

Cardiovascular and metabolic side effects of second-generation antipsychotics – narrative review

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Abstract

Since their introduction, the use of second generation antipsychotics (SGAs) has extended far beyond schizophrenia. With the increased usage of these agents, particular attention has been paid to their metabolic and cardiac side effects. This narrative review is an attempt to briefly summarize the conclusions from recently published systematic reviews on cardio-metabolic side effects of SGAs. Although no SGA is entirely free of these adverse effects, there are major differences in their prevalence between the specific medications. Numerous studies demonstrated particularly unfavorable side effect profiles of olanzapine and clozapine. The lack of conclusive data is a major limitation for many studies, particularly in the pediatric population. In this article we also discussed the meanings of these findings, suggested cardio-metabolic screening during SGA treatment and side effect management strategies.

Keywords: antipsychotics • adverse drug effects • metabolic side effects of drugs • narrative review

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Introduction

Since the introduction of second generation of antipsychotics (SGAs) in the 1990's, their indications have expanded beyond schizophrenia and include other disorders with psychotic symptoms, e.g. bipolar disorder or psychotic depression. More recently, increasing off-label prescribing of SGAs has been noted for the treatment of non-psychotic disorders, e.g. obsessive-compulsive disorder, personality disorders, anxiety disorders as well as child and adolescent mental health disorders [1-2].

There is a growing concern that with increased prevalence of treatment with antipsychotics, their side effects will also become also more prevalent [1]. The older first-generation antipsychotics (FGAs) were tolerated by only a limited group of patients, therefore SGAs were designed to have less harmful, at least with regard to extrapyramidal symptoms [3]. However, many studies have shown that SGA use is associated with significant risk of side effects outside the central nervous system, e.g. cardiovascular events (myocardial infarction, cerebral stroke) and metabolic disease (type 2 diabetes, weight gain) [3]. From the practical point of view, the above-mentioned risks should be assessed together instead of separately [4]. In recent years, more attention has been paid to the incidence of the above-mentioned disorders in drug-naïve or untreated individuals with severe mental disorders [5]. This may also suggest their intrinsic susceptibility to cardio-metabolic consequences and can be regarded as risk factor itself [4].

Well-established treatment effectiveness of SGAs, without comparable alternative treatment options, pushes mental health professionals to still rely on these drugs. Thus, there is a need for highest-quality scientific evidence to make the appropriate clinical decisions regarding treatment with antipsychotics. The purpose of this article is to provide a brief and practical overview of SGAs' cardio-metabolic side effects, based on the recently published meta-analyses and systematic reviews.

Materials and methods

This is a narrative type of review. Independent English-language literature search has been done by two first authors (PMW, NAP) was done on the 15th of November 2018, using the Scopus, Google Scholar and PubMed databases. We used a query containing title keywords "atypical" OR "second generation" AND "antipsychotics" AND "systematic review" combined with appropriate set of keywords from the particular topic of our interest e.g. weight gain, diabetes, meta-

bolic syndrome, dyslipidemia, cardiovascular events (myocardial infarction, cerebral stroke) and child and adolescents mental health. A detailed cross-review of references was also carried out if necessary. We focused mainly on articles published in the last five years. Exclusion criteria were: non-clinical laboratory research, single-drug studies, articles analyzing assessment and management of SGAs side effects. Due to narrative format of this review, no statistical calculations were performed.

Results

Weight gain

Weight gain is the side effect of antipsychotic treatment most frequently observed by patients. Furthermore, weight gain is also the most frequently analyzed variable in studies on the metabolic effects of antipsychotics. A large meta-analysis that included more than three hundred studies, revealed that almost all antipsychotics cause weight gain, especially in case of prolonged use (defined as >38 weeks) [6].

Olanzapine and clozapine were the most significantly associated with weight gain, while risperidone was less frequently reported in the analyzed studies [7]. In detail, clozapine was associated with the greatest risk of weight gain, with a high rate of >10% increase above the original body weight. To make matters worse for the patients, there is no convincing evidence that they will stop gaining weight stop once the SGA is discontinued [7]. No drug caused weight loss, whilst amisulpride, aripiprazole and ziprasidone were associated with no significant weight change [6].

Metabolic syndrome

The data from systematic review and meta-analysis suggest that patients receiving antipsychotics are at higher risk of metabolic syndrome, compared to those who are antipsychotic-naïve. The prevalence of metabolic syndrome is significantly higher with clozapine (47.2%, 95% CI:42%-52.6%); followed by olanzapine and quetiapine; (36.2%, 95% CI: 31.8%-40.9%) and 37,3% (37.3%, 95% CI:24.7%-47.8%) respectively. Patients treated with aripiprazole had lower odds of metabolic syndrome compared to other medications (19.4%, 95% CI:8%-34,2%) [8].

Type 2 diabetes

In a systematic review of the literature on population-based studies of SGA and metabolic dysfunction,

Hirsch et al. found strong association of using olanzapine and type 2 diabetes (T2DM) with seven out of nine studies showing correlation between olanzapine and this adverse event [9]. Also clozapine seems to carry greater risk of diabetes with three of four studies showing this association. The evidence was equivocal for risperidone and quetiapine, indicating that further research is needed to define relationship between other SGAs and T2DM [9].

Dyslipidemia

Dyslipidemia has rarely been analyzed in population studies. In the few published studies, SGAs were compared to heterogeneous substances (e.g. placebo, antidepressants) and non-uniform measurement methods were used (e.g. lipid profile, co-prescribed lipid-lowering drug). Olanzapine and clozapine also appear to be strong risk factors here, although the data is highly inconclusive. Aripiprazole may also be associated with dyslipidemia, while risperidone appears to be unrelated or even protective [9].

Hypertension

We identified only one systematic review which analyzed the association between treatment with SGAs and hypertension. It showed significant association between hypertension and olanzapine, quetiapine and ziprasidone treatment, while aripiprazole and risperidone were not associated with increased blood pressure [9].

Children and adolescents

The pediatric population is a special group due to the possible influence of drug side effects on further organ development. As noted earlier, the use of antipsychotics, especially SGAs, has significantly increased in this population. We adopted age criteria defined by Pillay et al. 2018, (≤ 24 years) [10].

In the pediatric population, SGAs have been shown to have a stronger effect on weight gain compared to FGAs. Metabolic complications were significantly more frequent in the SGAs than in the placebo/no treatment groups. In general SGAs caused 0.043 kg weight gain [95% CI, 0.015 to 0.072] per week of additional treatment [10]. The Network Meta-analyses for Body Composition comparison Outcomes compared the effects for individual drugs. The use of olanzapine was associated with the largest increase in body weight - an average of 4.12 kg (of BMI 1.51 kg/m²). Whereas risperidone (1.85 kg), quetiapine (1.25 kg) and aripiprazole (0.88 kg) have respectively milder effects. The other drugs' studies did not have consistent

results. Majority of the above results were drawn from studies with short follow-up (6-12 weeks). There were no significant dose-dependent differences in weight gain (Aripiprazole 15/30 mg /d vs. 10 mg /d; Asenapine 10 mg /d vs. 5 mg /d; Quetiapine 600/800 mg /d vs 400 mg /d) [10].

In the short-term, there were no differences in the occurrence of a pathologically prolonged QT interval between the SGAs and placebo administered groups [11]. Studies on serious complications have low levels of evidence, mainly due to small study samples secondary to the rarity of their prevalence. Studies on dyslipidemia and hyperprolactinemia were also characterized by equivocal results and frequently insignificant p values. However, in subgroup analysis, quetiapine and risperidone may increase serum prolactin more frequently in females than in males [10].

Compared to placebo, patients treated with any SGA for >1 year may have an increased risk of diabetes, 7.8 vs. 25.3 cases per 10,000 person-years follow-up (HR, 2.89, 95% CI, 1.64 to 5.10) [12]. What is important, this effect may persist up to one year after discontinuation of treatment (at least for the drugs tested in this analysis - risperidone, olanzapine, aripiprazole, quetiapine, and ziprasidone) [12]. Further large, observational studies are highly needed.

QTc prolongation

It is well-known that drug-induced changes in the QTc (Corrected QT Interval) can cause severe cardiac arrhythmias, including sudden cardiac death. In an extensive review, Hasnain & Vieweg (2014) did not find a clear link between drug-related QTc prolongation and Torsade de pointes and instead the authors draw attention to a much larger share of other QTc prolongation risk factors [13]. Due to inconsistent evidence, no attempt was made to stratify the risk of QTc prolongation depending on the SGA used, with exception to sertindole which causes statistically and clinically significant prolongation of the QTc interval [13]. Similarly, „limited but emerging data” showed potential association of iloperidone, clozapine, ziprasidone and quetiapine can cause prolonged QTc interval, while olanzapine and risperidone have modest effect [13]. Data from a systematic review of poly-pharmacotherapy confirm that the combination of these drugs may result in a clinically significant prolongation of the QTc interval [14].

Cerebrovascular and cardiovascular events

Schizophrenia itself is associated with a higher incidence of stroke, cardiovascular disease, congestive heart failure, and might also increase the risk of coro-

nary heart disease [15]. Because of their direct correlation with mortality, cerebrovascular incidents have a special clinical position among the analyzed adverse drug effects. The conclusions from a systematic review underline increase in the risk of cerebrovascular events in patients receiving any antipsychotic drug (OR 1.45; 95% CI 1.24-1.70) [16]. In subgroups analysis, particularly high risk has been reported in patients using FGAs (OR 1.49 95% CI 1.24-1.77). Slightly smaller, though not statistically significant, increased risk was reported for SGAs (OR 1.31, 95% CI 0.74- 2.30). The authors emphasize the significant divergence of component test results. In addition, the use of any antipsychotics in patients with dementia was associated with only a moderate increase in cerebrovascular event risk (OR 1.17, 95% CI 1.08-1.26) [16].

The use of any antipsychotic drug increased the risk of acute myocardial infarction compared to placebo (OR 1.88, 95% CI 1.39, 2.54) [17]. The analysis showed a divergence of this risk between FGAs (OR 2.19, 95% CI 1.46, 3.28) and SGAs (OR 1.72, 95% CI 0.96, 3.07). In one of the included studies, a significant increase in the risk of acute myocardial infarction was associated with the use of amisulpride (OR 5.65, 95% CI 2.97, 10.76) [17]. The subgroups analysis showed a significantly increased risk in patients with schizophrenia (OR 2.48, 95% CI 1.66, 3.69) and dementia (OR 1.82, 95% CI 1.16, 2.84). When the duration of treatment was analyzed, there was a significant reduction in the risk of acute coronary syndrome over time, with an odds ratio of 2.64 (95% CI 2.48, 2.81), 1.59 (95% CI 1.17, 2.18), 1.35 (95% CI 1.09, 1.67) respectively on 30 to 60 and 90 days since the beginning of antipsychotic treatment [17].

Discussion

When managing pharmacological treatment, clinician should always have in mind the potential adverse effects of prescribed drugs, because their occurrence may complicate the treatment outcome. Patients with mental illness, particularly those suffering from schizophrenia, have many risk factors for discontinuation of treatment, including lack of awareness of illness, psychoactive substance abuse and also drug-related complications [18].

Severely mentally ill patients have a substantially shorter lifespan (10-20 years) than the general population. Despite the advances in research and health care, this life-expectancy reduction is actually increasing [19]. Among schizophrenia patients, the coexistence of diabetes is significantly more frequent than in the general population, while the increased risk of cardiovascular diseases contributes significantly to the pre-

mature mortality of these patients [16,20]. Majority of cardio-metabolic side effects of SGAs are chronic and not obviously visible to patients at the very beginning of the treatment, while leading to excessive mortality. Thus, more intensive screening is recommended for patients receiving SGAs [5]. In fact, as shown by population studies, compared to those who have cardiovascular disease only, patients suffering from schizophrenia and cardiovascular disease face significant disparities in treatment e.g. less frequent referrals to specialists, fewer laboratory cholesterol tests or limited access to cardiac surgery procedures [21].

Recent evidence suggests that the incidence of cardiovascular diseases among people with severe mental illness is not only affected by antipsychotic treatment. To investigate this, more and more studies were carried out on patients who were untreated, during their first episode of the disease or with a high risk of developing psychosis. Data from systematic reviews on the first episode of psychosis confirmed the association of SGA treatment with insulin resistance, impaired glucose tolerance and elevated triglycerides, without elevations in fasting plasma glucose, total and low-density lipoprotein levels [6,22-23]. All this may suggest a more complex, multifactorial nature of cardio-metabolic complications in severely mental ill patients. Simply put, the risk of developing diabetes in a patient suffering from schizophrenia is defined as 50% dependent on traditional risk factors plus an additional increase in the total risk by 2-3 times [24]. Treatment with any antipsychotic drug increases this risk by a further 10%, with a mere 2% difference in risk between FGAs and SGAs [24].

An appropriate monitoring program for cardiovascular and metabolic risk factors for patients treated with antipsychotics has been established. Current European recommendations on monitoring and decision-making are based on the consensus of three scientific associations (European Psychiatric Association, European Association for the Study of Diabetes and the European Society of Cardiology) and are summarized in Table 1 [5]. Perhaps an even more frequent assessment should be adopted for patients with additional risk factors and/or those treated with drugs that are most associated with side effects: olanzapine, clozapine.

Interventions to manage the occurrence of individual side effects have also been tested. The first-line intervention is reducing the dose or changing the antipsychotic drug. In many cases this is a sufficient strategy [25]. Then, head to head comparisons are particularly useful at supporting the decision-making process when switching the pharmacologic agent and such analysis is summarized in Table 2 [26]. Unfortunately for some patients, a switch of the drug is associated with an unacceptably high risk of exacerbation of psychosis. Remaining medical interventions should focus on the proper

Table 1. Recommendations for metabolic risk factor monitoring in patients with severe mental illness or on antipsychotic medication (based on [4])

Routine monitoring	Timing of assessment	Treatment decisions
Personal and family history of diabetes, hypertension, coronary heart disease (myocardial infarction or stroke)	At baseline, at 12 months, and at least annually thereafter*	Choice of antipsychotic agent Switch medications
Smoking, exercise, dietary habits	At baseline, 6 weeks, 3 months, 6 months, at 12 months and at least annually thereafter*	Smoking cessation
Height and weight (BMI)	At baseline, 6 weeks, 3 months, 6 months, at 12 months and at least annually thereafter*	Behavioral interventions for obesity or prediabetes
Waist circumference	At baseline, 3 months, at 12 months and at least annually thereafter*	Behavioral interventions for obesity or prediabetes
Blood pressure	At baseline, 3 months, 6 months, at 12 months and at least annually thereafter*	Behavioral interventions for obesity, antihypertensive treatment
Fasting plasma glucose	At baseline, 6 weeks, 3 months, 6 months, at 12 months and at least annually thereafter*	Behavioral interventions for obesity and prediabetes, oral antidiabetes drugs
Fasting lipid profile	At baseline, 6 weeks, 3 months, 6 months, at 12 months and at least annually thereafter*	Behavioral interventions for obesity and dyslipidemia, lipid-lowering medication
Electrocardiographic parameters ⁵	At baseline**	Referral (external or internal)

*This frequency of assessment assumes that baseline results were normal; more-frequent follow-up is recommended for patients with abnormalities and those with cardiovascular and metabolic risk factors.

**Desirable for all patients, but only required in those with cardiac risk factors. Follow-up electrocardiography is conducted as needed to assess baseline abnormalities or new symptoms, especially palpitation at rest and without anxiety, arrhythmia, dizziness or syncope upon exertion.

treatment (by an appropriate specialist) of developed hypertension, dyslipidemia, hyperglycemia, diabetes and tobacco cessation [5]. Lifestyle changes have also been studied in the population of patients treated with SGAs [24, 27].

New directions in research focus on adjunct drugs (e.g. metformin, topiramate, aripiprazole) to correct the cardiovascular and metabolic side effects of SGAs [5, 27].

By reducing insulin resistance, metformin has the most proven evidence of efficacy in reducing antipsychotic-related weight gain [27]. Aripiprazole has its advantage due to additional antipsychotic action, while lowering the lipid level and therefore reducing weight on average by 2,13 kg compared to placebo [27]. Topiramate has been proven so far that it effective in diminishing only the olanzapine-induced weight gain by 4,4kg on average [27].

Table 2. General summary on antipsychotics cardiovascular and metabolic side effects (based on [3,8,24])

Adverse effect	Weight gain	Metabolic syndrome	Increase in QTc interval	Cardiovascular events (myocardial infarction and stroke)	Hyper-cholesterolemia
<i>Amisulpride</i>	0/+	0/+	0/+	++	0
<i>Aripiprazole</i>	0	0/+	0/+	0/+	+
<i>Asenapine</i>	+	0/+	0/+	+	0
<i>Brexpiprazole</i>	0	0/+	?	0/+	+
<i>Cariprazine</i>	0/+	0/+	?	?	0/+
<i>Clozapine</i>	+++	+++	++	++	+++
<i>Iloperidone</i>	+ /+++	+	++	?	++
<i>Lurasidone</i>	0/+	0/+	?	?	0/+
<i>Olanzapine</i>	+++	+++	+	++	+++
<i>Paliperidone</i>	++	+	+	+	+
<i>Quetiapine</i>	++	++	++	++	++
<i>Risperidone</i>	++	+	+	++	0
<i>Sertindole</i>	++	+	+++	0/+	+
<i>Ziprasidone</i>	0/+	0/+	++	+	+

Notes: +, ++, and +++ indicate comparative, not absolute, and side effect relevance among drugs. ? indicates no evidence available.

The major limitation of this review is its mainly narrative character, without possibility to employ systematic approach to collecting evidences and statistical analysis. To overcome this limitation, we decided to base our study on recent systematic reviews, a category considered the highest degree of evidence in medical sciences. Unfortunately, most studies still lack data on long-term effects. Also in some subgroups (e.g. the pediatric population) there is a lack of conclusive data on the most significant endpoints (e.g. particular drugs' association with cardiovascular events).

Conclusions

This short summary may help to understand the importance of cardio-metabolic side effect during SGAs treatment. This review brings together what is currently known about these risks. Further large and prospective long-term studies are needed to fill existing gaps in knowledge.

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