Antipsychotics and Cardiac Side Effects

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Contents

Abstract

During the last decades, the diagnosis of mental illness has dramatically grown especially in the pediatric population, and, in parallel, there has been an increasing widespread use of psychotropic drugs, mainly antipsychotics and especially those of second generation (SGA). SGAs are used effectively for several conditions, such as schizophrenia, irritability and aggression in autism spectrum disorder or intellectual disability, tics or Tourette's disorder, bipolar, conduct, and eating disorders, but only few of them have regulatory approval in youths. Although effective, these drugs could potentially determine several adverse effects, which are of particular concern especially among pediatric population; here we focus on cardiac, cardiovascular, and metabolic side effects.

Keywords

Antipsychotic drugs · Second-generation antipsychotics · Cardiac side effects · Cardiovascular side effects · Metabolic side effects

Introduction

Antipsychotic drugs are the cornerstone of pharmacological treatment for several psychiatric disorders, and in the last years, there has been

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an increasing use of them, especially those of second generation. Although they effectively control symptoms and behavior associated with psychiatric disorders, accumulating evidences suggest that antipsychotics exposure could lead to an increased risk of cardiac and also metabolic side effects. These adverse events seem to be more frequent in vulnerable populations, such as patients with a first episode of schizophrenia, those who are drug-naive, children, and adolescents [1–3].

Electrocardiographic Adverse Events

Antipsychotic drugs are associated with a variety of electrocardiographic abnormalities, including minor and frequent complications, such as sinus tachycardia, and more serious arrhythmias, such as the polymorphic ventricular tachycardia torsades de pointes, which may cause sudden cardiac death [4]. The World Health Organization defined sudden cardiac death as an unexpected death occurring within 1 h of symptom onset if witnessed and, if unwitnessed, within 24 h after the person has last been observed alive and symptoms-free [5]. Antipsychotics have shown the ability of blocking the delayed rectifier potassium current (IKr), by interacting with the alpha subunit Kv11.1 of the channel, which is coded by the hERG gene (also called *KCNH2*). This blockade is dose-dependent and able to prolong cardiac repolarization, seen as corrected QT (QTc) prolongation on the electrocardiogram (ECG). In clinical settings, concern arises on QTc prolongation as it may progress to torsades de pointes in rare cases. If not immediately managed, torsades de pointes can evolve into ventricular fibrillation and cause sudden cardiac death [5]. Among antipsychotics, first-generation ones like thioridazine, droperidol, mesoridazine, and pimozide have shown a marked QTc prolongation leading to an FDA warning and for some of them to the market withdrawal [6]. In addition, a similar QTc effect was observed with chlorpromazine [7]. Haloperidol also has carried an FDA warning for the increased risk of QTc prolongation and torsades de pointes, recommending a regular ECG monitoring when intravenous (IV) haloperidol is administered [8]. Moreover, in Italy, the Italian Medicines Agency has also published a warning (GU Serie Generale n.144 del 23-06-2010) in which it has specified that, in order to reduce the risk of QTc prolongation, the vial formulation should only be used for intramuscular administration and not for IV injection. However, evidence has also suggested that in case of a dose of IV haloperidol lower than 2 mg, this drug can be administered without ECG monitoring, in patients with no cardiovascular risk factors [9]. Among second-generation antipsychotics, those associated with FDA warnings for the risk of QTc prolongation are asenapine, clozapine iloperidone, paliperidone, quetiapine, sertindole, and ziprasidone. The greater risk of QTc prolongation was found with ziprasidone compared with other second-generation antipsychotics, but this does not imply that ziprasidone is more associated with torsades de pointes and sudden cardiac death [10]. In fact, only rare cases of torsades de pointes have been reported in patients treated with ziprasidone as well as with other second-generation antipsychotics [11]. Olanzapine, quetiapine, and risperidone showed a modest QTc prolongation when used in therapeutic doses [11]. Interestingly, aripiprazole has shown a QTc-shortening effect compared with placebo and active controls [12]. Evidence on amisulpride is too limited to categorize its effect on QTc prolongation [11]. Finally, special attention deserves clozapine that has been associated with substantial heart rate increases, which may complicate QTc measurement. Therefore, whether clozapine actually cause QTc prolongation is still an unresolved question [13].

Recently, weighted recommendations on commonly used antipsychotics have been made using pharmacovigilance data [14]. In this regard, aripiprazole, perphenazine, olanzapine, and zuclopenthixol were categorized as drugs with no risk of QTc prolongation or torsades de pointes. Chlorprothixene, levomepromazine, flupentixol, paliperidone, clozapine, quetiapine, amisulpride, sulpiride, and risperidone were categorized as drugs with propensity of QTc prolongation. Finally, sertindole, pimozide, haloperidol,

and ziprasidone were categorized as drugs with a pronounced effect on QTc prolongation, documented cases of torsades de pointes, or other types of serious arrhythmias. The risk of developing torsades de pointes increases in presence of genetic risk factors like mutations of hERG gene encoding for the subunit of the potassium channel protein Kv11.1 or poor metabolizers of the cytochrome P450 (CYP) 2D6 [5, 15]. Clinical risk factors include bradycardia, conduction disturbances, coronary artery disease, structural myocardial disease, including post-MI and cardiomyopathy, and electrolyte imbalance (especially hypokalemia). Finally, female sex and age $\geq$ 65 years represent risk factors for the development of torsades de pointes. Other risk factors include polypharmacy, overdose of antipsychotics, or exposure to drug abuse of central nervous system stimulants [5].

Antipsychotics are also able to block the fast sodium current (INa) reducing peak sodium influx and causing altered voltage gradients such as those seen in Brugada syndrome, a genetic ion channel disease that can also cause sudden cardiac death [16]. However, the evidence of the association between antipsychotics and Brugada syndrome is scarce [17].

Most antipsychotics can cause sinus tachycardia, defined as heart rate $\geq$ 100 beats/min. The underlying mechanism involves a combination of both anticholinergic and antiadrenergic effects, as well as indirect effects via baroreceptor reflexes. Antipsychotics are able to block M2 cardiac receptors, reduce the parasympathetic tone, and increase heart rate. Moreover, antipsychotics through the block of adrenergic α1 receptors can cause vasodilation and reflex tachycardia [18]. As a proof of this concept, an increased risk of sinus tachycardia has been observed with antipsychotics at high affinity for M2 receptors like clozapine, quetiapine, risperidone, and chlorpromazine. A lower risk is observed instead with olanzapine and ziprasidone [6, 19] and with aripiprazole due to the scarce anticholinergic and antiadrenergic effect [20].

Antipsychotics may also cause other less common electrocardiographic adverse events that potentially could contribute to increase the risk of sudden cardiac death. In this regard, second-generation antipsychotics like risperidone, ziprasidone, clozapine, olanzapine, and quetiapine have been associated with a risk of bradycardia, atrial fibrillation, ST-segment depression and elevation, QRS prolongation, T-wave inversion, bundle branch block, and first-degree atrioventricular block [19].

Vascular Adverse Events

Antipsychotics have been associated with a risk of developing orthostatic hypotension through the blockade of adrenergic α1 receptors [20]. Low- and mid-potency first-generation antipsychotics like chlorpromazine and perphenazine have been associated with a higher risk of orthostatic hypotension than high-potency first-generation antipsychotics (haloperidol and fluphenazine) and second-generation antipsychotics. Among second-generation drugs, clozapine and quetiapine were found to have the highest risk followed by ziprasidone, olanzapine, risperidone, and aripiprazole. Among the more recently introduced second-generation antipsychotic drugs, the highest risk was observed with iloperidone followed by asenapine and lurasidone [21].

Evidence of the hypertensive effect associated with antipsychotics is limited and contradictory [22, 23]. An increased risk of hypertension was observed with mid-potency first-generation agents (like perphenazine) and the second-generation clozapine, olanzapine, and ziprasidone, whereas a lower risk was found with risperidone and quetiapine [19, 24].

Cardiac Adverse Events

Despite electrocardiographic abnormalities represent the most important clinical concern related to the antipsychotic treatment, other direct cardiac adverse events have been found, including myocardial infarction, myocarditis, and cardiomyopathy, for which the underlying mechanisms are less clear. The risk of myocardial infarction associated with the use of antipsychotic is less clear

[25]. Amisulpride, clozapine, and risperidone seem associated with an increased risk [19].

Myocarditis associated with antipsychotics is identified as a type I hypersensitivity reaction that is typically characterized by the accumulation of eosinophils and the release of toxins that could induce apoptosis and necrosis of cardiomyocytes [18]. Among antipsychotics, clozapine is most associated with myocarditis [26]. Other antipsychotics associated with this adverse event are fluphenazine, chlorpromazine, haloperidol, olanzapine, quetiapine, and risperidone [18, 27]. Myocarditis can lead to myocardial fibrosis, arrhythmias, and eventually sudden cardiac death. It can occur within the first months of treatment, and patients may present symptoms like fever, fatigue, and dyspnea. In case of myocarditis, antipsychotic treatment should be discontinued, and, if indicated, patients should start a therapy with corticosteroids [17, 20].

A less common cardiovascular adverse event of antipsychotics is cardiomyopathy, defined as a deterioration of the function of the myocardium, often caused by untreated myocarditis or other factors. Usually, its onset is slower than myocarditis [18]. Among antipsychotics, clozapine is most commonly associated with the development of cardiomyopathy [26]. Other antipsychotics associated with this risk include amisulpride and quetiapine [18]. Common symptoms are fatigue, tachypnea, and dyspnea. In case of diagnosis of cardiomyopathy, antipsychotic should be withdrawal, and patients should receive an appropriate heart failure treatment [20].

Metabolic Adverse Events

Beyond the potential direct cardiac and/or vascular effects, there is a growing body of evidence about cardio-metabolic side effects due to antipsychotics exposure. This is of concern especially for pediatric population since weight gain, dyslipidemia, or insulin resistance are known to predispose to cardiac and vascular disease in adulthood. Metabolic adverse events associated with antipsychotics are weight gain, especially abdominal obesity, impaired glucose metabolism, and dyslipidemia. Several studies and meta-analyses have shown a different degree of weight gain associated with individual antipsychotics [28–34]. Among first-generation drugs, those with low potency, such as chlorpromazine and thioridazine, are associated with a higher risk of weight gain than mid- (molindone and perphenazine) or high-potency antipsychotics (fluphenazine, haloperidol, and pimozide). Among second-generation antipsychotics, a high risk of weight gain was observed with clozapine and olanzapine; an intermediate risk with iloperidone, quetiapine, risperidone, paliperidone, sertindole, and zotepine; and a smaller risk with amisulpride, aripiprazole, asenapine, lurasidone, and ziprasidone [35]. Despite this different risk's magnitude, we can consider all antipsychotics associated with weight gain, with a risk even higher in those patients who have taken them for the first time [32, 36, 37]. In fact, in a 12-month trial conducted on patients with a first episode of schizophrenia, antipsychotics at low risk such as amisulpride, ziprasidone, and low doses of haloperidol were associated with a significant weight gain [32]. The period at major risk for gaining weight in drug-naive patients with schizophrenia is the first few months of therapy. In this regard, a meta-analysis has shown a mean gain in BMI and weight within the first 12 weeks of antipsychotic treatment in previously drug-naive patients older than 15 years [36]. Predictors of antipsychotic-induced weight gain are shown in Table 1.

In children and adolescents, second-generation antipsychotics such as aripiprazole, olanzapine, quetiapine, and risperidone are used for the treatment of bipolar mania, schizophrenia, irritability, and aggression associated with autistic disorder. Evidence has shown a greater orexigenic effect in this subpopulation than in adults [32]. In fact, young patients treated with antipsychotics have an increased risk of being obese or overweight [1, 29, 31]. However, long-term data on this metabolic risk during antipsychotic treatment are limited. In a systematic review of randomized, placebo-controlled trials of patients aged <18 years treated with second-generation antipsychotic drugs, a similar hierarchy was found in the risk of weight gain than that observed

Table 1 Predictors of antipsychotic-induced weight gain

Predictors	Predictors related to
Family history of obesity	Familial factors
Parental BMI	
Cannabis use	Patients
Young age (children and adolescents)	
Sex (mixed evidence)	
High levels of negative symptoms (such as alogia, affective flattening, avolition)	
Lack of cognitive restraint in the presence of increased appetite	
Low BMI (<25 kg/m^2)	
Non-smoking status	
Nonwhite ethnicity	
Improved symptom reduction (limited or inconclusive data)	Psychiatric illness
First-episode status of psychiatric illness	
Lack of prior antipsychotic treatment	
Early weight gain (within the first 2–4 weeks of antipsychotic treatment)	Treatment
Good treatment adherence	
High antipsychotic dose	
Polypharmacy (limited or inconclusive data)	
Long-term treatment	
Specific medications (such as clozapine and olanzapine, which have a high risk of metabolic dysregulation)	

in adult patients [1], whereby clozapine and olanzapine were associated with the great weight gain, followed by risperidone, quetiapine, aripiprazole, and ziprasidone. Finally, it is important to consider that despite the differential risk of weight gain associated with the antipsychotics seems consistent across adults, adolescents, and children, the high inter-individual variability in weight gain among patients treated with a specific drug suggests that other factors like personal, familial, or genetic factors can come into play influencing the degree of weight gain [3, 31, 36]. In fact, allelic variants of CYP-2D6 and -3A4 were found to alter the metabolic pathways of antipsychotics [38, 39]. Similarly, allelic variants of ABCB1 and ABCG2 genes, codifying for transport proteins belonging to the ATP-binding cassette superfamily, were found to influence the plasma concentrations of antipsychotics [40–42]. In this regard, a pharmacogenetic study has investigated the impact of allelic variants of CYP3A, CYP2D6, ABCB1, and ABCG2 genes on second-generation antipsychotics plasma concentrations and their association with the occurrence of adverse drug reactions, finding no association for the investigated allelic variants of CYP3A (CYP3A4*22 C > T C_59013445_10, CYP3A5*3A > G C_26201809_30) and CYP2D6 (*3 del A C_32407232_50, *6 del T C_32407243_20, *4 G > A C_27102431_D0, and assay ID Hs00010001_cn gene duplication), while the ABCB1 haplotype (G2677 T/A-C3435T) and the ABCG2 (c.421 C>A) allelic variants were associated with lower plasma concentrations of aripiprazole and risperidone. Moreover, the ABCG2 c.421 CA/AA functional variant was found associated with a higher risk of developing metabolism and nutrition disorders [43]. These results, if confirmed in larger studies, underline the importance of combining therapeutic drug monitoring, pharmacogenetic, and pharmacovigilance methods to tailor the treatment with these drugs in the pediatric population.

The underlying mechanisms involved in antipsychotic-induced weight gain include different functional pathways and neurotransmissions [3]. Among them, the histaminergic transmission seems to recover an important role as histamine H1 receptors are involved in the energy homeostasis. In fact, the extent of H1 receptor antagonism of antipsychotic drugs has been identified as predictor of the magnitude of the weight gain in clinical studies [44, 45]. Moreover, serotonin 5-HT2a and 5-HT2c receptors can also play a role in the control of food intake and body weight. Accordingly, most second-generation antipsychotics such as clozapine and olanzapine are potent 5-HT2c antagonists. On the contrary, although aripiprazole and ziprasidone have a high affinity for 5-HT2c receptors, they have shown only a weak association with metabolic dysregulation. This could be explained by the influence of other receptors that can potentially counterbalance the inhibition of 5HT2c receptors like the partial agonist effect of aripiprazole on 5-HT1a receptors [46]. Another potential

mechanism involved in antipsychotic drug-induced weight gain is the block of dopamine D2 and D3 receptors as this blockade has been associated with a strong effect on feeding behavior [3]. This can also explain the effect on weight observed with antipsychotic agents that interact exclusively with dopaminergic receptors, such as amisulpride [32]. Polymorphism of the promoter region of the 5-HT2C receptor gene has been associated with antipsychotic-induced weight gain [47], and polymorphisms of the MTHFR gene [48] and the D2 receptor gene [49] have been associated with an increased risk of metabolic syndrome in patients receiving second-generation antipsychotics. Evidence of the role of adrenergic α1 and α2 receptors blockade in inducing weight gain or metabolic dysregulation is instead lacking [31]. Finally, genetic data suggest a role for G-protein signalling, promelanin-concentrating hormone signalling, leptin signalling and leptin receptor activity, and cannabinoid receptor activity in antipsychotic drug-induced weight gain [3, 50].

Another adverse event associated with antipsychotic drugs is the potential to cause or exacerbate the metabolic syndrome, which appears with central obesity, hypertension, dyslipidemia, and glucose intolerance or insulin resistance. In general, the risk of developing the metabolic syndrome is high with clozapine, olanzapine, and chlorpromazine, moderate with quetiapine, mild with risperidone, paliperidone, amisulpride, and sertindole, and low with aripiprazole and ziprasidone [29, 35, 37, 51, 52]. Among second-generation antipsychotics, olanzapine and clozapine have been associated with the highest risk of dyslipidemia whereas risperidone and quetiapine with an intermediate risk and aripiprazole and ziprasidone with a low risk of this metabolic abnormality. Moreover, the risk of dyslipidemia with olanzapine, clozapine, and quetiapine was found independent of BMI or in addition to weight-related effects [3, 53]. In fact, dyslipidemia should be considered as a separate and direct adverse event of antipsychotic drugs other than a consequence of weight gain. The dyslipidemic adverse effects of clozapine, olanzapine, and quetiapine display as abnormal elevations in serum triglyceride levels and as an increase in total cholesterol, low-density lipoprotein (LDL), and non-high-density lipoprotein (non-HDL) cholesterol levels. The lowest risk of serum lipid abnormalities has been found with risperidone [31], although a significant elevation of serum triglyceride levels was observed in young, antipsychotic-drug-naive patients [53]. Finally, a neutral effect on lipid levels was observed with aripiprazole and ziprasidone [3, 53]. The receptors involved in the antipsychotic-drug-associated dyslipidemia are not completely understood; however, transcriptional regulators of lipid and carbohydrate metabolism, peroxisome proliferator-activated receptors, and the inhibition of AMP-activated protein kinase activity may play a relevant role [54, 55].

Clozapine and olanzapine treatment has been also associated with the dysregulation of glucose homeostasis (hyperglycemia and insulin resistance), independent of weight gain and adiposity [33]. Quetiapine has been associated with a moderate risk of hyperglycemia, lower than that associated with clozapine or olanzapine but higher than risperidone. As with dyslipidemia, the lowest risk of hyperglycemia was observed with aripiprazole and ziprasidone [35]. Antipsychotics have also been associated with the risk of developing type 2 diabetes mellitus [56], with a higher risk found in patients treated with second-generation antipsychotics than in those treated with first-generation drugs [57]. Furthermore, the risk of diabetes mellitus differs for individual drugs. In this regard, olanzapine and clozapine, followed by quetiapine and risperidone, are associated with a significant increase in the risk of diabetes mellitus [58–60]. Patients aged 0–24 years seem to have the highest risk of diabetes mellitus associated with antipsychotic drugs [61], although the incidence rates of diabetes mellitus generally increase with age. This contradiction seems to be related to the low risk for diabetes mellitus at a younger age, which makes the effect of antipsychotic drugs on the glycemic control more noticeable, whereas at an older age, the effect of other risk factors can become more pronounced than that related to the antipsychotic treatment. In inducing impaired glucose metabolism, a role

seems to be played by muscarinic M2 and M3 receptors that are expressed on the surface of pancreatic cells. The affinity of second-generation antipsychotic agents for these receptors is relevant as M3 receptors can control insulin release [31, 62, 63]. In fact, some antipsychotics with a high affinity for the M3 receptor (such as clozapine and olanzapine) might unbalance both cholinergic-dependent and glucose-dependent insulin secretion from pancreatic cells promoting glucose dysregulation and type 2 diabetes mellitus [31].

Finally, all these metabolic abnormalities seen above have shown a dose-dependent relationship with the serum concentrations of the second-generation antipsychotics [46, 64].

Conclusion

Antipsychotic medications have been implicated in the development of cardiovascular disorders via direct and indirect effects. These agents are frequently cited as causing electrocardiographic adverse events especially QTc prolongation that rarely may progress in torsades de pointes. In this regard both FDA and the Italian Medicines Agency published a warning on the parenteral use of haloperidol. These agents have also been directly linked to vascular effects such as increased or reduced blood pressure. Less clear is their association with the risk of myocarditis, myocardial infarction, and cardiomyopathy, although some evidences have shown this association for both first and second generation of antipsychotics. On the contrary, several findings suggest the correlation between antipsychotic use, both first- (chlorpromazine and thioridazine) and second-generation (clozapine, olanzapine, risperidone) antipsychotics, and metabolic side effects, such as weight gain, impaired glucose metabolism, and dyslipidemia. The underlying mechanisms involved in antipsychotic-induced metabolic effects are strongly related to their effects on serotoninergic, histaminergic, and dopaminergic receptors. It's important to highlight that this risk can be higher in children and adolescents. In fact, young patients treated with antipsychotics have an increased risk of being obese or overweight. However, long-term data on this metabolic risk during antipsychotic treatment are limited. Finally, it is important to consider that also genetic factors can influence the risk and severity of metabolic side effects.

Cross-References

- ▶ Cardiovascular Adverse Effects of Psychotropic Drugs
- ▶ Cardiovascular Manifestations in Schizophrenia

References

1. De Hert M, Dobbelaere M, Sheridan EM, Cohen D, Correll CU. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: a systematic review of randomized, placebo controlled trials and guidelines for clinical practice. Eur Psychiatry. 2011;26:144–58.
2. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and metaanalysis. Neuropsychopharmacology. 2010;35:1520–30.
3. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. Trends Mol Med. 2011;17:97–107.
4. Nielsen J. The safety of atypical antipsychotics: does QTc provide all the answers? Expert Opin Drug Saf. 2011;10:341–4.
5. Nielsen J, Graff C, Kanters JK, et al. Assessing QT interval prolongation and its associated risks with antipsychotics. CNS Drugs. 2011;25:473–90.
6. Michelsen JW, Meyer JM. Cardiovascular effects of antipsychotics. Expert Rev Neurother. 2007;7:829–39.
7. Shah AA, Aftab A, Coverdale J. QTc prolongation with antipsychotics: is routine ECG monitoring recommended? J Psychiatr Pract. 2014;20:196–206.
8. Hassaballa HA, Balk RA. Torsade de pointes associated with the administration of intravenous haloperidol: a review of the literature and practical guidelines for use. Expert Opin Drug Saf. 2003;2:543–7.
9. Meyer-Massetti C, Cheng CM, Sharpe BA, et al. The FDA extended warning for intravenous haloperidol and torsades de pointes: how should institutions respond? J Hosp Med. 2010;5:E8E16.
10. Citrome L. Drug safety evaluation of ziprasidone. Expert Opin Drug Saf. 2011;10:437–48.
11. Hasnain M, Vieweg WV. QTc interval prolongation and torsade de pointes associated with second-generation antipsychotics and antidepressants: a comprehensive review. CNS Drugs. 2014;28:887–920.
12. Polcwiartek C, Sneider B, Graff C, et al. The cardiac safety of aripiprazole treatment in patients at high risk

for torsade: a systematic review with a meta-analytic approach. Psychopharmacology. 2015;232:3297–308.
13. Nielsen J. QTc prolongation and clozapine: fact or artefact? Aust N Z J Psychiatry. 2012;46:793–4.
14. Fanoe S, Kristensen D, Fink-Jensen A, et al. Risk of arrhythmia induced by psychotropic medications: a proposal for clinical management. Eur Heart J. 2014;35:1306–15.
15. Brown CS, Farmer RG, Soberman JE, et al. Pharmacokinetic factors in the adverse cardiovascular effects of antipsychotic drugs. Clin Pharmacokinet. 2004;43:33–56.
16. Sicouri S, Antzelevitch C. Sudden cardiac death secondary to antidepressant and antipsychotic drugs. Expert Opin Drug Saf. 2008;7:181–94.
17. Polcwiartek C, Kragholm K, Schjerning O, Graff C, Nielsen J. Cardiovascular safety of antipsychotics: a clinical overview. Expert Opin Drug Saf. 2016; 15:679–88.
18. Leung JY, Barr AM, Procyshyn RM, et al. Cardiovascular side-effects of antipsychotic drugs: the role of the autonomic nervous system. Pharmacol Ther. 2012;135:113–22.
19. Feinstein RE. Cardiovascular effects of novel antipsychotic medications. Heart Dis. 2002;4:184–90.
20. Nielsen J, Correll CU, Manu P, et al. Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided? J Clin Psychiatry. 2013;74:603–13.
21. Gugger JJ. Antipsychotic pharmacotherapy and orthostatic hypotension: identification and management. CNS Drugs. 2011;25:659–71.
22. Henderson DC, Daley TB, Kunkel L, et al. Clozapine and hypertension: a chart review of 82 patients. J Clin Psychiatry. 2004;65:686–9.
23. Lund BC, Perry PJ, Brooks JM, et al. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. Arch Gen Psychiatry. 2001;58:1172–6.
24. Bodén R, Edman G, Reutfors J, et al. A comparison of cardiovascular risk factors for ten antipsychotic drugs in clinical practice. Neuropsychiatr Dis Treat. 2013;9:371–7.
25. Brauer R, Douglas I, Smeeth L. The association between antipsychotic agents and the risk of myocardial infarction: a systematic review. Br J Clin Pharmacol. 2011;72:871–8.
26. Fitzsimons J, Berk M, Lambert T, et al. A review of clozapine safety. Expert Opin Drug Saf. 2005;4: 731–44.
27. Vang T, Rosenzweig M, Bruhn CH, et al. Eosinophilic myocarditis during treatment with olanzapine – report of two possible cases. BMC Psychiatry. 2016;16:70.
28. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373:31–41.
29. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W, Davis JM, Leucht S. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. Schizophr Bull. 2012;38: 167–77.
30. Parsons B, Allison DB, Loebel A, Williams K, Giller E, Romano S, Siu C. Weight effects associated with antipsychotics: a comprehensive database analysis. Schizophr Res. 2009;110:103–10.
31. Coccurello R, Moles A. Potential mechanisms of atypical antipsychotic-induced metabolic derangement: clues for understanding obesity and novel drug design. Pharmacol Ther. 2010;127:210–51.
32. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, Gheorghe MD, Rybakowski JK, Galderisi S, Libiger J, Hummer M, Dollfus S, López-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors N, Riecher-Rössler A, Grobbee DE, EUFEST Study Group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. 2008;371:1085–97.
33. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs. 2005;19(Suppl 1): 1–93.
34. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209–23.
35. DE Hert M, Correll CU, Bobes J, Cetkovich-Bakmas-M, Cohen D, Asai I, Detraux J, Gautam S, Möller HJ, Ndetei DM, Newcomer JW, Uwakwe R, Leucht S. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry. 2011;10:52–77.
36. Tarricone I, Ferrari Gozzi B, Serretti A, Grieco D, Berardi D. Weight gain in antipsychotic-naive patients: a review and metaanalysis. Psychol Med. 2010;40:187–200.
37. Alvarez-Jiménez M, González-Blanch C, Crespo-Facorro B, Hetrick S, Rodríguez-Sánchez JM, Pérez-Iglesias R, Vázquez-Barquero JL. Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: a systematic critical reappraisal. CNS Drugs. 2008;22:547–62.
38. de Leon J, Armstrong SC, Cozza KL. The dosing of atypical antipsychotics. Psychosomatics. 2005;46: 262–73.
39. Spina E, de Leon J. Clinical applications of CYP genotyping in psychiatry. J Neural Transm. 2015;122: 5–28.
40. Gunes A, Spina E, Dahl M-L, Scordo MG. ABCB1 polymorphisms influence steady-state plasma levels of 9-hydroxyrisperidone and risperidone active moiety. Ther Drug Monit. 2008;30:628–33.

41. Yoo H-D, Lee S-N, Kang H-A, Cho H-Y, Lee I-K, Lee Y-B. Influence of ABCB1 genetic polymorphisms on the pharmacokinetics of risperidone in healthy subjects with CYP2D6∗10/∗10. Br J Pharmacol. 2011;164:433–43.
42. Xiang Q, Zhao X, Zhou Y, Duan JL, Cui YM. Effect of CYP2D6, CYP3A5, and MDR1 genetic polymorphisms on the pharmacokinetics of risperidone and its active moiety. J Clin Pharmacol. 2010;50:659–66.
43. Rafaniello C, Sessa M, Bernardi FF, Pozzi M, Cheli S, Cattaneo D, Baldelli S, Molteni M, Bernardini R, Rossi F, Clementi E, Bravaccio C, Radice S, Capuano A. The predictive value of ABCB1, ABCG2, CYP3A4/5 and CYP2D6 polymorphisms for risperidone and aripiprazole plasma concentrations and the occurrence of adverse drug reactions. Pharmacogenomics J. 2018;18:422–30.
44. Kim SF, Huang AS, Snowman AM, Teuscher C, Snyder SH. From the cover: antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. Proc Natl Acad Sci U S A. 2007;104:3456–9.
45. Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Meltzer HY, Roth BL. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology. 2003;28:519–26.
46. Correll CU. From receptor pharmacology to improved outcomes: individualizing the selection, dosing, and switching of antipsychotics. Eur Psychiatry. 2010;25:S12–21.
47. Reynolds GP, Hill MJ, Kirk SL. The 5-HT2C receptor and antipsychotic induced weight gain: mechanisms and genetics. J Psychopharmacol. 2006;20:15–8.
48. van Winkel R, Rutten BP, Peerbooms O, Peuskens J, van Os J, De Hert M. MTHFR and risk of metabolic syndrome in patients with schizophrenia. Schizophr Res. 2010;121:193–8.
49. Hong CJ, Liou YJ, Bai YM, Chen TT, Wang YC, Tsai SJ. Dopamine receptor D2 gene is associated with weight gain in schizophrenic patients under long-term atypical antipsychotic treatment. Pharmacogenet Genomics. 2010;20:359–66.
50. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011;8:114–26.
51. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). Eur Psychiatry. 2009;24:412–24.
52. Nielsen J, Skadhede S, Correll CU. Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naive schizophrenia patients. Neuropsychopharmacology. 2010;35:1997–2004.
53. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA. 2009;302:1765–73.
54. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor binding profiles. Mol Psychiatry. 2008;13:27–35.
55. Oh KJ, Park J, Lee SY, Hwang I, Kim JB, Park TS, Lee HJ, Koo SH. Atypical antipsychotic drugs perturb AMPK-dependent regulation of hepatic lipid metabolism. Am J Physiol Endocrinol Metab. 2011;300:E624–32.
56. Liao CH, Chang CS, Wei WC, Chang SN, Liao CC, Lane HY, Sung FC. Schizophrenia patients at higher risk of diabetes, hypertension and hyperlipidemia: a population-based study. Schizophr Res. 2011;126:110–6.
57. Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K. First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. Br J Psychiatry. 2008;192:406–11.
58. Ramaswamy K, Masand PS, Nasrallah HA. Do certain atypical antipsychotics increase the risk of diabetes? A critical review of 17 pharmacoepidemiologic studies. Ann Clin Psychiatry. 2006;18:183–94.
59. Yood MU, DeLorenze G, Quesenberry CP Jr, Oliveria SA, Tsai AL, Willey VJ, McQuade R, Newcomer J, L'Italien G. The incidence of diabetes in atypical antipsychotic users differs according to agent – results from a multisite epidemiologic study. Pharmacoepidemiol Drug Saf. 2009;18:791–9.
60. Starrenburg FC, Bogers JP. How can antipsychotics cause diabetes mellitus? Insights based on receptor-binding profiles, humoral factors and transporter proteins. Eur Psychiatry. 2009;24:164–70.
61. Hammerman A, Dreiher J, Klang SH, Munitz H, Cohen AD, Goldfracht M. Antipsychotics and diabetes: an age-related association. Ann Pharmacother. 2008;42:1316–22.
62. Johnson DE, Nedza FM, Spracklin DK, Ward KM, Schmidt AW, Iredale PA, Godek DM, Rollema H. The role of muscarinic receptor antagonism in antipsychotic-induced hippocampal acetylcholine release. Eur J Pharmacol. 2005;506:209–19.
63. Silvestre JS, Prous J. Research on adverse drug events. I. Muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes. Methods Find Exp Clin Pharmacol. 2005;27:289–304.
64. Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. J Clin Psychiatry. 2009;70:1041–50.