventions in clinical practice[53,57].

Table 2. Summary of clinical evidence on the relationship between SGAs and inflammatory and prothrombotic markers.

Authors (year)	Methods	Results
Inflammatory Markers		
Marcinowicz et al. (2021)	Meta-analysis of 12 clinical studies. Sample: 427 patients with FEP. Duration: Variable.	Significant reduction of levels of IL-1β (p=0.006), IL-6 (p=0.0001), TNF-α (p=0.03), IFN-γ (p=0.003), IL-4 (p=0.01) and IL-10 (p=0.02) after antipsychotic treatment.
Kamaeva et al. (2023)	Comparative clinical study. Sample: 40 patients with SCZ (25 on SGAs, 15 on FGAs). Duration: 6 weeks.	Treatment with SGAs significantly lowered IL-6 levels (p=0.036), while FGAs were associated with an increase in proinflammatory cytokines.
Zhao et al. (2024)	Prospective study. Sample: 142 drug-naive patients with FEP. Duration: 6 weeks.	Treatment with olanzapine reduced IL-8 concentrations (p<0.001), but increased IL-10 and TNF-α concentrations (both p<0.05).
Boiko et al. (2021)	Prospective clinical study. Sample: 101 patients with SCZ, categorized by presence/absence of MetS. Duration: 6 weeks.	The effects of SGAs depended on the presence of MetS: Without MetS: □IFN-γ (p=0.011), □IL-1β (p=0.035), □IL-6 (p=0.043), □TNF-α (p=0.012). With MetS: □IFN-α2 (p=0.010), □IL-1α (p=0.024).
Koricanac et al. (2022)	Cross-sectional, comparative clinical study. Sample: 60 stable patients with SCZ.	Correlation of serum TNF-α levels with fasting blood glucose (Rho=0.515, p=0.020) and HOMA (Rho=0.499, p=0.025) in patients on risperidone.
Fathian et al. (2022)	Randomized controlled trial. Sample: 128 patients with SCZ. Duration: 12 months.	Aripiprazole was associated with a transient reduction of CRP levels in comparison with amisulpride in the first week of treatment (b=-0.98, p < 0.01).
Martins et al. (2023)	Meta-analysis of 19 studies. Sample: 689 patients treated with clozapine. Duration: Variable.	La clozapina aumenta IL-6 y activa CIRS (Hedges's g = +1.049; IC 95%: +0.62 – +1.47, p < 0.001).
Leung et al. (2023)	Systematic review of 75 studies. Sample: Patients treated with clozapine. Duration: Variable.	Chronic treatment with clozapine is consistently associated with higher levels of CRP, IL-6 and TNF-α.
Karampas et al. (2024)	Prospective study. Sample: 53 patients with treatment-resistant SCZ. Duration: 12 weeks (clozapine phase).	Clozapine treatment significantly increased levels of resistin (p < 0.001) and IL-4 (p = 0.030), and decreased adiponectin (p < 0.001).
Kose et al. (2021)	Systematic review of 17 studies. Sample: Patients with psychosis. Duration: Variable.	Higher levels of CRP and IL-6 were associated with worse clinical outcomes. Higher levels of IL-10 were associated with symptom improvement.
Burghardt et al. (2022)	Meta-analysis of 28 studies. Sample: Healthy volunteers. Duration: Variable.	No apparent effect when assessing individual cytokines. A general pro-inflammatory effect was observed when evaluating the markers as a whole (SMD=0.347, p=0.013).
Prothrombotic Markers		
Liu et al. (2021)	Meta-analysis of 28 observational studies. Sample: Aggregate data. Duration: Variable.	SGA use was associated with increased risk of VTE (OR=1.55; CI 95%: 1.36–1.76) and PE (OR=3.68; CI 95%: 1.23–11.05). The risk was greater in new users (OR=2.06; CI 95%: 1.81–2.35).
Di et al. (2021)	Meta-analysis of 22 studies (14 case-control studies, 8 cohort studies). Sample: Aggregate data. Duration: Variable.	Antipsychotic use was associated with increased risk of VTE (OR=1.60; CI 95%: 1.39–1.85).
Zheng et al. (2023)	Case-control study. Sample: 81 subjects (27 FEP, 27 CS, 27 controls). Duration: Cross-sectional and 4-8 weeks of follow-up for the FEP group.	Drug-naïve FEP patients showed baseline hypercoagulability vs controls: □PAI-1 (p=0.006), □sP-sel (p=0.009), □TpP (p<0.001). Acute treatment with SGAs improved this profile.
Kim et al. (2019)	Retrospective study. Sample: 16 patients with SCZ. Duration: 1-6 weeks.	Significant reduction of MPC after initiation of SGAs (from 26.67 to 25.21 g/dL; p=0.01).
DeLoughery (2024)	Pharmacovigilance analysis. Sample: 1,169 reports VTE in FAERS database for 6 SGAs. Design: Evaluation of PRR.	Olanzapine (PRR = 2.63; CI 95%: 2.50–2.76) and quetiapine (PRR = 2.18; CI 95%: 2.05–2.32) showed a disproportionate signal for VTE risk. Risperidone returned a signal for DVT (PRR = 2.12; CI 95%: 1.92–2.33).
Masopust et al. (2019)	Case series. Sample: 10 patients with VTE treated with olanzapine.	6 of 10 events occurred within the first 6 months of treatment. All patients had comorbid risk factors (obesity n=7, smoking n=6).
Li et al. (2024)	Data mining of the FAERS and Mendelian randomization analysis. Sample: Large-scale database. Duration: N/A.	No causal association was found between the expression of SGA target genes and VTE risk (e.g., in brain tissue p=0.317).

CRP: C-reactive protein. DVT: Deep venous thrombosis. FAERS: FDA Adverse Events Reporting System. CIRS: sistemas inmuno-reguladores compensatorios. FEP: First-episode psychosis. FGA: First-generation antipsychotic. HOMA: Homeostasis model assessment. MetS: Metabolic syndrome. PE: pulmonary embolism. SCZ: Schizophrenia. SGA: Second-generation antipsychotic. VTE: Venous thromboembolism.

Cardiovascular disease: Critical differences between long- and short-term risk

The impact of SGAs on cardiovascular health is a central clinical preoccupation. Current evidence on their link with major events—such as coronary artery disease (CAD), stroke, heart failure (HF) and arrhythmias—is complex and varies with specific agents, patient features and clinical setting, and thus merits a detailed examination[60,36].

In a meta-analysis of 53 cohort studies which included more than 2,5 million patients with SCZ, Solmi et al.[61] determined clozapine specifically to be associated with lower risk of cardiovascular mortality in comparison to subjects without treatment. In contrast, in cohorts of patients with FEP, use of FGAs was associated with increased cardiovascular and cerebrovascular mortality (RR=1.70; IC 95%: 1.20-2.41), while SGAs were neutral in this regard. Complementarily, in a 20-year follow-up study (median: 14.1 years) on 62,250 patients with SCZ, Taipale et al.[62] found use of any antipsychotic was not associated with increased risk of hospitalization due to cardiovascular causes (aHR=1.00; CI 95%: 0.92-1.07). On the contrary, antipsychotic use was related with substantially lower cardiovascular mortality (aHR=0.62; CI 95%: 0.57-0.67), clozapine most prominently (aHR=0.55; CI 95%: 0.47-0.64).

Beyond global cardiovascular mortality, data on specific events is also valuable. In a population-based matched cohort study on 35,339 patients with newly prescribed antipsychotics, after 90 days of treatment, Mok et al.[63] determined an increased risk of stroke (HR=1.61; CI 95%: 1.52-1.71), myocardial infarction (HR=1.28; CI 95%: 1.15-1.42), and HF (HR=1.27; CI 95%: 1.18-1.37). In line with this, in a case-control study on patients with SCZ in China, Peng et al. (60) reported antipsychotic use to be related with increased risk of any CVD ECV (weighted OR=1.54; CI 95%: 1.32-1.79), principally owing to CAD (weighted OR=2.26; CI 95%: 1.71-2.99).

Patient-specific characteristics also bear an important influence. In a retrospective cohort study with over a million patients, Lai et al.[64] found antipsychotic use to be linked with a 32% rise in the risk of acute CAD in females (HR: 1.32; CI 95%: 1.05-1.67), and not in males. Likewise, treatment adherence also appears to be relevant. In a cohort study by Perreault et al.[65] on 42,650 new users of antipsychotics aged 66 years and older with a 5-year follow-up, higher treatment adherence (≥60%) was associated with greater risk of cardiovascular events in comparison with lower adherence (<60%): 36% greater for antipsychotic users with SCZ, and 25% as much for those with dementia

In regards to arrhythmias, evidence is more disparate. Extensive studies such as the report by Mok et al.[63] have not found a significant relationship between ventricular arrhythmia and antipsychotic use. However, research on their role as a risk factor for QTc interval prolongation is abundant.

Concerning arrhythmias, evidence is more nuanced. While Mok et al.[63] found no increased risk of ventricular arrhythmia associated with the use of antipsychotics, research on risk factors such as QTc interval prolongation is extensive. A secondary analysis of a randomized clinical trial conducted by Stollings et al. in 566 ICU patients with delirium found that intravenous ziprasidone did not significantly increase QTc intervals compared with placebo[66]. Similarly, He et al.[67] conducted a retrospective cohort study based on a hospital information system that included 5,130 patients with schizophrenia to compare the risk of QTc prolongation associated with SGAs, concluding that ziprasidone, amisulpride, and olanzapine were the only SGAs associated with a higher risk of QTc prolongation.

In summary, at present, findings suggest that although antipsychotics may reduce cardiovascular mortality in the long term in patients with SCZ; significant increases in the risk of ischemic events and HF are seen in the short term, especially in more vulnerable patients, such as elderly subjects with dementia. On the contrary, the risk of clinically significant arrhythmias seems to be low[61-63].

Table 3. Summary of clinical evidence on the relationship between SGAs and diabetes and cardiovascular disease as clinical outcomes.

Authors (Year)	Methods	Results
Diabetes as outcome		
Bernardo et al. (2021)	Systematic review. Sample: 40 population-based studies on adult patients treated with SGAs. Follow-up: Variable.	Clozapine and olanzapine were consistently associated with higher risk. Risperidone and quetiapine returned mixed results. Aripiprazole and ziprasidone did not show a clear increase in risk.
Hirsch et al. (2017)	Systematic review. Sample: 15 population-based studies on patients treated with SGAs. Follow-up: Variable.	Clozapine and olanzapine showed the stronger association. Moderate and mixed evidence was found for risperidone and quetiapine.
Poulos et al. (2023)	Cohort analysis (TMLE model). Sample: 38,762 adult patients with severe mental illness. Follow-up: 3 years.	Compared with a reference low-risk SGA, absolute risk at 3 years increased with risperidone (+1.4 percentage points; CI 95%: 0.7–2.2) and olanzapine (+1.9 percentage points; CI 95%: 1.0–2.8).
Vassilopoulou et al. (2021)	Prospective study. Sample: 35 forensic psychiatry patients in treatment for >5 years. Follow-up: 3 years.	The group receiving SGAs with high metabolic risk (e.g. olanzapine, clozapine) required antidiabetic medication more often than those on SGAs with low-moderate metabolic risk.
Cardiovascular disease as outcome		
Solmi et al. (2024)	Meta-analysis. Sample: 53 cohort studies (>2.5 million patients) with SCZ. Follow-up: N/A.	In patients with FEP, FGAs increased risk (RR=1.70; CI 95%: 1.20–2.41), while SGAs had a neutral effect.
Taipale et al. (2020)	National cohort study including 62,250 patients with SCZ. Follow-up: Up to 20 years.	Antipsychotic use reduced CV mortality (aHR=0.62; CI 95%: 0.57–0.67), but had no effect on the risk of CV hospitalization (aHR=1.00; CI 95%: 0.92–1.07).
Mok et al. (2024)	Population-based matched cohort study on 35,339 dementia patients with newly prescribed antipsychotics. Follow-up: 90 days.	Increased risk of stroke (HR=1.61; CI 95%: 1.52–1.71), myocardial infarction (HR=1.28; IC 95%: 1.15–1.42) and heart failure (HR=1.27; IC 95%: 1.18–1.37).
Peng et al. (2023)	Case-control study in cohort of Chinese patients with SCZ. Follow-up: Variable.	Increased risk for all CVD (OR=1.54; CI 95%: 1.32–1.79), mainly for CAD (OR=2.26; CI 95%: 1.71–2.99)
Perreault et al. (2024)	Cohort study on 42,650 new antipsychotic users aged >66 years. Follow-up: 5 years.	High adherence (≥60%) increased the risk of CVD and cerebrovascular disease by 36% for SGA users with SCZ, and by 25% for FGA users with dementia
Stollings et al. (2024)	Secondary analysis of RCTs. Sample: 566 ICU patients with delirium. Follow-up: Acute.	Haloperidol and ziprasidone did not significantly increase QTc interval vs placebo.

CAD: coronary artery disease. CVD: Cardiovascular disease. FEP: First-episode psychosis. FGA: First-generation antipsychotic. RCT: Randomized controlled trial. SCZ: Schizophrenia. SGA: Second-generation antipsychotic. TMLE: Targeted minimum loss-based estimation.

Conclusions

The load of cardiometabolic adverse effects imposed by SGAs should not represent a deterrent for their use, as for most patients, benefits may still outweigh disadvantages[68]. However, this landscape does highlight the advantages of performing individualized cardiometabolic risk assessment from the beginning of treatment, shifting the focus on drug selection from chiefly prioritizing efficacy.

Thus, key points for future research revolve around enhancing the monitoring and diagnosis of these cardiometabolic disturbances, as well as interventions for their prevention and treatment. Regarding the former, highly precise evaluation tools such as direct measures of body composition, the euglycemic-hyperinsulinemic clamp and systematic surveillance of HbA1C levels remain underutilized in patients on SGAs. Further investigation involving these, along with their implementation in clinical practice, may yield valuable improvements in risk assessment and clinical outcomes. Consequently, they may aid in the selection of preventive and therapeutic interventions; which themselves constitute an independent object of study in patients on SGAs, especially concerning their efficacy and safety.

Moreover, certain clinically relevant populations remain underexplored, in particular children and adolescents. Likewise, at present, most research focuses on patients with psychotic disorders; yet SGAs are widely prescribed—for both off-label and approved uses—for several other conditions, including bipolar disorders, depressive disorders, anxiety disorders, obsessive-compulsive disorders and many others. Given the particularities of the SCZ-chronic inflammation-SGAs, it may be valuable to analyze the cardiometabolic response to these agents in other disorders, as clinically significant differences may be ascertained.

Finally, a call to action is in order. Historically, psychiatric patients, most prominently those with psychotic disorders have seen their biopsychosocial needs neglected systematically, with their physical health and care being no exception. Upon the pressing presence of the CVD epidemic and the extensive use of SGAs, improving the management of the cardiometabolic health of patients on SGAs should be considered a priority for public health systems and research.

LIST OF ABBREVIATIONS

aHR = adjusted Hazard Ratio ANP = Antipsychotic-naïve Patients BMI = Body Mass Index CAD = Coronary Artery Disease CIRS = Compensatory Immune-Regulatory Systems CRP = C-Reactive Protein CRWG = Clinically Relevant Weight Gain CT = Computerized Tomography CVD = Cardiovascular Disease DBP = Diastolic Blood Pressure DEXA = Dual X-ray Absorptiometry DM / DM2 = Diabetes Mellitus / Type 2 Diabetes Mellitus DVT = Deep Venous Thrombosis FAERS = FDA Adverse Events Reporting System FBG = Fasting Blood Glucose FEP = First-Episode Psychosis FGA = First-Generation Antipsychotic HDL-C = Serum High-Density Lipoprotein Cholesterol HF = Heart Failure HOMA / HOMA-IR = Homeostasis Model Assessment / Homeostasis Model Assessment-Insulin Resistance IR = Insulin Resistance LAI = Long-Acting Injection

LDL-C = Serum Low-Density Lipoprotein Cholesterol MetS = Metabolic Syndrome NMA = Network Meta-Analysis OR = Odds Ratio PE = Pulmonary Embolism PRR = Proportional Reporting Ratio QTc = Corrected QT Interval RCT = Randomized Controlled Trial RR = Relative Risk SBP = Systolic Blood Pressure SCZ = Schizophrenia SGA = Second-Generation Antipsychotic SMD = Standardized Mean Difference TC = Total Serum Cholesterol TG = Serum Triglycerides TMLE = Targeted Minimum Loss-Based Estimation TRS = Treatment-Resistant Schizophrenia VAT = Visceral Adipose Tissue VTE = Venous Thromboembolism WC = Waist Circumference

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