

Antipsychotics cardiotoxicity: What's known and what's next

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Abstract

Chronic use of antipsychotic medications entails a dilemma between the benefit of alleviating psychotic symptoms and the risk of troubling, sometimes life-shortening adverse effects. Antipsychotic-induced cardiotoxicity is one of the most life-threatening adverse effects that raises widespread concerns. These cardiotoxic effects range from arrhythmia to heart failure in the clinic, with myocarditis/cardiomyopathy, ischemic injuries, and unexplained cardiac lesions as the pathological bases. Multiple mechanisms have been proposed to underlie antipsychotic cardiotoxicity. This review aims to summarize the clinical signs and pathological changes of antipsychotic cardiotoxicity and introduce recent progress in understanding the underlying mechanisms at both the subcellular organelle level and the molecular level. We also provide an up-to-date perspective on future clinical monitoring and therapeutic strategies for antipsychotic cardiotoxicity. We propose that third-generation antipsychotics or drug adjuvant therapy, such as cannabinoid receptor modulators that confer dual benefits – *i.e.*, alleviating cardiotoxicity and improving metabolic disorders – deserve further clinical evaluation and marketing.

Key Words: Antipsychotics; Cardiotoxicity; Sudden cardiac deaths; Cannabinoid receptor; Adrenoceptor

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Core Tip: Antipsychotic drug-induced cardiotoxicity is troubling and sometimes life-threatening, which restricts their clinical application. Herein, we summarize the clinical signs and pathological changes of antipsychotic cardiotoxicity and introduce recent progress in understanding the underlying mechanisms at both the subcellular organelle level and the molecular level. Future perspectives regarding clinical monitoring and therapeutic strategies for antipsychotic cardiotoxicity are also discussed.

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INTRODUCTION

The use of antipsychotics is an important and integral part of psychiatric care and often lasts for a lifetime. Antipsychotics are primarily prescribed for the treatment of schizophrenia and other psychotic diseases[1] and are commonly categorized as first-generation antipsychotics (FGAs, or typical antipsychotics) and second-generation antipsychotics (SGAs, or atypical antipsychotics). Recently, several new and emerging antipsychotic medication strategies, termed third-generation antipsychotics (TGAs), have been marketed or are under clinical development for the treatment of mental disorders[2]. Generally, the evolution of antipsychotics has largely improved therapeutic outcomes in the clinic. However, inevitable side effects remain a clinical limitation that unfortunately results in drug withdrawal or discontinuation of potentially successful regimens[3]. These toxic effects range from minor issues (*e.g.*, mild sedation or dry mouth) to troubling issues (*e.g.*, weight gain or metabolic disturbances) to even life-threatening issues (*e.g.*, cardiotoxicity).

Clinical statistics have reported a clear link between the use of antipsychotics and increased incidence and mortality of sudden cardiac death (SCD)[4]. In a large Danish retrospective study, the incidence of SCD was 14.8 deaths per 100000 person-years in psychiatric individuals[5]. Current users of FGAs and SGAs had higher rates of SCD than nonusers of antipsychotic drugs, with adjusted incidence-rate ratios of 1.99 [95% confidence interval (CI): 1.68 to 2.34] and 2.26 (95%CI: 1.88 to 2.72), respectively[6]. Autopsy-based evidence also confirmed that approximately 3.5% of schizophrenia patients under antipsychotic use died from cardiac causes[7]. Moreover, SGAs seem to predispose patients to a mildly higher risk of SCD than FGAs, with an incidence-rate ratio of SGAs to FGAs of 1.14 (95%CI: 0.93 to 1.39). The incidence of antipsychotic-induced SCD is also dose-related. The incidence-rate ratios of FGA users increased from 1.31 (95%CI: 0.97 to 1.77) for those taking low doses to 2.42 (95%CI: 1.91 to 3.06) for those taking high doses ($P < 0.001$). Among users of SGAs, the incidence-rate ratios increased from 1.59 (95%CI: 1.03 to 2.46) for those taking low doses to 2.86 (95%CI: 2.25 to 3.65) for those taking high doses ($P = 0.01$)[6].

In recent decades, our knowledge of antipsychotic cardiotoxicity has been increasingly improved. This review aims to provide an up-to-date summary of recent progress in understanding the clinical manifestations, pathological alterations, and cellular and molecular mechanisms underlying this critical issue. We also propose future perspectives that await implementation.

CLINICAL MANIFESTATIONS OF ANTIPSYCHOTICS CARDIOTOXICITY

Multiple studies have reported antipsychotic cardiotoxicity from clinical perspectives. These cardiovascular effects range from heart rate (HR) changes and blood pressure (BP) alterations to more severe and fatal issues such as QTc prolongation and congestive heart failure. These manifestations and their closely associated drugs are illustrated in [Figure 1](#).

Heart rate changes

Tachycardia: Antipsychotic agents have anticholinergic properties and thus could cause cardiovascular side effects when vagal tone is significantly decreased by antagonism of type 2 muscarinic receptors. The anti-muscarinic effects include sinus tachycardia and other systemic anticholinergic effects, such as dry mouth, constipation, and urinary retention. Antipsychotic-induced tachycardia is most commonly observed in low-potency FGAs (*e.g.*, chlorpromazine and thioridazine) and some SGAs (*e.g.*, clozapine). Compared with an average of 72 ± 14 beats/min in 42 unmedicated controls, the mean HR significantly increased to 83 ± 14 beats/min in the 111 patients receiving FGAs. It has been estimated that an increase in HR of 10-15 beats/min could be observed in 1/4 of patients taking clozapine. Consistently, data showed that treatment with clozapine (21 d under 200-600 mg/d), haloperidol (18 d

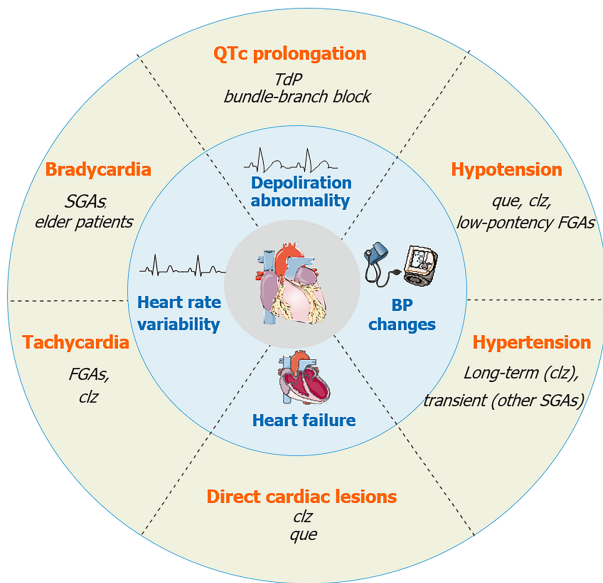


Figure 1 Summary of clinical manifestations of antipsychotic cardiotoxicity. Typical characteristics for each manifestation are concisely listed in black texts. SGA: Second-generation antipsychotic; FGA: First-generation antipsychotic; TdP: Torsades de pointes.

under 5-10 mg/d), and olanzapine (17 d under 5-20 mg/d) increased patients' HRs to 107, 86, and 89 beats/min, respectively, which were significantly higher than those of their matched control subjects (62 beats/min)[8]. Of note, clozapine-induced tachycardia does not seem to be dose-dependent. In a rat model receiving different doses of clozapine administration, a low dose (1.5 mg/kg) and a high dose (5 mg/kg) of clozapine increased the HR by 51 ± 8 and 47 ± 15 beats/min, respectively[9]. This effect was distinct from those of haloperidol and risperidone[8].

Most patients may develop milder tachycardia with drug treatment extension, a phenomenon referred to as drug tolerance, with clozapine being the sole exception. Clozapine-induced tachycardia may be persistent and requires the addition of β -adrenergic receptor antagonists to avoid severe cardiovascular effects for symptomatic patients with HRs over 110-120 bpm[10]. In addition, antipsychotic-induced tachycardia may increase myocardial oxygen demand and aggravate cardiac ischemia in patients with basic cardiovascular diseases. Persistent tachycardia may also contribute to cardiomyopathy[11]. All of these outcomes mandate clinical interventions.

Bradycardia: Some cases also reported antipsychotic impacts on lowering the HR, particularly SGAs such as risperidone[12], quetiapine[13], amisulpride[14], olanzapine [15], and paradoxically clozapine[16]. These cases were mostly elderly patients with signs abated after discontinuation of drugs. It has been reported that risperidone induced bradycardia in an 82-year-old woman (43 beats/min) and 69-year-old man (39 beats/min). Prompt initiation of appropriate resuscitative and supportive measures, along with discontinuation of the offending medication, led to clinical improvement [12]. Quetiapine-induced bradycardia has also been reported in elderly patients, in which settings, a time sequential improvement was achieved after decreasing the drug dosage[13]. A male patient developed symptomatic bradycardia during usage of amisulpride (400-800 mg/d), which dramatically improved after the complete termination of amisulpride usage[14]. An 84-year-old patient presented with conscious depression, bradycardia (40 beats/min), hypotension, miosis, and hypothermia after 2.5 mg/day olanzapine therapy, and his condition improved with supportive therapy [15]. Clozapine also induced bradycardia in elderly patients[16], albeit with more reports of clozapine-induced tachycardia.

Antipsychotics-induced bradycardia may be explained by age-related changes in the pharmacokinetics and pharmacodynamics of drugs in older patients that increase their susceptibility to the side effects of psychotropic medications[16]. The antipsychotic-induced slowdown of HR may lead to more severe outcomes, such as cardiac arrest and SCD. It is hence strongly suggested that clinicians remain vigilant for the signs or symptoms of adverse effects such as bradycardia in their elderly patients who take SGAs.

Blood pressure

Hypertension: In a 24-wk follow-up study, only four (22%) of the 18 patients fulfilled the criteria for hypertension at baseline levels. However, 12 (67%) in 18 patients developed hypertension ($\chi^2 = 6.25$, $df = 1$, $P = 0.0124$) with regard to both systolic BP (SBP) and diastolic BP (DBP) during clozapine treatments[17]. Consistently, a 5-year follow-up observation of 82 patients showed significant increases in SBP ($P = 0.0004$) and DBP ($P = 0.0001$) after clozapine therapy. In these patients, 27% developed hypertension, the rate of which significantly surpassed that in FGA therapy (4%) or in other SGA (olanzapine and risperidone) therapies (9%)[18].

Interestingly, clozapine tended to reduce SBP in the early period after drug initiation, whereas olanzapine and risperidone raised SBP to a statistically significant degree within 3 d of initiation[19]. Aripiprazole, another SGA, was also observed to induce arterial hypertension shortly after drug initiation in two geriatric patients[20]. Both somatic and psychiatric outcomes were favorable after discontinuation of aripiprazole or the introduction of FGAs.

Orthostatic hypotension: Orthostatic hypotension is one of the most common cardiovascular adverse effects of antipsychotics and is more common in elderly patients[21,22]. In a cardiovascular health study enrolling 5201 patients over 65 years old, the prevalence of asymptomatic orthostatic hypotension was 16.2% to 18%, although only 2% were symptomatic[23]. The risk of orthostatic hypotension associated with antipsychotics is increased in patients with autonomic nervous system diseases and fluid imbalance and in those taking concomitant drug therapy that affects hemodynamic tone. Elderly individuals taking multiple medications, such as antipsychotics and hypotensive drugs, constitute a higher risk factor for symptomatic orthostatic hypotension. The incidence of FGA-induced orthostatic hypotension is approximately 77% compared with only 15% in patients receiving placebo[24], with the accepted mechanism being α_1 adrenergic blockade and other putative mechanisms such as calcium blockade, inhibition of centrally mediated pressor reflexes, and negative inotropic effects[25]. Low-potency phenothiazine antipsychotics (*i.e.*, chlorpromazine and thioridazine) are generally considered the most common FGAs that cause orthostasis[26].

Unlike FGAs, most SGAs, with the exception of clozapine and quetiapine, are less likely to cause orthostatic hypotension due to their low affinity for α_1 -adrenergic receptors[26]. Based on available data, the hierarchy of hypotension production was quetiapine (27%) > clozapine (24%) > iloperidone (19.5%), compared with 8.3% in patients taking placebo, while other SGAs (*i.e.*, risperidone, olanzapine, and ziprasidone) barely cause orthostatic hypotension[26,27]. Of note, orthostatic hypotension is dose-dependent and transient. The long-term effect of SGAs may be more associated with hypertension, as mentioned above. Therefore, orthostatic hypotension can frequently be overcome with close monitoring and conservative dosing[28].

Ventricle repolarization abnormalities

QT prolongation: Antipsychotic agents are commonly correlated with repolarization abnormalities, which manifest as iatrogenic prolongation of the QT interval. The QT interval is measured on the electrocardiogram (ECG) from the beginning of the QRS complex (initial deflection or Q wave) to the end of the T wave, which reflects depolarization and repolarization of the ventricles, respectively[29]. An imbalance in ion flow across the cell membrane, especially potassium current impairment, can result in delayed repolarization manifesting a prolonged QT interval[30]. Since this interval is inversely proportional to HR, the QT interval is typically corrected for HR (QTc). The QTc interval in healthy people ranges from 380 ms to 450 ms under the combined impact of age and gender. Some antipsychotic medications are associated with the prolongation of QTc interval (> 450 ms in men and > 460 ms in women). In a cohort study enrolling 4825345 patients, approximately 40% were prescribed an antipsychotic medication and later presented with QTc prolongation[31]. In particular, the Pfizer 054 study conducted by Pfizer Inc. reported the order of QTc interval elongation to be thioridazine (35.6 ms), ziprasidone (20.3 ms), quetiapine (14.5 ms), risperidone (11.6 ms), olanzapine (6.8 ms), and haloperidol (4.7 ms)[32,33]. The U.S. FDA has therefore increased concerns of this serious issue; five different medications have been withdrawn from the market, and several others have received different kinds of product warnings[34].

It is noteworthy that although most antipsychotics are associated with QTc prolongation, it is rather difficult to rank the risk of malignant arrhythmia for the individual antipsychotic drug since ECG measurement methods vary across studies. A

recent clinical review therefore integrated pharmacovigilance data from several international databases. Data from various authorities on the risk of arrhythmia associated with psychotropic medications were weighted and categorized into three risk categories. Aripiprazole, olanzapine, perphenazine, and zuclopenthixol were categorized as class A drugs [no risk of QTc prolongation or torsades de pointes (TdP)]. Amisulpride, chlorprothixene, clozapine, flupentixol, levomepromazine, paliperidone, quetiapine, risperidone, and sulpiride were categorized as class B drugs (a drug with a propensity of QTc prolongation). Finally, haloperidol, pimozide, sertindole, and ziprasidone were categorized as class B* drugs (a drug with pronounced QTc prolongation, documented TdP cases, or other serious arrhythmias) [35].

Serious conduction abnormality: QT prolongation is associated with ventricular arrhythmias, specifically TdP, and SCD. TdP can be inherited (congenital long-QT syndrome, LQTS) or acquired, with the most common reason being medications[36]. The following conditions increase the risk of drug-induced TdP: (1) Disease states/electrolyte levels (heart failure, structural cardiac disease, bradycardia, and hypokalemia); (2) pharmacogenomic variables (presence of congenital LQTS, subclinical ion-channel mutations, and history of or having a relative with history of drug-induced long QT/TdP); and (3) pharmacodynamic and kinetic factors (high doses, women, being elderly, metabolism inhibitors, combining two or more QT prolonging drugs, drugs that prolong the QT and increase QT dispersion, and drugs with multiple actions on ion channels)[37]. Until now, QT prolongation has remained the most extensively used surrogate marker for TdP, while the existing means for precisely measuring prolongation have been debated[38,39]. Moreover, TdP is known to occur at therapeutic doses of SGAs when the QTc interval is < 500 ms. Thus, establishing a clinically standardized threshold of the QTc interval is difficult but important.

Serious conduction system alterations also include right and left bundle-branch block (RBB and LBB) and partial or complete atrioventricular block. It has been reported that an abnormal cardiac conduction system was the second most common cause of death in 24 patients dying suddenly from long-term antipsychotic use[40]. The main mechanisms are antipsychotic-induced pericarditis involving the sinus node, atrial muscle, and atrioventricular node or endocarditis involving the RBB, LBB, and Purkinje fibers.

Heart failure

Antipsychotic-induced heart failure is a consequence of prior direct cardiac lesions in response to drug stimuli. These pathological lesions included myocarditis, cardiomyopathy, ischemic heart diseases (IHD), *etc.*[41].

Currently available reports have mainly linked clozapine with an increased risk of heart failure. A psychiatric patient on chronic low-dose clozapine (75 mg/d) therapy presented with congestive heart failure secondary to the cardiotoxic effects of psychiatric medication, a condition that failed to be corrected by conventional heart failure treatments. Drug discontinuation is commonly issued when confronting clozapine-induced heart failure[42]. An exclusive report also presented the case of a 37-year-old woman who developed cardiomyopathy under high doses of quetiapine and recovered in the course of the next months after quetiapine was stopped[43]. While temporary cessation of treatment can lead to severe psychotic exacerbation and nonengagement with cardiac specialists, more evidence is required for continued use of antipsychotics in patients with cardiac complications[42].

PATHOLOGICAL CHANGES OF ANTIPSYCHOTICS CARDIOTOXICITY

Chronic exposure to antipsychotics may directly damage cardiac muscles that lead to irreversible cardiac remodeling, pathologically diagnosed as myocarditis, dilated cardiomyopathy (DCM), and some other conditions, including ventricular hypertrophy, IHD, and pulmonary thromboembolism (PTE). In addition, emerging studies have reported that substantial fatal cases are negative for autopsy findings or with only mild pathological lesions, the causes of which are referred to as cardiac arrhythmia (summarized in [Figure 2](#)).

Myocarditis and DCM

Myocarditis is defined as inflammation of the myocardium. Clozapine is by far the

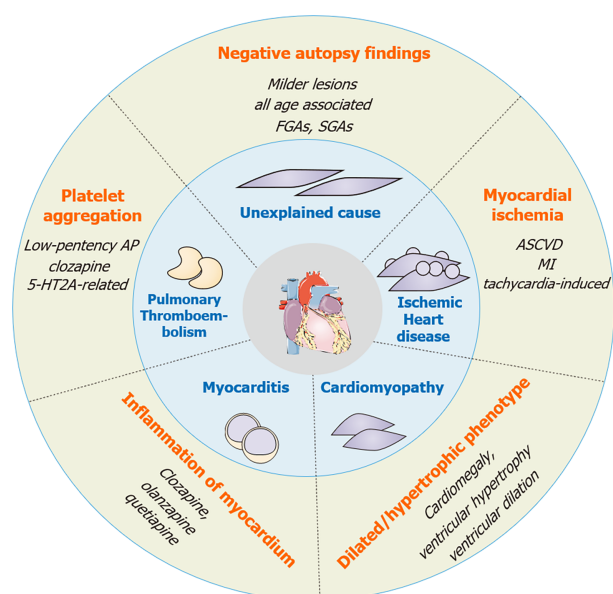


Figure 2 Summary of cardiac pathological changes in response to antipsychotic treatments. Typical characteristics of each pathological change are concisely listed in black text. SGA: Second-generation antipsychotic; FGA: First-generation antipsychotic; ASCVD: Atherosclerotic cardiovascular disease; MI: Myocardial infarction.

most commonly used antipsychotic that has been associated with myocarditis. The World Health Organization has suggested that clozapine, which caused over 200 cases of myocarditis and cardiomyopathy in 2001[44], has a closer association with myocarditis and cardiomyopathy than any other kind of antipsychotic drug[45]. According to statistics, clozapine-associated myocarditis has been estimated to increase from 1 in 10000 to 1 in 500 patients. Most of these cases occurred in the first 2 mo after clozapine therapy[46], while at the beginning of drug use, the incidence of clozapine-related myocarditis is between 0.03% and 0.19%[47]. Furthermore, the death rate caused by clozapine-induced acute myocarditis is approximately 25%[48]. An autopsy report also confirmed antipsychotic-induced myocarditis, which showed that in 24 sudden death cases, 11 (45.8%) died from myocarditis, and 7 (29.2%) were on clozapine medication[49].

The histopathological features in the case of clozapine-related myocarditis are myocytolysis and necrosis with florid infiltration, accompanied by lymphocytes, neutrophils, and prominent eosinophils[41]. If acute myocarditis is not recognized at the early stage, it may progress to DCM, a disease characterized by ventricular dilation and heart dysfunction. According to Kilian *et al*[41], the incidence of DCM in the general population was 0.75% to 1%, while that in clozapine-treated patients was approximately 5.15% (over a 5-fold increase compared with the general population). In an autopsy report, 6 (42.9%) in 14 cases died suddenly from DCM, which developed after chronic antipsychotic use[50].

The mechanism by which antipsychotics induce myocarditis or DCM remains unclear. Numerous hypotheses have been proposed, including immunoglobulin (Ig)E-mediated pathways, cytokine-driven responses, and oxidative stress-related hypercatecholaminergic states[51]. While IgE-mediated hypersensitivity used to be considered the main attributor, a recent study found that clozapine treatment caused an elevated plasma catecholaminergic state, and the blockade of β -adrenoceptors may be helpful in decreasing the occurrence and severity of clozapine-induced myocarditis, implicating a membrane receptor-involved mechanism[52]. We also reported that myocarditis is not always accompanied by aberrant eosinophils in experimental murine models[53], implying IgE-independent mechanisms underlying antipsychotic-induced cardiac muscle disorders.

Olanzapine- and quetiapine-induced myocarditis has also been sparsely reported due to their chemical structure similarity with clozapine. Quetiapine induced cardiomyopathy in a 37-year-old woman after high dosages[43]. From the spontaneous adverse drug reports database of the Danish Health and Medicines Authority, two fatal cases of eosinophilic myocarditis were associated with the use of olanzapine [54]. Another case report with 10-year olanzapine intake also suggested that the use of olanzapine may cause DCM since echocardiography shows decreased global biventricular function[55]. It has also been mentioned in another report that the

adverse drug reaction of psychotropic drugs (clozapine and olanzapine) is very likely to be related to DCM[56].

Ischemic heart diseases

It has been reported that most patients with schizophrenia do not die from suicide or during psychotic episodes but from IHD[57]. IHD has become the primary cause of death among schizophrenia patients[58] and tends to be sex biased. According to a statistical analysis, antipsychotics increased the prevalence of acute IHD by 32% among women but caused no significant changes among men[59]. The four antipsychotic drugs associated with high mortality of IHD were clozapine, quetiapine, olanzapine, and thioridazine, all of which share high affinity to the 5-HT_{2A} receptor [60], and blockade of the 5-HT_{2A} receptor might confer protection against IHD and buffer the deleterious metabolic effects of antipsychotics[61].

Among IHDs, myocardial infarction (MI) is a severe pathological alteration after the use of antipsychotic drugs[62]. It has been reported that antipsychotic users were 1.88-fold more likely to have MI[63], although this conclusion was challenged by a meta-analysis reporting no significant association with antipsychotic drugs[62]. The high incidence of MI might be attributed to atherosclerotic cardiovascular diseases (ASCVDs), which account for 67.3% of the natural deaths among schizophrenia patients in Maryland, USA[58]. ASCVD may manifest ischemic syndromes, including acute coronary syndromes, congestive heart failure, and sudden and nonsudden cardiac death[64]. The mechanism of ASCVD being common among schizophrenia patients is multifaceted, with the gut microbiome interrupted by antipsychotic use being recently introduced as a novel mechanism[65]. Interestingly, a study showed that haloperidol, a representative FGA, inhibited atherosclerosis in mice lacking LDL receptors by decreasing ABCA1-mediated cholesterol efflux from macrophages to apolipoprotein A1[66]. Another contributor to myocardial ischemia might be antipsychotic-induced tachycardia that increases myocardial oxygen demand and aggravates cardiac ischemia in schizophrenia patients[35].

Ventricular hypertrophy

In an autopsy-based study, two (14.3%) in 14 cases were found to have remarkable left ventricular hypertrophy, leading to the diagnosis of hypertrophic cardiomyopathy [50]. We also reported a case of sudden death from hypertrophic cardiomyopathy after over 20 years of chlorpromazine therapy[40]. Ventricular hypertrophy might be an adaptive response in the early stage of antipsychotic stimuli. When maladapted, the heart may progress to pathological hypertrophy, a condition that predisposes patients to sudden death.

Pulmonary thromboembolism

Antipsychotic drugs have also been reported to cause thrombotic complications such as lupus-like syndromes. Both typical and atypical antipsychotics can cause PTE[67]. Female sex and the use of antipsychotics were two risk factors for PTE, with odds ratios of 4.22 (95% CI: 1.82-9.78) and 10.49 (95% CI: 3.95-27.85), respectively[68]. Among 28 patients who died of PTE, eight (28.6%) used antipsychotics, and all were female [68]. High-dose and parenteral administration were also more likely to cause PTE. For oral administration, the odds ratio was 1.07 for the low dose ($P = 0.04$) and 1.40 for the high dose ($P < 0.001$). For parenteral administration, the odds ratio was 1.18 for the low dose ($P < 0.001$), while it was 1.43 for the high dose ($P < 0.001$)[69]. In particular, the use of low-potency antipsychotic drugs was associated with a higher risk of venous thromboembolism (risk ratio = 1.90, 95% CI: 1.04-3.47), a condition that predisposes patients to PTE[70]. Generally, chlorpromazine, thioridazine, and clozapine are common antipsychotics that cause PTE.

The development of PTE has been associated with increased platelet aggregation due to the strong affinity of these drugs for 5-HT_{2A} receptors. According to statistics, atypical antipsychotic drugs have a more than 10-fold greater affinity for 5-HT_{2A} receptors than for D₂ receptors[68]. Antipsychotics may also block dopamine and then cause hyperprolactinemia, which is a significant risk factor for PTE in patients using antipsychotics. Of note, although aripiprazole and quetiapine act on 5-HT_{2A} receptors, they did not increase the risk of PTE. Another report also showed no increase in platelet aggregation caused by haloperidol, olanzapine, and risperidone[71], although this finding contradicts sporadic case reports of olanzapine and risperidone-associated PTE[72]. These studies imply extra 5-HT_{2A} receptor-independent mechanisms or potential between-study heterogeneity.

Sudden unexplained death

It is noteworthy that even after systemic autopsy and toxicological screening, some cases may have no definitive cause of death, the so-called “unexplained” autopsy-negative cases that are probably caused by cardiac arrhythmia. Many autopsy-based studies have documented unexplained cases among sudden deaths of schizophrenia, with rates ranging from 2.8% [58] to 52% [73]. A nationwide cohort study from Denmark found that SCDs in psychiatric patients were more often unexplained than those in nonpsychiatric patients (65% *vs* 40%, $P = 0.02$) [5]. The incidence of unexplained deaths tends to increase across years, as the deaths per 100000 patient-years dramatically increased from 7 (95%CI: 3.7-19.4) in 1984-1998 to 125 (95%CI: 88.9-175.1) in 2005-2009 [73]. The unexplained cases were similar to the explained cases regarding demographic features, psychiatric diagnoses, and use of psychotropic classes (FGAs and SGAs). Dyslipidemia ($P = 0.012$), diabetes ($P = 0.054$), and comorbid dyslipidemia and diabetes ($P = 0.006$) were more common in the unexplained group [73].

In particular, there have been six autopsy-based reports that highlight unexplained deaths. The detailed forensic characteristics are documented in Table 1. Specifically, these unexplained cases were found at all ages, ranging from 2 to 86 years old. Male decedents were more common (57.8%). All decedents were overweight or worse, which conforms to the notion that dyslipidemia and diabetes were more common in unexplained deaths [73]. Approximately half of these unexplained deaths were negative for any autopsy findings. Before the introduction of SGAs, the FGAs chlorpromazine and haloperidol were common drugs, while after the introduction of SGAs, quetiapine, olanzapine, and clozapine were the primary drugs associated with unexplained deaths. Most of these cases were at a therapeutic dose, with the exception of the eight unexplained cases whose postmortem levels of antipsychotics were up to toxic concentrations [74].

MECHANISMS UNDERLYING ANTIPSYCHOTICS CARDIOTOXICITY

Subcellular organelles

Mitochondria: It has been reported that the antipsychotic drug clozapine undergoes bioactivation to a reactive nitronium ion by dehydrogenation in mitochondria; subsequently, this electrophilic intermediate is detoxified by conjugation with reduced glutathione [76]. The clozapine-glutathione conjugates are then eliminated in the bile of rats and mice over a 3-h period [77]. Thus, cardiac mitochondria may be a target for antipsychotic-associated adverse cardiac effects. Drug-induced functional and/or structural variations of cardiac mitochondria may result in myocarditis and cardiomyopathy by various approaches [78]. One possible mechanism of cardiac mitochondrial damage may involve antipsychotic bioactivation by cardiac tissue-specific microsomal CYPs and/or soluble oxidases/peroxidases, translocation of the resultant reactive metabolite to mitochondria, and alkylation of mitochondrial proteins [79], a mechanism similar to paracetamol-induced hepatotoxicity [80]. Furthermore, the parent drug and/or its metabolite(s) may enter cardiac mitochondria to form nitronium ions, which localize within this organelle and consequently cause drug accumulation in the heart [79]. In addition, chronic dosing with haloperidol and some SGAs (*i.e.*, clozapine and risperidone) could result in loss of complex I, the electron transport chain component in mitochondria, to generate side effects [81,82] and negatively affect mitochondrial bioenergetics [81]. Proteomic profiling revealed that mitochondrial function and oxidative phosphorylation were significantly affected in risperidone- and olanzapine-treated mouse hearts, additional evidence supporting risperidone-altered cardiac mitochondrial oxygen consumption [83].

Lysosomes: Lysosomes contain over 30 acid hydrolases and are a significant acidic compartment to digest and phagocytose during antipsychotic metabolism [84]. Most antipsychotics are basic lipophilic compounds, the distribution of which is determined by cellular membrane phospholipid binding [85] or by lysosomal trapping [86]. For lysosomal trapping, basic lipophilic drugs permeate membranes and aggregate in lysosomes. The acidic interior of lysosomes then protonates the parent drugs or metabolites, preventing them from returning to the cytosol, an approach directly leading to detoxification of drugs [84]. Unfortunately, unlike the liver, lung, and kidney, the heart is a lysosome-deficient organ that exerts a very weak capacity to capture and protonate drugs [87]. This natural defect directly results in failure of drug protonation after entering cardiac cells and explains the exclusive cardiotoxicity of

Table 1 Six autopsy-based studies assessing demographic and forensic characteristics of sudden unexplained deaths after antipsychotic use

Category	Sweeting <i>et al</i> [7]	Ifteni <i>et al</i> [75]	Sun <i>et al</i> [58]	Ye <i>et al</i> [40]	Jusic and Lader[74]	Manu <i>et al</i> [73]
Publication year	2013	2014	2019	2018	1994	2011
Case region	Sydney, Australia	Brasov, Romania	MD, United States	Shanghai, China	London, United Kingdom	New York, United States
Reported case number	72/683	6/57	11/391	5/24	8 case reports	52/100
Age, yr (mean ± SD)	53 ± 14	55 ± 13	36 ± 17	57 ± 5	36 ± 14	50 ± 13
Males, n (%)	41 (56.9)	4 (66.7)	7 (63.6)	1 (20.0)	5 (62.5)	31 (59.6)
BMI (kg/m ²)	26.0 ± 7.1	26.0 ± 4.8	31.0 ± 7.2	NA	NA	NA
Autopsy finding ¹ , n (%)	NA					NA
Mild atherosclerosis		3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Chronic pericarditis		1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Myocardial dystrophy or fibrosis		1 (16.7)	2 (18.2)	0 (0.0)	1 (12.5)	
Ventricular dilation		0 (0.0)	2 (18.2)	0 (0.0)	0 (0.0)	
Cardiomegaly		0 (0.0)	2 (18.2)	0 (0.0)	0 (0.0)	
Conduction system abnormality		0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	
Lung edema, congestion		1 (16.7)	0 (0.0)	0 (0.0)	4 (50.0)	
None		0 (0.0)	5 (45.5)	3 (60.0)	4 (50.0)	
Postmortem toxicology ¹ , n (%)	NA	NA				
First-generation						4 (7.7)
Chlorpromazine			0 (0.0)	2 (40.0)	5 (62.5)	
Haloperidol			0 (0.0)	1 (25.0)	5 (62.5)	
Thioridazine			0 (0.0)	0 (0.0)	1 (12.5)	
Droperidol			0 (0.0)	0 (0.0)	2 (25.0)	
Promazine			0 (0.0)	0 (0.0)	1 (12.5)	
Trifluoperazine			0 (0.0)	0 (0.0)	1 (12.5)	
Pimozide			0 (0.0)	0 (0.0)	2 (25.0)	
Fluphenazine			0 (0.0)	0 (0.0)	2 (25.0)	
Second-generation						
Olanzapine			0 (0.0)	2 (40.0)	0 (0.0)	2 (3.8)
Quetiapine			4 (36.4)	1 (25.0)	0 (0.0)	11 (21.2)
Clozapine			2 (18.2)	1 (25.0)	0 (0.0)	5 (9.6)
Risperidone			0 (0.0)	0 (0.0)	0 (0.0)	4 (7.7)
Ziprasidone			0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Negative			5 (45.5)	0 (0.0)	0 (0.0)	0 (0.0)

¹Some cases are presented with ≥ 2 autopsy findings or drugs, so the sum may exceed the total number of columns. BMI: Body mass index; NA: Not available.

antipsychotics. Moreover, polypharmacy is common among patients with mental disorders. When two or more basic lipophilic drugs are trapped by lysosomes, the pH increases more than when a single drug is trapped. Lysosomes are then oversaturated and diminish the drug intake capacity[84]. This is a phenomenon called synergistic

effect.

Molecular mechanisms

Ion channels: Cardiac action potentials are generated by transmembrane movements of ion species, flowing principally through specific channels. Antipsychotics can affect a variety of cardiac ion channels, especially the potassium channel (particularly the potassium rapid delayed rectifier channel, K_r), which is associated with QT interval prolongation and lethal cardiac arrhythmias such as TdP[88]. The K_r channel, also known as the hERG channel, is encoded by the human ether-a-go-go related gene (*hERG*). Almost all antipsychotics could modulate cardiac K_r channels. Risperidone and its active metabolite paliperidone inhibited the potassium current by interacting with the open and inactivated states of the I_{Kr} channel without affecting channel protein trafficking[89]. FGAs (chlorpromazine and thioridazine) and clozapine suppress the current of the K_r channel and consequently result in QT prolongation. Olanzapine, a first-line SGA in the clinic, blocked the K_r current in a concentration-dependent manner with a tail current decrease of 50% at 3.8 mmol/L olanzapine[90]. Of note, the 50% inhibition concentration (IC_{50}) of this ion channel has drug-based differences, ranging from 1 nmol/L (haloperidol)[91] to 6 μ mol/L (olanzapine)[92]. This variation is not related to a class effect (FGAs *vs* SGAs) but seems to relate to the potency of antipsychotics to block hERG channels[93].

Genetic susceptibility, namely, mutations in the genes encoding potassium ion channel proteins (*i.e.*, *KCNH2*, *KCNQ1*, and *SCN5A*) is also directly associated with an increased risk of malignant arrhythmias[94]. In addition to the inherited *hERG* mutations that are associated with congenital long QT syndrome, suppression of native I_{Kr} by psychotropic therapy also predisposes individuals to polymorphic ventricular tachycardia of the TdP type[95]. Hence, genetic screening should be implemented in selected patients who have previous episodes of drug-induced arrhythmias.

Biological membrane receptors: As mentioned above, due to their lipophilic nature, antipsychotics might exert their cardiac effects by perturbing the physical properties of biological membranes[96]. The membrane-resided receptors may thus be involved.

Adrenoceptors: There are many antipsychotics that have a strong affinity for adrenoceptors. For example, the FGA droperidol competitively interacts with vascular α -adrenoceptors but has no effect on β -adrenoceptors[97]. The potency of binding to α 1- and α 2-adrenergic receptors varies among these medications, with a 532-fold range for α 1 antagonism and a 400-fold range for α 2 antagonism among atypical antipsychotics [98]. There are several lines of evidence for the involvement of adrenoceptors in antipsychotic cardiotoxicity. First, as the endogenous ligand of adrenoceptors, plasma noradrenaline levels significantly increased in patients upon clozapine maintenance treatment[99]. Similarly, in a rat model receiving multiple doses of the FGA haloperidol and SGAs (risperidone, clozapine, and olanzapine), the plasma catecholamine levels were found to be significantly elevated by all antipsychotics, although the elevation was drug- and dose-dependent[100]. Compared to other antipsychotics, intravenous injection of olanzapine and clozapine seemed to cause a more significant increase in plasma epinephrine. Second, a β -adrenergic blocking agent, propranolol, was found to significantly attenuate clozapine-induced myocarditis in a murine model[52], posing a direct linkage of adrenoceptors to antipsychotic cardiotoxicity.

Cannabinoid receptors: Given that β -adrenoceptor blockade produced only a partial reduction in clozapine-induced TNF- α levels[52], other receptors were later proposed to be functional. In our serial works, we found that clozapine[53] or quetiapine[101] treatments caused a decrease in cannabinoid receptor 1 (CB1R) while increasing CB2R expression within approximately 2 wk of treatment in mice. The ligands of these receptors were disrupted in a dose- and time-dependent manner. Furthermore, in cultured cardiomyocytes, the CB1 receptor was observed to translocate from the cytomembrane in intact cells to the cytoplasm/nuclei in SGA-treated cells, whereas the CB2 receptor went the opposite way in SGA-treated cells[53,101], suggesting a functional rivalry between the cannabinoid receptor subtypes[102]. Furthermore, both cannabinoid receptors regulated a new type of necrotic cell death[101], termed necroptosis, which explained the clinical association of antipsychotic use with inflammatory states. The opposite roles of cannabinoid receptors suggested that the treatment of antipsychotic cardiotoxicity might only be beneficial when based on single-receptor agonism or antagonism[102].

Other molecular mechanisms: Several pathways were also reported to be associated with clozapine-induced myocarditis. Clozapine, particularly at relatively high doses, has a clear cardiotoxic effect, as evidenced by increased myocardial oxidative stress, inflammatory cytokines, DNA damage, and apoptosis with attenuation of antioxidant defenses. The use of captopril, an angiotensin-converting enzyme inhibitor, significantly protected against the above clozapine-induced effects in rats[103]. In a rat model, olanzapine-induced cardiotoxicity was reported to be associated with increased acetyl-CoA carboxylase phosphorylation and tissue ATP levels and lower phosphorylation levels of Akt and its downstream product AS160[104]. These generally descriptive studies reinforced the mitochondria-involved mechanisms and implied that inflammatory cell death might be critically involved in antipsychotic cardiotoxicity. By integrating proteomic and transcriptomic approaches, we recently further found that representative SGAs share a similar cardiac pathological basis to cause cardiotoxicity, and spliceosome signaling represents a common intracellular mechanism underlying SGA-induced cardiotoxicity[105]. SGA-dysregulated spliceosome signaling was only partially rescued by pretreatment with an agonist of histamine 1 receptor (HRH1)[105], implying additional membrane receptor-involved mechanisms.

FUTURE PERSPECTIVES

Clinical monitoring

Many approaches have been recommended for the clinical monitoring of antipsychotic cardiotoxicity, including biomarker detection (*i.e.*, CRP, creatine kinase, and cardiac troponins), ECG monitoring, echocardiogram monitoring, and B-type natriuretic peptide (BNP) detection.

Creatine kinase has been found to be less useful than troponin to assess myocardial injury due to its low sensitivity (approximately 22%)[106]. Troponins appear to have a higher sensitivity of approximately 39% but can only be true-positive in the first month after disease onset. The specificity of troponin is approximate 89%[107]. The sensitivity of ECG monitoring is approximately 35% (equal to that of peripheral eosinophilia detection), while creatine kinase isoenzyme (CK-MB) only has a 5.7% sensitivity rate[107]. The test with the highest sensitivity is left-ventricle hypokinesia and/or reduced ejection fraction by echocardiogram, although only 48%[108]. A clinical study over the years 1994-2009 concluded that combining troponin (over twice the upper limit) and CRP (over 100 mg/L) had an estimated diagnostic sensitivity of 100% for symptomatic clozapine-induced myocarditis[109]. A recommendation was also proposed to regularly monitor CRP, troponins, and ECG at baseline and at weeks 1, 2, 3, and 4 to improve the early detection of clozapine-induced myocarditis[110].

The above approaches have been clinically practiced for decades and, however, are not exclusive for monitoring antipsychotic-induced cardiotoxicity. BNP is a 32-amino acid vasoactive peptide that is primarily secreted by the ventricular wall[111]. It acts as a key response to increased wall stress and a vital regulator in the homeostasis of water and salt excretion[112]. A clinical study has documented the potential of using an N-terminal fragment of BNP (NT-proBNP)[113] in combination with QTc measurement as a highly accurate marker for the early detection of acute antipsychotic drug-induced cardiotoxicity. Of note, these clinical studies are limited to a small number of patients. Multicenter studies with larger sample sizes are mandated to verify the association between NT-proBNP levels and acute cardiac toxicity.

In recent years, implantable cardioverter defibrillators (ICDs) have been considered the most effective treatment for patients at high risk of SCD[114]. Individual wrist-worn medical devices with the capability of monitoring several fatal biometrics, such as HR and BP, as well as ECG have also been recommended[115]. This high-tech wrist-worn device has multiple advantages over other biochemical tests due to better prediction and management of patients and the real-time notice of irregular heart rhythm and other warnings to users receiving antipsychotic therapy.

Therapeutic agents

Some studies have reached a consensus that the addition of β -blockers has been an effective clinical alternative for the treatment of clozapine-associated tachycardia[116]. Taking low doses of bisoprolol, for example, can be well tolerated and may offer symptomatic relief in patients who are aware of and suffer from tachycardia[117].

In addition, we have provided profound data that two subtypes of cannabinoid receptors (CB1R and CB2R) are critically involved in antipsychotic cardiotoxicity. Specific antagonists of CB1R or agonists of CB2R bring beneficial effects, including inflammation suppression and fibrosis remission in the heart[53,101]. Meanwhile, it would not profit from dual antagonists or agonists since dual binding might neutralize the effect of each other. Therapeutics should be mono-receptor based[53,101]. In particular, antagonists of CB1R have been marketed for weight loss, and CB2R agonists have also been associated with a welcome metabolic process[118]. Since metabolic and cardiovascular adverse effects are the major dilemma associated with antipsychotic drug use[119], the use of CB1R antagonists or CB2R agonists in combination with antipsychotics might be conceived to exert dual protection: One to inhibit drug cardiotoxicity and the other to ameliorate antipsychotic-induced weight gain. Of note, individual CB1R antagonists may cause additional psychiatric disorders due to brain penetrance and have been withdrawn from clinical use (*i.e.*, rimonabant [120]). Therefore, the development of peripherally restricted CB1R antagonists or CB2R agonists would provide dual protection against these clinical concerns without causing additional toxicity[121].

Third-generation antipsychotics

There are several new and emerging antipsychotic medications, termed TGAs, recently marketed or under clinical development for the treatment of several mental disorders [2]. Overall, TGAs display a good safety profile, with a well-demonstrated lower metabolic liability than SGAs. Furthermore, TGAs appear to specifically target negative symptomatology and improve cognitive domains[2].

Comparing the cardiac adverse effects of recently developed antipsychotics (brexpiprazole, cariprazine, lurasidone, pimavanserin, and roliperidone)[122], roliperidone showed the lowest incidence of cardiovascular effects and metabolic influences, such as hypotension, QTc prolongation, weight gain, and metabolic syndrome, which indicates a potential therapeutic method to offset the defects of SGAs. Further clinical trials are needed for safety and efficacy evaluation.

CONCLUSION

This review introduces the clinical manifestations and pathological lesions in antipsychotic cardiotoxicity. Although largely unknown, many mechanisms at the subcellular organelle level (mitochondria and lysosomes) and at the molecular level (membrane receptors and ion channels) have been independently reported. This merits future evaluation of the efficacy (sensitivity and specificity) of the recently developed monitoring approaches. To avoid drug discontinuation or withdrawal from the market, drug adjuvant therapy to alleviate both cardiotoxic and metabolic effects is preferentially favorable. TGAs, particularly those with favorable cardiac and metabolic outcomes, deserve clinical application. Larger cohort-based clinical evaluations are needed for the development of receptor-targeted adjuvant drugs.

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