Metabolic and cardiovascular adverse effects associated with antipsychotic drugs

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Abstract | Antipsychotic medications can induce cardiovascular and metabolic abnormalities (such as obesity, hyperglycemia, dyslipidemia and the metabolic syndrome) that are associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease. Controversy remains about the contribution of individual antipsychotic drugs to this increased risk and whether they cause sudden cardiac death through prolongation of the corrected QT interval. Although some drug receptor-binding affinities correlate with specific cardiovascular and metabolic abnormalities, the exact pharmacological mechanisms underlying these associations remain unclear. Antipsychotic agents with prominent metabolic adverse effects might cause abnormalities in glucose and lipid metabolism via both obesity-related and obesity-unrelated molecular mechanisms. Despite existing guidelines and recommendations, many antipsychotic-drug-treated patients are not assessed for even the most easily measurable metabolic and cardiac risk factors, such as obesity and blood pressure. Subsequently, concerns have been raised over the use of these medications, especially pronounced in vulnerable pediatric patients, among whom their use has increased markedly in the past decade and seems to have especially orexigenic effects. This Review outlines the metabolic and cardiovascular risks of various antipsychotic medications in adults and children, defines the disparities in health care and finally makes recommendations for screening and monitoring of patients taking these agents.

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Introduction

The introduction of chlorpromazine into clinical practice half a century ago sparked a revolution in the treatment of schizophrenia. Antipsychotic medications rapidly became the cornerstone of pharmacological treatment for schizophrenia.[1] Although their primary indication remains schizophrenia and schizophrenia-related disorders, most antipsychotic drugs are now used on-label to treat a broad range of symptoms and disorders, including bipolar mania and depression, unipolar depression that is unresponsive to standard antidepressant treatment, Tourette's disorder and irritability associated with autistic disorder. In the past decade, the use of antipsychotic drugs has substantially increased, especially among children and adolescents,[2] partly owing to the regulatory broadening of the indications for several antipsychotic drugs.[3,4]

Antipsychotic drugs are arbitrarily divided into first-generation and second-generation agents (Table 1). Although second-generation agents result in improved treatment persistence, relapse prevention and a reduced risk of extrapyramidal adverse effects (including motor symptoms and tardive dyskinesia),[5] they are no more effective overall than the first-generation treatments.[6–9] Some antipsychotic drugs also have a particular propensity to induce weight gain as well as cardiovascular and metabolic abnormalities, thereby increasing the patient's risk of obesity, the metabolic syndrome, type 2 diabetes mellitus and associated cardiovascular morbidity (Box 1). These adverse effects are especially prominent in vulnerable populations, such as patients with a first episode of schizophrenia, those who have not previously taken antipsychotic agents (drug-naive), children and adolescents.[3,10,11] Nevertheless, patients receiving antipsychotic treatment, including these especially vulnerable groups, are often insufficiently assessed for cardiovascular and metabolic risk factors.[12–14]

This Review outlines the metabolic and cardiovascular risks associated with various antipsychotic drugs in adults and pediatric patients. This article highlights the disparities in health care between individuals in the general population and patients with mental illness who have a

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high risk of metabolic and cardiovascular abnormalities and includes recommendations for screening and monitoring patients treated with antipsychotic drugs.

Key points

- Although all antipsychotic drugs can induce cardiovascular and metabolic dysfunction (especially in drug-naive, first-episode and pediatric populations), olanzapine and clozapine are most likely to cause such adverse effects
- Drug affinities for histamine, dopamine, serotonin and muscarinic receptors are closely linked to cardiovascular risk accumulation and metabolic dysfunction, but the exact underlying pharmacological mechanisms remain to be elucidated
- Abnormalities in glucose and lipid metabolism often occur via increased abdominal adiposity; however, antipsychotic drugs associated with pronounced metabolic adverse effects can also have a direct molecular effect
- Patients with a history of heart disease, arrhythmia, or syncope, or a family history of prolonged QT syndrome or early sudden cardiac death should not receive QT-prolonging antipsychotic drugs
- Monitoring cardiovascular risk is insufficient; patients' weight, blood pressure and fasting glucose and lipids should be assessed routinely, and, if possible, every patient should undergo electrocardiography before initiation of antipsychotic treatment
- Healthy diet, regular exercise and smoking cessation reduce patients' cardiovascular and metabolic risk; low-risk antipsychotic agents, adding weight-lowering medications and/or treating significant cardiovascular and metabolic abnormalities might also help

Cardiovascular and metabolic risks

Weight gain in adults

An increasing body of evidence indicates that, compared with the general population, people with early-stage or previously untreated schizophrenia and bipolar disorder are at an increased risk of overweight (BMI 25–<30 kg/m^2), obesity (BMI ≥30 kg/m^2) and central obesity (waist circumference >102 cm in men and >88 cm in women; that is, a 2.8–3.5-fold increase in the risk of obesity in patients with schizophrenia and a 1.2–1.5-fold increase in patients with bipolar disorder).[15,16] In addition, weight gain is a well-established adverse effect of acute and maintenance antipsychotic treatment in patients with schizophrenia, and affects between 15% and 72% of patients.[15,16] Accumulating evidence suggests that similar effects occur in patients with bipolar disorder.[16–18]

Individual antipsychotic drugs are consistently associated with different degrees of weight gain, as confirmed by several studies and meta-analyses.[8,9,19–23] Among first-generation drugs, the so-called low-potency agents, such as chlorpromazine and thioridazine, are associated with a higher risk of weight gain than either mid-potency or high-potency agents (Table 1). However, weight gain is greatest with the second-generation agents, clozapine and olanzapine. Compared to iloperidone, quetiapine, risperidone, paliperidone, sertindole and zotepine, which confer an intermediate risk of weight gain, amisulpride, aripiprazole, asenapine, lurasidone and ziprasidone are associated with a small increase in body weight (Table 1).[16] No antipsychotic agent, however, should be considered entirely body-weight-neutral, as the proportion of individuals who experience clinically relevant weight gain (defined as ≥7% of pretreatment body weight) is greater with any antipsychotic agent than with placebo.[24] Moreover, all antipsychotic drugs can cause notable weight gain in patients who are taking these agents for the first time.[21,25–27] For example, in a 12-month trial involving patients with a first episode of schizophrenia who were treated with antipsychotic drugs that are considered body-weight-neutral (such as amisulpride, ziprasidone and low doses of haloperidol), each drug was associated with a notable weight gain (9.7 kg, 4.8 kg and 6.3 kg, respectively) by the end of the study.[21] Interestingly, the greatest amount of weight gain associated with antipsychotic therapy in previously drug-naive patients with schizophrenia seems to occur in the first few months, suggesting an asymptotic weight gain trajectory. For example, a meta-analysis reported a mean weight gain of about 3.8 kg and a mean gain in BMI of 1.2 kg/m^2 within the first 12 weeks of antipsychotic treatment in previously drug-naive patients who were >15 years old.[25]

Although several predictors of antipsychotic-drug-related weight gain have been identified (Box 2), the exact mechanisms underlying this effect remain to be elucidated (discussed below).[11] Factors that influence a patient's risk of antipsychotic-drug-induced weight gain include demographic variables, treatment setting (inpatient versus outpatient), illness characteristics, past and current treatment with antipsychotic drugs and other

Table 1 | Metabolic risks associated with antipsychotic drugs

Antipsychotic drug	Potency	Associated risk of weight gain	Associated risk of lipid and/or glucose metabolism abnormalities
First-generation agents			
Chorpromazine	Low	Substantial	High (limited data)
Fluphenazine	High	Neutral/low	Low (limited data)
Haloperidol	High	Neutral/low	Low
Molindone	Mid	Neutral	Low (limited data)
Perphenazine	Mid	Neutral/low	Low
Pimozide	High	Neutral/low	Low (limited data)
Thioridazine	Low	Intermediate	High (limited data)
Second-generation agents			
Amisulpride	NA	Neutral/low	Mild
Aripiprazole	NA	Neutral/low	Low
Asenapine	NA	Low	Low (limited data)
Clozapine	NA	Substantial	High
Iloperidone	NA	Intermediate	Mild (limited data)
Lurasidone	NA	Neutral/low	Low (limited data)
Olanzapine	NA	Substantial	High
Paliperidone	NA	Intermediate	Mild
Quetiapine	NA	Intermediate	Moderate
Risperidone	NA	Intermediate	Mild
Sertindole	NA	Intermediate	Mild
Ziprasidone	NA	Neutral/low	Low
Zotepine	NA	Intermediate	NR

Abbreviations: NA, not applicable; NR, not reported.

Box 1 | Adverse effects of antipsychotic therapy

Motor symptoms

Acute extrapyramidal adverse effects

- Dystonic reaction
- Akinesia
- Tremor
- Parkinsonism
- Akathisia
- Neuroleptic malignant syndrome

Chronic extrapyramidal adverse effects

- Tardive dyskinesia, dystonia and akathisia

Metabolic adverse effects

Weight gain, especially abdominal obesity

Impaired glucose metabolism

- Hyperglycemia
- Type 2 diabetes mellitus
- Diabetic ketoacidosis and coma

Dyslipidemia

- Hypercholesterolemia
- Hypertriglyceridemia
- Low HDL

Cardiovascular adverse events

Arterial hypertension

Disorders of the heart and blood vessels related to atherosclerosis

Sudden cardiac death

medications, and the patient's pretreatment diet, activity levels, and body composition. Mediators of antipsychotic-drug-related weight gain include treatment adherence, dose of the antipsychotic drug, other concurrent medications and medication-related adverse effects, as well as changes in diet and activity levels.[11] The findings of some, but not all, studies suggest that women have a greater vulnerability to antipsychotic-drug-induced weight gain than men.[11,20] Although the results are not entirely clear-cut, some evidence suggests that olanzapine and clozapine treatment have a dose-dependent relationship with weight gain.[11]

Weight gain in children and adolescents

The second-generation antipsychotic agents aripiprazole, olanzapine, quetiapine and risperidone have been approved by the FDA for the treatment of bipolar mania in children aged 10–17 years (or, for olanzapine, 13–17 years) and of schizophrenia in children aged 13–17 years, followed by the FDA approval of paliperidone for the treatment of schizophrenia in adolescents. In addition, aripiprazole and risperidone have also been approved for the treatment of irritability and aggression associated with autistic disorder in children (aged 5–17 years for risperidone and 6–17 years for aripiprazole).

Increasing evidence shows that antipsychotic drugs have a greater orexigenic effect in children and adolescents than in adults,[21,28] and that young patients receiving antipsychotic treatment are at an increased risk of being overweight or obese.[3,20,29–31] However, reliable data on the long-term metabolic effects of antipsychotic treatment are scarce. A systematic review of randomized, placebo-controlled trials of second-generation antipsychotic drugs in patients <18 years of age identified a hierarchy in the risk of weight gain, similar to that seen in adult patients,[3] whereby clozapine and olanzapine were associated with the most weight gain, followed by risperidone, quetiapine, aripiprazole, and finally ziprasidone. Another review of 34 head-to-head and placebo-controlled studies, involving a total of 2,719 young patients with psychotic and bipolar disorders who received olanzapine, clozapine, risperidone, quetiapine or aripiprazole for a duration of 3 weeks to 12 months (in 79.4% of these studies, the treatment duration was ≤3 months) reported an average weight gain of 3.8–16.2 kg with olanzapine, 0.9–9.5 kg with clozapine, 1.9–7.2 kg with risperidone, 2.3–6.1 kg with quetiapine and 0–4.4 kg with aripiprazole.[32]

An analysis of retrospective and prospective clinical reports suggested that a patient's risk of weight gain might be influenced by a synergistic interaction between age and polypharmacy.[11,20] Further research indicated that young age and polypharmacy demonstrated strong, positive associations with an increased risk of obesity (OR 2.28, 95% CI 1.49–3.65)[33] and cardiovascular, cerebrovascular or hypertensive adverse events (OR 1.72, 95% CI 1.10–2.69).[34]

Importantly, although the differential risk of weight gain associated with the various antipsychotic drugs seems to be consistent across adult, adolescent and child populations, high inter-individual variability in weight gain among patients treated with a given agent suggests that personal, familial or genetic factors also influence how much weight is gained.[11,20,25,35] According to post-marketing data on olanzapine collected in 474 adult patients treated in the US, the distribution of weight gain after 24 months of exposure to this drug was ≤0 kg in 23.2% of patients, 0–5 kg in 23.4% of patients, 5–10 kg in 24.1% of patients, 10–15 kg in 11.4% of patients, 15–20 kg in 9.3% of patients, 20–25 kg in 5.1% of patients, 25–30 kg in 2.3% of patients and >30 kg in 1.2% of patients.[36] However, as medication adherence was not measured, the lack of weight gain in almost one-quarter of patients treated with olanzapine could have resulted from poor treatment adherence.

The metabolic syndrome and its components

The major components of the metabolic syndrome are generally agreed to include central obesity, hypertension, dyslipidemia, and glucose intolerance or insulin resistance. The metabolic syndrome confers a 5–6-fold increase in the risk of developing type 2 diabetes mellitus and a 3–6-fold increase in the risk of death from coronary heart disease.[37–39] A review of prospective, longitudinal studies of the early cardiovascular and metabolic adverse effects (such as weight gain, hyperglycemia, hypertension and dyslipidemia) of antipsychotic drug treatment in patients treated for a first-episode psychotic disorder revealed that cardiovascular risk increased significantly after the patients' initial exposure to the antipsychotic

drug.[40] The potential for various antipsychotic drugs to cause or exacerbate the metabolic syndrome in patients is not, however, restricted to those with first-episode disease (Table 1). In general, the risk of developing the metabolic syndrome is greatest with clozapine, olanzapine and chlorpromazine; quetiapine confers a moderate increase in risk, whereas risperidone, paliperidone, amisulpride and sertindole are associated with a mild increase in risk, and aripiprazole and ziprasidone generally carry a low risk for development of the metabolic syndrome.[9,16,26,41–43] However, these associations can differ substantially in naturalistic cohorts of patients,[44] probably owing to confounding by indication (meaning that low-risk agents are mostly prescribed to patients at high risk of developing the metabolic syndrome).

In a meta-analysis of 112 studies ($n = 23{,}799$) in patients with schizophrenia and related psychotic diseases, the metabolic syndrome was most prevalent in patients taking clozapine (49.7%),[29] whereas patients treated for their first psychotic episode and those who had not previously taken antipsychotic drugs had the lowest rates of the metabolic syndrome (15.3% and 12.6%, respectively).[29] In addition, 51.2% of patients with schizophrenia and 49.3% of those with schizophrenia-related psychotic diseases were overweight. About 25% of antipsychotic-drug-treated patients with schizophrenia or related psychotic diseases had elevated blood glucose levels (≥100 mg/dl or ≥5.55 mmol/l) and about 50% had dyslipidemia.[29] However, mental illness is not consistently associated with hypertension. Antipsychotic drugs can lead to or worsen hypertension via weight gain, but this effect can also be attenuated or offset by the hypotensive properties of these medications, conferred by their intrinsic antagonistic action on adrenergic receptors.[41]

Olanzapine and clozapine are associated with the highest risk of dyslipidemia, whereas risperidone and quetiapine confer an intermediate risk, and aripiprazole and ziprasidone confer a low risk of this metabolic abnormality. Moreover, the deleterious effects of olanzapine, clozapine and quetiapine on serum lipids can be independent of BMI or in addition to weight-related effects.[11,30] Dyslipidemia should not, therefore, be viewed only as a consequence of weight gain, but also as a separate and direct adverse effect of antipsychotic drug therapy. The dyslipidemic adverse effects of clozapine, olanzapine and quetiapine manifest as abnormal elevations in levels of serum triglycerides and as an increase in total, LDL and non-HDL cholesterol levels. The effects of antipsychotic drugs on triglyceride levels seem to be greater than those on cholesterol levels, at least for clozapine, olanzapine and quetiapine.[11,30] Interestingly, risperidone has been associated with a low risk of adverse effects on cholesterol and triglyceride levels,[20] although a significant elevation of serum triglyceride levels was observed in young, antipsychotic-drug-naive patients who initiated treatment with this drug.[30] Aripiprazole and ziprasidone, however, seem to have a neutral effect on lipid levels.[11,30]

Dysregulation of glucose homeostasis (hyperglycemia and insulin resistance), independently of weight gain and adiposity, has been described in conjunction with clozapine and olanzapine treatment.[22] Quetiapine is considered to confer a moderate risk of hyperglycemia—lower than that associated with clozapine and olanzapine, but possibly higher than that associated with risperidone. As with dyslipidemia, the risk of hyperglycemia is lowest with aripiprazole and ziprasidone treatment.[16]

Although the mechanism involved in the antipsychotic-drug-related adverse metabolic outcomes is not clear, preliminary evidence suggests a dose-dependent relationship between the serum concentrations of olanzapine and clozapine (and possibly risperidone) and metabolic abnormalities.[30,45] One study showed a potential correlation between the plasma levels of olanzapine, and possibly risperidone, and weight gain.[45] Another study conducted in antipsychotic-drug-naive pediatric patients showed a dose-dependent effect of olanzapine on serum lipid profiles and blood glucose levels, and a dose-dependent effect of risperidone on weight gain, as well as serum lipid profiles.[30] A systematic review and meta-analysis also found that treatment with olanzapine and clozapine produced a greater increase in blood glucose levels than that induced by amisulpride, aripiprazole, quetiapine, risperidone and

Box 2 | Moderators* and mediators‡ of weight gain[11,22]

Familial factors
- Family history of obesity
- Parental BMI

Personal factors
- Cannabis use
- 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)
- Nonsmoking status
- Nonwhite ethnicity

Factors related to psychiatric illness
- Improved symptom reduction (limited or inconclusive data)
- First-episode status of psychiatric illness
- Lack of prior antipsychotic treatment

Treatment-related factors
- Early weight gain (within the first 2–4 weeks of antipsychotic 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)

*Factors that alter the strength of a causal relationship, and represent an intermediate step between cause and effect. Moderators indicate when or under which circumstances certain effects will occur. ‡Factors that interact with the primary causal factor and increase or reduce its influence. Mediators indicate how or why certain effects occur.

ziprasidone.[46] However, lifestyle and behavioral patterns (such as smoking, physical inactivity and poor dietary habits), as well as genetic risk factors, also have an important role in the prevalence of the metabolic syndrome and the risk of dyslipidemia and hyperglycemia in patients treated with antipsychotic drugs.[11,47–49]

Diabetes mellitus

The biological and behavioral risk factors for type 2 diabetes mellitus are well identified. The most important factors are overweight and obesity, particularly central obesity (relative risk [RR] 4.10–17.50)[50] and physical inactivity (RR 1.12–2.18).[50–52] Additional behavioral risk factors include smoking and a poor-quality diet (for example, low in whole grains and fiber).[16]

The risk of type 2 diabetes mellitus is 1.3-fold higher in people with schizophrenia taking second-generation antipsychotic agents than in those taking first-generation drugs.[53] Another study found an increased risk of type 2 diabetes mellitus in both patients treated with second-generation agents (adjusted hazard ratio [HR] 1.32, 95% CI 1.01–1.75) and those treated with first-generation agents (adjusted HR 1.82, 95% CI 1.30–2.55) versus control patients without schizophrenia.[54] Furthermore, the risk of diabetes-mellitus-related adverse events differs for individual agents. For example, olanzapine and clozapine, and to a lesser extent quetiapine and risperidone, are associated with a significant increase in the risk of diabetes mellitus.[55–57]

In a large, population-based study conducted in Denmark (which included 345,937 patients treated with an antipsychotic drug and 1,426,488 unexposed control individuals) the researchers found statistically significant increases in the incidence of diabetes mellitus among patients treated with clozapine, olanzapine or risperidone compared with the general population (RR 1.45, 95% CI 1.28–1.64 for clozapine; RR 1.29, 95% CI 1.20–1.37 for olanzapine and RR 1.23, 95% CI 1.15–1.32 for risperidone).[44] The incidence of diabetes mellitus was not significantly increased in patients treated with aripiprazole, amisulpride or quetiapine; however, patients treated with sertindole (RR 1.94, 95% CI 1.32–2.84), perphenazine (RR 1.57, 95% CI 1.48–1.67), ziprasidone (RR 1.94, CI 1.62–2.31) and even haloperidol (RR 1.17, 95% CI 1.08–1.26), which are generally not thought to increase the risk of diabetes mellitus, still had a higher rate of diabetes mellitus than controls.[44] The findings of this non-randomized pharmacoepidemiological study might, therefore, reflect the presence of potential unmeasured confounding variables that could affect the antipsychotic-drug-related diabetogenic effects.

The FDA's database of adverse events associated with haloperidol or second-generation antipsychotic drugs (in which the spectrum of diabetes-mellitus-related events ranged from new-onset hyperglycemia to life-threatening ketoacidosis) has been analyzed to estimate the strength of the association between a drug and diabetes-mellitus-related adverse events, relative to that for all drugs and events. The adjusted reporting ratios for diabetes-mellitus-related adverse outcomes were: olanzapine 9.6, 95% CI 9.2–10.0; risperidone 3.8, 95% CI 3.5–4.1; quetiapine 3.5, 95% CI 3.2–3.9; clozapine 3.1, 95% CI 2.9–3.3; ziprasidone 2.4, 95% CI 2.0–2.9; aripiprazole 2.4, 95% CI 1.9–2.9; and haloperidol 2.0, 95% CI 1.7–2.3.[58] Selective reporting of adverse events and confounding by indication (meaning that low-risk agents are preferentially prescribed to high-risk patients) make these data difficult to interpret. By contrast, a systematic review of 22 prospective, randomized, controlled trials found no difference in the incidence of glycemic abnormalities between groups of patients who received either placebo or an antipsychotic agent, and all the drugs studied had a similar association with impaired glycemic control.[59] Although the trials included in this systematic review were mostly of short duration (a common limitation of controlled trials when evaluating the risk of distal adverse outcomes), the inconsistency of the findings further illustrates that associations with adverse effects are dependent on the patient population, the type of mental illness and study-specific factors.

However, in patients with a first episode of schizophrenia, treatment with the same agents associated with the greatest risk of diabetes mellitus in patients with chronic disease—olanzapine and clozapine—also seem to have the strongest diabetogenic potential. Importantly, the only prospective pharmacoepidemiological study conducted in antipsychotic-drug-naive patients, which involved 7,139 patients with a first episode of schizophrenia who were followed for 47,297 patient-years, the time to onset of diabetes mellitus was significantly shorter during the first year of treatment with the second-generation agent olanzapine (HR 1.41, 95% CI 1.09–1.83) and the mid-potency first-generation agents zuclopenthixol, periciazine, prochlorperazine and perphenazine (HR 1.60, 95% CI 1.07–2.39) when compared with patients who were not taking these drugs.[42] Relevant factors associated with the risk of incident diabetes mellitus within 3 months of the onset of outcome, adjusted for exposure time to antipsychotic drugs, included treatment with the low-potency first-generation agents chlorpromazine, levomepromazine, chlorprothixen, melperone and pipamperone (OR 1.45, 95% CI 1.08–1.96) and the second-generation agents olanzapine (OR 1.57, 95% CI 1.17–2.11) and clozapine (OR 2.31, 95% CI 1.55–3.44). Notably, patients who were not taking any antipsychotic drugs (OR 0.60, 95% CI 0.43–0.84) and those taking aripiprazole (OR 0.53, 95% CI 0.34–0.82) had a reduced risk of diabetes mellitus.[42]

Clinicians should be aware that the increased risk of diabetes mellitus associated with antipsychotic drugs seems to be greatest in patients aged 0–24 years (OR 8.9, CI 7.0–11.3 versus age-matched individuals not treated with these agents),[60] although diabetes mellitus incidence rates generally increase with age. This contradiction seems to be due to a low background risk for diabetes mellitus at a young age, which makes the diabetogenic effect of the antipsychotic drugs noticeable, whereas at an old age, the effect of the biological and behavioural risk factors becomes more pronounced than that of antipsychotic drugs. One study,[61] which compared 80 antipsychotic-drug-naive individuals with 65 young

patients treated with second-generation antipsychotic agents, showed that 21.5% of the drug-treated group had elevated fasting plasma glucose levels or type 2 diabetes mellitus, compared with 7.5% of the drug-naive group ($P = 0.01$).

Potential underlying mechanisms

Antipsychotic-drug-induced weight gain and metabolic abnormalities cannot be attributed to a single functional pathway;[11] however, robust evidence suggests that histaminergic transmission is involved in energy homeostasis. This mechanism also seems to be relevant to the adverse effects of antipsychotic agents, as the extent of histamine H_1 receptor antagonism of antipsychotic drugs was the best predictor of the degree of weight gain in clinical studies.[62,63]

Serotonin and its receptors, 5-HT_{2a} and 5-HT_{2c}, have a major role in the control of food intake and body weight. As most second-generation antipsychotic drugs, especially clozapine and olanzapine, are potent 5-HT_{2c} antagonists, this receptor has also been implicated in antipsychotic-drug-related weight gain. The fact that aripiprazole and ziprasidone have only a weak association with metabolic dysregulation, despite their high affinities for 5HT_{2c} receptors, could be explained by other receptor-specific mechanisms that potentially counterbalance inhibition of the 5HT_{2c} receptors. For example, aripiprazole is a partial agonist of 5-HT_{1a} receptors.[64]

Blockade of the dopamine D_2 and D_3 receptors is another potential mechanism involved in antipsychotic-drug-induced weight gain, as D_2 receptor blockade has a strong effect on feeding behavior.[11] All antipsychotic drugs bind to and act either as antagonists or partial agonists for D_2 receptors, and a clinically significant weight gain (that is, ≥7% of pretreatment body weight) can be observed even with antipsychotic agents that interact exclusively with D_2 and D_3 receptors, such as amisulpride.[21] Moreover, synergistic effects between the blockade of D_2 receptors and 5-HT_{2a} or 5-HT_{2c} receptors might have a key role in triggering a cascade of events that lead to increased energy intake and weight gain.[11]

Muscarinic M_2 and M_3 receptors are found on pancreatic β cells, as well as many other cells. The affinity of second-generation antipsychotic agents for M_2[65] and M_3 receptors[20,35,66] seems to be relevant, especially for glucose homeostasis, perhaps because M_3 receptors control cholinergic-dependent insulin release. Some antipsychotic drugs (such as clozapine and olanzapine) might impair both cholinergic-dependent and glucose-dependent insulin secretion from pancreatic β cells.[20] Among antipsychotic agents, a high affinity for the M_3 receptor, as is seen with clozapine and olanzapine, seems to be the best predictor of a propensity to promote glucose dysregulation and type 2 diabetes mellitus.[20,66] Similarly to aripiprazole, risperidone, amisulpride and lurasidone, asenapine, which has a relatively low propensity to cause weight gain, shows no appreciable affinity for muscarinic receptors.[67]

Clear evidence of a similar association between blockade of adrenergic α_1 and α_2 receptors and antipsychotic-drug-induced weight gain or metabolic dysregulation is lacking,[20] although genetic data point toward a potential role of α-adrenergic transmission.[11,68] Genetic data also suggest a role for G-protein signaling, leptin signaling and leptin receptor activity, promelanin-concentrating hormone signaling and cannabinoid receptor activity in the weight gain induced by antipsychotic drugs.[11,13,68–71] The receptor-binding profiles that correlate with antipsychotic-drug-associated dyslipidemia are not well understood; however, peroxisome proliferator-activated receptors and transcriptional regulators of lipid and carbohydrate metabolism may have a relevant role.[72] Studies suggest that antipsychotic-drug-related dysregulation of hepatic lipid metabolism could result from the inhibition of AMP-activated protein kinase activity.[73]

Risk of sudden cardiac death

Consistently with prior studies,[74,75] a large pharmacoepidemiological study in patients receiving antipsychotic monotherapy (44,218 users of first-generation drugs, 46,089 users of second-generation and 186,600 non-users matched for cardiovascular disease risk based on patient data on file), showed a similar, dose-dependent increase in the risk of sudden cardiac death (SCD) for patients treated with either first-generation or second-generation agents (Box 1).[76] The adjusted incidence rate ratios for SCD were similar for both typical and atypical antipsychotic drugs: 1.31 (95% CI 0.97–1.77) versus 1.59 (95% CI 1.03–2.46) for low doses (equivalent to <100 mg of chlorpromazine), 2.01 (95% CI 1.62–2.50) versus 2.13 (95% CI 1.70–2.65) for moderate doses (equivalent to 100–299 mg of chlorpromazine), and 2.42 (95% CI 1.91–3.06) versus 2.86 (95% CI 2.25–3.65) for high doses (equivalent to ≥300 mg of chlorpromazine).[76] However, these data have been questioned, as the arrhythmogenic reason for SCD was largely undocumented. Moreover, SCD is over-reported in mentally ill patients, who often have undiagnosed and untreated ischemic heart disease (which is by far the largest contributor to cardiac mortality).[77] In addition, high doses of antipsychotic drugs are usually given to patients with more severe mental illness who have worse somatic health. Nevertheless, the excess of SCDs associated with antipsychotic use might be related to the effect of these drugs on myocardial repolarization, which is evident through their varying, but well-established, propensity to prolong the corrected QT (QTc) interval. Among cardiologists, the consensus view is that a QTc >500 ms, or a relative increase in QTc of at least 60 ms from baseline (drug-free) values, are associated with a significantly increased risk of torsade de pointes, ventricular fibrillation and SCD.[78,79]

Antipsychotic drugs associated with a high risk of QTc prolongation include the first-generation agents pimozide, thioridazine[80] and mesoridazine,[79] and the second-generation drugs sertindole and ziprasidone.[81,82] Owing to their strong QTc prolonging effects, mesoridazine and thioridazine have been removed from the market in the US and many other countries. However, the largest randomized study to date ($n = 18,154$) did not find a statistically or clinically significant difference in SCD risk between patients with schizophrenia

who were treated with either ziprasidone—the second-generation antipsychotic drug with the highest risk of QTc prolongation—or olanzapine, which causes minimal or no QTc prolongation.[82] Similarly, another large randomized study ($n = 9,858$) observed no statistically significant difference in rates of cardiac events, including arrhythmias requiring hospitalization, between patients treated with either sertindole (another second-generation antipsychotic drug with a high risk of QTc prolongation) or risperidone, although overall mortality from cardiac events was higher with sertindole than with risperidone.[81] One caveat in relation to these findings, however, is that patients with medically unstable or high-risk cardiac disease are generally excluded from large-scale studies.[83]

Disparities in health care

The majority of patients receiving antipsychotic treatment in psychiatric hospitals or general health-care clinics are not monitored for metabolic risk factors, even those that are simple to measure, such as obesity and high blood pressure.[12,13,84–86] Several large-scale pharmacoepidemiological studies, which compared large groups of control individuals without a psychiatric disorder to individuals taking a second-generation antipsychotic agent, showed low mean rates of baseline testing for metabolic risk factors. Follow-up assessments were performed in only few patients. Even after publication of FDA warnings and recommendations from the American Diabetes Association (ADA) and the American Psychiatric Association (APA), the frequency of baseline testing for blood glucose and serum lipid levels in patients receiving second-generation antipsychotic agents have changed very little.[12,87] Another study of medical records from >23,000 patients treated with antipsychotic drugs included in a managed health-care database compared the use of screening before and after publication of the ADA and APA guidelines.[12] Only slight increases in testing occurred for blood glucose and serum lipid levels, both at baseline (from 17.3% to 21.8% for glucose and from 8.4% to 10.5% for lipids) and after 12 weeks of drug use (from 14.1% to 17.9% for glucose and from 6.8% to 9.0% for lipids).[12]

A systematic review and meta-analysis of 48 studies examining routine metabolic screening in patients taking antipsychotic drugs, both before (39 studies, $n = 218,940$) and after (9 studies, $n = 71,594$) the publication of monitoring guidelines, showed that although guidelines slightly increased monitoring, most patients do not receive adequate testing for cardiovascular and metabolic abnormalities—a prerequisite for timely treatment of these abnormalities.[14] Likewise, most children, who initiated treatment with a second-generation antipsychotic drug, did not receive the recommended screening for blood glucose and serum lipids. Paradoxically, young patients, who are most vulnerable to metabolic dysregulation, were the least likely to be tested for metabolic risk factors.[12,13] These findings emphasize the importance of establishing and implementing a standardized monitoring system for all patients receiving antipsychotic drugs.

The same disparities in health care are found with regard to the treatment of cardiovascular risk factors and disorders. Patients with schizophrenia and bipolar disorder have a high mortality from cardiovascular disease, but a low chance of receiving circulatory medications, or surgical interventions, such as stents and coronary artery bypass grafting.[8,88–90] Evidence suggests that people with schizophrenia are not adequately screened and treated for either dyslipidemia (up to 88% of such patients remain untreated) or hypertension (up to 62% of such patients remain untreated).[88,91–96] Poor quality medical care contributes greatly to excessive mortality in elderly people with mental disorders, second only to heart failure.[91] Another important barrier is that few patients with mental illness seek medical help,[91] even when they have acute cardiovascular syndromes.[97]

Recommendations for monitoring

Assessment of metabolic risk factors associated with antipsychotic therapy should begin with taking the patient's personal and family history of type 2 diabetes mellitus, hypertension, cardiovascular diseases (such as myocardial infarction and stroke, including the age at onset), smoking, diet and physical activity levels (Table 2). Secondly, the individual components of the metabolic syndrome, which are critical in predicting morbidity and mortality from cardiovascular disease and diabetes mellitus, as well as other nonmetabolic risk factors associated with antipsychotic treatment, should be evaluated at baseline and measured regularly thereafter (Table 2).[98] Patients who are taking antipsychotic drugs for the first time or being treated for a first episode of schizophrenia, children and adolescents (all of whom are at an increased risk of metabolic disorders), and those with substantial weight gain should be monitored particularly closely.[3,30,92]

Central obesity

Psychiatrists should monitor and record the BMI and waist circumference of every patient at each clinic visit regardless of the type of antipsychotic drug they have been prescribed; patients should also be encouraged to monitor and record their own weight. Waist circumference, which is simple and inexpensive to measure, is a better predictor than BMI of systolic blood pressure, HDL cholesterol and triglyceride levels.[99,100] This parameter has, therefore, been proposed as the best single measurement to identify individuals at a high risk of cardiovascular disease and the metabolic syndrome,[100] to assess the likelihood of insulin resistance and to predict the future occurrence of type 2 diabetes mellitus.[101] Nonetheless, waist circumference is rarely measured.[14,84]

As antipsychotic drugs also have potential weight-independent metabolic effects, several other parameters relevant to the metabolic syndrome, such as blood pressure, fasting plasma glucose levels and fasting lipid profiles, should also be assessed routinely (Table 2), even in patients with normal BMI or waist circumference, or in those with minimal observed weight gain.

Table 2 | Recommendations for management of patients receiving with antipsychotic drugs[16]

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)

The psychiatric care provider should take responsibility for at least the monitoring of metabolic adverse effects of antipsychotic agents. *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. ‡Recommended in children and adolescents, as well as antipsychotic-drug-naive adults, as abnormalities in these groups abnormalities are most pronounced at the beginning of treatment. §Recommended at each clinic visit during the first 6–8 weeks of antipsychotic drug treatment, as the initial rate of weight gain predicts total weight gain. ‖Recommended in Europe, but not in the US, to rule out precipitous diabetes onset. ¶Recommended in Europe, but not in the US. **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. Adapted from European Psychiatric Association, European Association for the Study of Diabetes and European Society of Cardiology recommendations by De Hert *et al.* (2009).[41]

Blood pressure

As hypertension (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg)[102] is an important risk factor for cardiovascular disease, blood pressure should be assessed at the same time as the fasting blood glucose and lipid levels are measured. However, high blood pressure in patients taking antipsychotic agents is often missed due to lack of monitoring.[41] A diagnosis of hypertension requires at least two separate abnormally elevated measurements.[41] Moreover, individuals with a systolic blood pressure of 120–139 mmHg or a diastolic blood pressure of 80–89 mmHg are at risk of hypertension and require lifestyle modifications.[103]

Fasting blood glucose and lipid levels

Baseline fasting plasma glucose levels should be obtained for all patients before starting antipsychotic treatment. Thereafter, tests should be performed at 6 weeks and 3 months to capture early cases of hyperglycemia, and then at least annually thereafter. Fasting plasma glucose levels between 100 mg/dl (5.6 mmol/l) and 125 mg/dl (6.9 mmol/l), or HbA_{1c} values of 5.7–6.4% indicate a high risk of future diabetes mellitus, which should prompt close assessment and follow-up, as well as referral to a primary care physician or endocrinologist. An international expert committee, whose members were appointed by the ADA, European Association for the Study of Diabetes and the International Diabetes Federation, specifically considered whether HbA_{1c} testing should be used to diagnose diabetes mellitus.[104] Although the sensitivity and specificity of HbA_{1c}-based testing for diabetes mellitus in people with severe mental illness needs to be established, the preliminary evidence seems to be promising. In a European population of patients with psychiatric disease treated with antipsychotic drugs, the largest contributor to the identification of prediabetes (defined according to the ADA criteria) was elevated HbA_{1c}, which was the sole diabetes-related abnormality in 120 of 290 patients (41.4%) identified as having prediabetes.[105]

Patients who have multiple risk factors for diabetes mellitus (such as a family history of diabetes mellitus, BMI ≥25 kg/m^2, central obesity, gestational diabetes, or nonwhite ethnicity) or who have gained ≥7% of their pre-treatment weight should have their fasting plasma glucose levels monitored at the same times as for other patients within the first 3 months (that is, at baseline, week 6 and week 12 of antipsychotic treatment), but more frequently thereafter (approximately every 3–6 months).

Lipid profiles (that is, triglycerides and total, HDL and LDL cholesterol) should also be assessed at baseline, as well as 6 weeks and 3 months after initiation of antipsychotic treatment, with annual assessments thereafter. The calculated triglyceride:HDL ratio—a simple, readily available and inexpensive measure—can be a useful surrogate measure of insulin resistance in antipsychotic-drug-treated patients with schizophrenia without prior diabetes mellitus.[106] In case of abnormal values of lipids or a triglyceride:HDL ratio >3.5, more frequent monitoring is required. If lifestyle measures are insufficient to correct dyslipidemia, treatment with lipid-lowering agents, such as statins, has been effective in patients taking antipsychotic drugs.[107,108]

Cardiovascular disease

Regardless of which type of antipsychotic therapy is intended, the patient should be asked about clinical

Box 3 | Risk factors for cardiovascular events[107,108]

Personal history

- Fainting or dizziness upon exertion
- Seizures
- Rheumatic fever
- Hearing loss
- Chest pain or shortness of breath or unusual fatigue with exercise
- Palpitations, increased heart rate or skipped beats
- High blood pressure
- Heart murmur or other cardiac problems
- Intercurrent viral illness with chest pains or palpitations
- Current treatment with drugs known to prolong QTc
- Active eating disorder with low BMI
- Type 1 or type 2 diabetes mellitus
- Substance abuse disorders, including with cocaine or stimulants
- Hypokalemia or hypomagnesemia

Family history

- Sudden cardiac death, heart attack, or cardiac event requiring resuscitation at <50 years of age for men and <55 years of age for women
- Cardiac arrhythmias
- Cardiomyopathy
- Abnormal electrocardiographic findings
- Marfan syndrome
- Prolonged QT syndrome

Indications from physical examination

- Cardiomegaly
- Murmurs
- Arrhythmias
- Hypertension
- Marfan syndrome features

Data obtained from Perrin *et al.*[109] and Vetter *et al.*[110] Abbreviation: QTc, corrected QT interval.

risk factors for arrhythmias, such as a family history of early sudden cardiac death (<50 years of age in men and <55 years of age in women), any personal history of heart murmur, previous prescriptions of cardiac medications or antihypertensive agents, hypertension, the metabolic syndrome or diabetes mellitus, tachycardia at rest, irregular heart beat and syncope (particularly that during exertion).[109,110] Each patient's cardiovascular disease risk should be calculated according to their age and sex, with reference to the European SCORE (Systemic Coronary Risk Evaluation) guidelines for estimating the relative risk of fatal cardiovascular disease in people with severe mental illness.[41] Alternatively, local protocols and online risk calculators, which take into account the presence of diabetes mellitus, smoking habit, systolic blood pressure and total cholesterol levels, or total cholesterol:HDL cholesterol ratio, can be used.[111]

Although high-quality, longitudinal data investigating the utility of electrocardiographic assessments for prevention of cardiac events are lacking and electrocardiography can be difficult to conduct in outpatient settings, several guidelines on physical health in antipsychotic-drug-treated adults with a severe mental illness have recommended that, whenever possible, every patient should undergo electrocardiography before the initiation of antipsychotic treatment.[112] Baseline electrocardiography is especially important, and should be mandatory, in patients with risk factors for QTc prolongation, cardiac arrhythmias or SCD (Box 3).[109,110] For patients with a high risk of SCD, such as those with diabetes mellitus or the metabolic syndrome, annual electrocardiography should be considered. Children without clinical or historical risk factors for arrhythmias do not need to undergo baseline electrocardiography, however,[113] as pre-existing coronary heart disease, which alters the cardiac conduction system, is probably a prerequisite for the arrhythmogenic potential of antipsychotic drugs to become clinically manifest.[77]

Antipsychotic medications associated with QTc prolongation (such as mesoridazine, pimozide, thioridazine, sertindole and ziprasidone) should not be prescribed to patients with known heart disease, a personal history of syncope, a family history of early SCD (<50 years of age for men and <55 years of age for women, especially if both parents were affected), or those with congenital long QT syndrome.[114,115] The American College of Cardiology, the American Heart Association and the European Society of Cardiology Committee (ACC/AHA/ESC) guidelines also recommend withdrawal of any antipsychotic drug and correction of electrolyte abnormalities in patients who present with cardiac arrhythmias, particularly torsade de pointes.[116]

Managing adverse effects

Strategies to minimize or reverse cardiovascular and metabolic adverse effects associated with antipsychotic drugs include promotion of a healthy lifestyle, use of or switching to a low-risk antipsychotic medication, or addition of medications that reduce weight and/or reverse metabolic abnormalities.[10,26,117]

Many, but not all, antipsychotic-drug-treated patients are either unaware of the need to alter their lifestyle or unable to make the necessary changes. Psychiatrists, physicians, nurses and other members of the multidisciplinary care team can educate these patients, as well as their carers, about healthy lifestyles, and should use effective behavioral interventions to motivate patients to make the necessary changes, including smoking cessation, adoption of a healthy diet and regular physical exercise.[86,117,118] If such lifestyle interventions do not succeed, however, additional medications (such as statins, antihypertensive therapy or antidiabetes agents) might be indicated. These drugs are generally well tolerated and should be prescribed and managed as for the general population.

Many doctors are reluctant to switch antipsychotic medications, even for patients who have or develop physical health issues.[41,119] Nevertheless, if a patient gains ≥7% of the pretreatment weight, or develops hyperglycemia, hyperlipidemia, hypertension or other clinically significant cardiovascular or metabolic adverse effects during antipsychotic therapy, switching to a low-risk drug

should be considered.[41,43] The decision to switch drugs should take into consideration the entire psychiatric and physical condition of the patient and the pharmacological profiles of current and proposed drugs.[64] Analysis of the largest randomized controlled efficacy trial in schizophrenia to date confirmed that antipsychotic-drug-related weight gain was not associated with clinically relevant efficacy advantages, meaning that antipsychotic agents with low risk of weight gain was associated with similar effectiveness as the agents with high risk of weight gain.[120]

If switching drugs is not an option, then medications can be added to counteract antipsychotic-drug-induced adverse events; for example, metformin or topiramate have been shown to only partially (and not completely[10]) reverse the weight gain associated with antipsychotic treatment.[117] If a metabolic or cardiovascular disease is diagnosed, the patient should be referred to specialist diabetology, endocrinology and cardiology or other services to receive appropriate care.

Conclusions

Second-generation antipsychotic agents offer similar efficacy to first-generation agents, but are associated with fewer extrapyramidal symptoms and reduced risks of treatment discontinuation and relapse. However, concerns about extrapyramidal symptoms have been replaced by those about cardiovascular and metabolic adverse effects, such as obesity, impaired glucose tolerance, diabetes mellitus and dyslipidemia.

The potential of antipsychotic drugs to induce or trigger metabolic dysregulation, including type 2 diabetes mellitus and the metabolic syndrome, is firmly established. Although weight gain and cardiovascular and metabolic abnormalities are possible in patients treated with any antipsychotic agent, individual agents differ markedly in their propensities for inducing weight gain and metabolic abnormalities. In general, second-generation antipsychotic drugs are associated with an increased risk of these adverse effects versus first-generation drugs. The second-generation drugs ranked from high to low in terms of cardiovascular and metabolic adverse effects are as follows: clozapine = olanzapine, >quetiapine, ≥risperidone = paliperidone, >amisulpride, ≥aripiprazole, ≥ziprasidone. Of the first-generation agents, the low-potency agents have the highest, and the high-potency agents have the lowest, potential to cause cardiovascular and metabolic dysfunction; the risk profiles of the first-generation antipsychotic group is comparable to those of the high-risk and low-risk second-generation agents. Moreover, these same patterns are found in all populations treated with antipsychotic agents. Exactly where in this hierarchy newly approved second-generation agents will fall needs to be determined. However, children and adolescents, as well as previously untreated and first-episode patients, are particularly at risk of cardiovascular and metabolic adverse effects with any antipsychotic drug.

Despite improved understanding of the biochemical effects of these drugs, the pharmacological mechanisms underlying their association with cardiovascular and metabolic abnormalities remain unclear. The affinity of antipsychotic drugs for the histamine H_1 receptor is most closely linked to increased weight gain, although their affinity for dopamine D_2 and serotonin 5-HT_{2c} receptors might also be involved. An affinity specifically for the muscarinic M_3 receptor correlates with an increased risk of diabetes mellitus. However, the drug receptor-binding profiles that underlie dyslipidemia are not well understood.

Baseline and follow-up assessment of cardiovascular and metabolic abnormalities in patients treated with second-generation antipsychotic drugs is currently insufficient. Clearly, lifestyle-related factors that are easy to measure, such as weight, waist circumference and blood pressure, should be monitored at appropriate intervals in all patients treated with antipsychotic drugs. Although controversy surrounds the possible association of these drugs with SCD, performing electrocardiography before the initiation of antipsychotic therapy also seems to be reasonable. Annual electrocardiography should be considered for all patients at risk of SCD. In addition, psychiatrists, physicians, nurses and other members of the multidisciplinary care team can educate and motivate people with severe mental illness to improve their lifestyle through effective behavioral interventions, including smoking cessation, dietary measures and regular exercise. However, if lifestyle interventions do not succeed, other medications, including statins, antihypertensive therapy or antidiabetic agents, might be indicated. Moreover, pharmacologic treatments (such as metformin or topiramate) can be added to reduce antipsychotic-drug-related weight gain. New antipsychotic drugs should be developed that are weight-neutral and that do not have metabolic adverse effects, or that can even reverse pre-existing cardiovascular and metabolic abnormalities in patients with mental illness who are at an increased risk of cardiovascular and cerebrovascular morbidity and mortality.

Review criteria

We searched MEDLINE and PubMed for original articles on the adverse effects of antipsychotic drugs published between 1966 and 2011. We used the following Medical Subject Heading search terms, alone and in combination: "antipsychotic drugs", "schizophrenia", "bipolar disorder", "obesity", "weight gain", "dyslipidemia", "hyperglycemia", "diabetes mellitus", "metabolic syndrome", "cardiovascular disorders", and "sudden cardiac death". We included epidemiological, morbidity and mortality data, as well as pertinent reviews, and checked the reference lists from relevant articles to identify additional literature.

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Author contributions
M. De Hert and J. Detraux researched the data for the article and contributed equally to writing the article. R. van Winkel, W. Yu and C. U. Correll made substantial contribution to discussion of content and to reviewing and editing the manuscript before submission.