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Antipsychotic drugs and their possible cardiovascular adverse effects – literature review

Sercowo-naczyniowe działania niepożądane leków przeciwpsychotycznych – przegląd literatury

Alicja Gładysz ABEF, https://orcid.org/0009-0004-7366-274X,
Maciej Zamorski AC, https://orcid.org/0000-0003-3588-4240,
Agata Stebel BD, https://orcid.org/0009-0001-6370-0069,
Julia Ligoda CF, https://orcid.org/0009-0002-6898-3704,
Radosław Machaj DF, https://orcid.org/0009-0009-0029-8162,
Franciszek Mach BD, https://orcid.org/0009-0004-0364-1070,

Institute of Heart Diseases, Medical University of Wroclaw

Abstract

Introduction: Antipsychotic medication, frequently prescribed for managing psychosis, significantly enhance the quality of life for psychiatric patients. Nonetheless, they also harbor the risk of triggering cardiovascular side effects, which can range in severity and may pose challenges for patients, potentially disrupting their therapy. This study aims to elucidate these adverse effects, their potential etiology, and their prevalence.

Material and methods: A review of available literature was performed by searching PubMed and Google Scholar, using the following keywords: antipsychotic drugs, adverse effects, cardiotoxicity, arrhythmia for original papers, review papers and meta-analyses published from 1992 to 2024.

Discussion: It has been well-known for a long time that antipsychotic medication carries a lot of possible adverse effects. The cardiovascular adverse effects associated with antipsychotic medication encompass orthostatic hypotension, prolongation of the QT interval, atrial fibrillation, alterations in heart rate and cardiotoxicity, which may include myocarditis and cardiomyopathy. Fortunately, the occurrence of the most severe complications stemming from these effects is relatively uncommon. While the adverse effects of first and second-generation antipsychotics are extensively documented, further research is warranted to investigate the potential side effects of third-generation antipsychotic drugs.

Conclusions: Cardiovascular adverse effects associated with antipsychotics can pose significant challenges and may even be life-threatening for patients. However, awareness of these effects should not discourage clinicians from prescribing them. Instead, it should motivate them to deepen their understanding and expertise. It would definitely lead to the improvement of patient care and treatment outcomes.

Keywords: antipsychotic medication, myocarditis, cardiotoxicity, cardiac arrhythmia, orthostatic hypotension

Streszczenie

Wstęp: Leki przeciwpsychotyczne, używane głównie w leczeniu schizofrenii, znacznie poprawiają jakość życia pacjentów psychiatrycznych. Niemniej jednak, pacjenci ci są zagrożeni sercowo-naczyniowymi działaniami niepożądanymi tych leków. Działania te różnią się intensywnością i mogą znacznie zakłócać przebieg terapii. Celem niniejszej pracy jest przedstawienie i omówienie tych efektów niepożądanych, ich etiologii oraz częstości występowania.

Materiał i metody: Przeprowadzono przegląd dostępnej literatury za pomocą baz danych PubMed oraz Google Scholar. Wykorzystano następujące frazy wyszukiwania: leki przeciwpsychotyczne, efekty niepożądane, kardiotoksyczność, arytmia, dla prac oryginalnych, przeglądowych oraz meta-analiz opublikowanych w okresie od 1992 do 2024 roku.

Dyskusja: Od długiego czasu powszechnie znana jest duża liczba działań niepożądanych powodowanych przez leki przeciwpsychotyczne, szczególnie tych o charakterze sercowo-naczyniowym. Należą do nich: hipotensja ortostatyczna,

wydłużenie odstępu QT, migotanie przedsionków, zmiany częstości akcji serca, a także kardiotoksyczność obejmującą zapalenie mięśnia sercowego i kardiomiopatie. Korzystnie, najpoważniejsze powikłania spowodowane związane z tymi efektami są stosunkowo rzadkie. Choć działania niepożądane leków przeciwpsychotycznych pierwszej i drugiej generacji są dokładnie opisane, to potencjalne efekty uboczne leków przeciwpsychotycznych trzeciej generacji wciąż wymagają dalszych badań.
Wnioski: Sercowo-naczyniowe efekty niepożądane związane ze stosowaniem leków przeciwpsychotycznych mogą stanowić poważne wyzwanie dla opieki zdrowotnej, a nawet zagrozić życiu pacjentów. Niemniej jednak, świadomość możliwych reakcji niepożądanych nie powinna zniechęcać lekarzy do przepisywania tych farmaceutyków, a raczej motywować ich do pogłębienia swojej wiedzy na ich temat. W ten sposób możliwe będzie poprawienie opieki nad pacjentami oraz skuteczności leczenia.

Słowa kluczowe: leki przeciwpsychotyczne, zapalenie mięśnia sercowego, kardiotoksyczność, zaburzenia rytmu serca, hipotensja ortostatyczna

Introduction

Nowadays, there is a noticeable rise in the prescription of psychotropic medications, partly attributed to the COVID-19 pandemic [1]. According to data from the Ministry of Health, approximately 25% of the Polish population experiences psychiatric disorders [2]. The population attributes this prevalence to various factors, including unemployment, substance abuse (alcohol and drugs), family crises, poverty, interpersonal conflicts, future uncertainties, and the excessive pace of modern life. A large meta-analysis conducted in 2022 investigated the average age of onset for various psychiatric disorders within the global population. The results revealed that the first occurrence of a mental disorder happens before the age of 14 in one-third of individuals, before 18 in almost half (48.4%), and before 25 in 62.5% of individuals. The peak age of onset is 14.5 years, and the median age of onset is 18 years across all mental disorders [3]. These findings may raise concerns about the quality of life of modern people. Given that this study focuses on antipsychotic drugs, it is important to highlight the prevalence of schizophrenia. The global prevalence of schizophrenia is generally estimated to be around 1%. Studies have indicated that prevalence rates are higher in developed countries [4]. Since 1990, the prevalence of schizophrenia has risen by over 65% up to 2019 [5]. This underscores the necessity for well-tailored treatments and the advancement of our understanding of the disorder. Unfortunately, psychotropic drugs in general, including antipsychotics, are known for their diverse side effects, which frequently cause significant distress to patients and discourage them from adhering to the treatment [6]. It is essential to emphasize that the utilization of multiple psychotropic medications increases the probability of adverse effects manifesting [7].

General characteristics of antipsychotics

Antipsychotics represent a class of psychotropic drugs utilized in the treatment of psychosis, encompassing manifestations like hallucinations and delusions. While primarily indicated for schizophrenia, they are also beneficial in addressing conditions such as bipolar disorder and psychotic depression. Antipsychotics are categorised into three generations. The first generation of antipsychotics(FGAs), also named typical antipsychotics, emerged in the 1950s [8]. Examples include chlorpromazine and haloperidol. These medications are categorized according to their receptor potency, with chlorpromazine classified as a low-potency typical antipsychotic and haloperidol classified as high-potency. The primary pharmacological action of FGAs is their binding to dopamine D2 receptors in the four major dopamine pathways, resulting in the blockade of these receptors. The four dopamine pathways involved are the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways. The major drawback of blocking all these pathways is the occurrence of significant adverse effects across various systems of the body. In addition to dopamine receptors, typical antipsychotics also block cholinergic muscarinic M1 receptors, alpha-1-adrenergic receptors, and histaminic H1 receptors. Due to the side effects associated with long-term use outweighing the benefits, FGAs are not the preferred first-line treatment for schizophrenia [9].

The second generation antipsychotics (SGAs), also known as atypical antipsychotics, were introduced in the 1970s [10]. This class comprises medications such as clozapine, olanzapine, risperidone, quetiapine and ziprasidone. What sets atypical drugs apart from typical ones is their dual action of blocking both dopamine D2 receptors and serotonin 5HT2A receptors. Second-generation antipsychotics (SGAs) are sometimes called serotonin-dopamine antagonists (SDAs). Their pharmacological properties arise from a specific balance between dopamine release and dopamine blockade across different dopamine pathways. Since serotonin inhibits dopamine release, blocking 5HT2A receptors alters dopamine release. In the nigrostriatal,

tuberoinfundibular, and mesocortical pathways, dopamine release predominates over dopamine blockade. Reversely, in the mesolimbic pathway, dopamine blockade prevails. This results in effective management of schizophrenia symptoms with a reduced likelihood of adverse effects. Similar to FGAs, SGAs also bind to M1, alpha-1, and H1 receptors; however, this varies depending on the specific medication [9]. Clozapine warrants special attention due to its complex binding properties as an SDA. It has demonstrated high effectiveness in treating treatment-resistant schizophrenia. However, clozapine also has the most adverse effects among SDAs, making it a second-line treatment despite its exceptional efficacy [11]. The procedures for initiating and monitoring clozapine treatment will be discussed later.

Third-generation antipsychotics (TGAs), such as aripiprazole, cariprazine, and brexpiprazole, represent the latest class of antipsychotic drugs [12]. They are characterized by their partial agonist activity at dopamine D2 receptors, which, similar to SGAs, helps achieve physiological balance across different dopamine pathways. This also lowers the likelihood of adverse events. Regarding serotonin receptors, these medications act as antagonists at 5HT2A receptors with varying affinity [13]. Conversely, TGAs exhibit partial agonist activity at 5HT1A receptors. The pharmacological profile of TGAs positively impacts both positive and negative symptoms of schizophrenia. Additionally, their partial agonist activity at dopamine receptors can enhance dopaminergic activity in the prefrontal cortex, making them particularly useful for substance-induced psychosis [12]. However, TGAs have not surpassed SGAs as the first-line treatment for schizophrenia. A summary of the mechanisms of action of antipsychotic drugs is provided in Table 1.

While antipsychotic medications effectively manage psychotic symptoms, they are accompanied by a range of adverse effects, including cardiotoxicity and arrhythmias. Data indicates that adverse cardiovascular events account for nearly 10% of withdrawals from the market, as long as all types of drugs are concerned [14]. A study of causes behind sudden death in schizophrenia patients revealed that as many as 178 out of 251 natural deaths were caused by cardiovascular diseases [15]. Notably, within this class of drugs, clozapine has emerged as the most cardiotoxic [16]. Despite its designation as the most efficacious medication for treatment-resistant schizophrenia [17] and its demonstrated effectiveness in reducing the risk of suicide [18], clinicians face considerable challenges when managing cardiovascular adverse effects associated with its use. Nonetheless, a thorough understanding of potential cardiovascular adverse effects can assist clinicians in both anticipating and preventing such complications.

The aim of this review is to offer valuable insights into the potential cardiovascular impacts of antipsychotic medications, including their possible mechanisms and potential consequences.

Table 1.

	D2[1]	5HT2A[2]	5HT1A[3]	M1[4]	H1[5]	α1[6]
FGA[7]	antagonism	-[8]	-	antagonism	antagonism	antagonism
SGA[9]	antagonism	antagonism	-	antagonism	antagonism	antagonism
TGA[10]	partial agonism	antagonism	partial agonism	-	-	-

1 Dopamine D2 receptor
2 Serotonin 5HT2A receptor
3 Serotonin 5HT1A receptor
4 Muscarinic acetylcholine M1 receptor
5 Histamine H1 receptor
6 α1-adrenoceptor
7 First generation antipsychotics
8 means binding to this receptor is unknown/irrelevant to the mechanism of the medication
9 Second generation antipsychotics
10 Third generation antipsychotics

Orthostatic hypotension

First common cardiovascular adverse effect of antipsychotics is orthostatic hypotension, which is also the most often autonomic effect of these drugs [19]. Orthostatic hypotension refers to a significant decrease in blood pressure upon standing, which elevates the risk of adverse outcomes, even in the absence of noticeable symptoms [20]. Orthostatic hypotension arises due to the blocking of anticholinergic or α1-adrenoceptor pathways. α1-adrenoceptors typically induce vasoconstriction in specific blood vessels. When these receptors are blocked, vasodilation occurs, resulting in a decrease in blood pressure [21]. Among FGAs, low-potency phenothiazine antipsychotics, like chlorpromazine, are the most likely to cause this side effect. SGAs, except clozapine and quetiapine, are less likely to do that because of their low affinity for α1-adrenergic receptors. In the study of 300 hospitalized schizophrenia patients under observation, 98 of them experienced orthostatic hypotension [22]. It was observed that patients treated with either haloperidol or

clozapine, whether as monotherapy or in combination, often encountered orthostatic hypotension. This side effect was evident across both typical and atypical antipsychotic medication groups. It is important to highlight that orthostatic hypotension is transient and dosage-dependent [23]. Among individuals receiving antipsychotic treatment, elderly patients concurrently using multiple medications, individuals with autonomic system disorders, and those with fluid imbalances are particularly susceptible to this adverse effect [24]. Special attention should be directed towards elderly patients when assessing the likelihood of orthostatic hypotension, given their heightened risk of sustaining bone fractures resulting from falls triggered by such episodes[21].

QT interval prolongation

Another dangerous adverse effect of antipsychotics is QT interval prolongation. Due to the variation of the QT interval with alterations in heart rate, several formulas have been developed to adjust it, resulting in a corrected QT (QTc) value [25]. When referring to QT prolongation, it denotes a QT interval exceeding 450 milliseconds in men and 460 milliseconds in women[25]. In a cohort study involving nearly 5 million patients, around 40% who were prescribed antipsychotic medications subsequently were diagnosed QT prolongation [26]. It has been identified that the mechanism underlying QT prolongation involves the inhibition of the rectifier potassium channel (Kir) in the myocardium [19]. This channel regulates the outward movement of potassium ions, which are crucial for ventricular depolarization. Research indicates that QT prolongation may precipitate cardiac arrhythmias, notably polymorphic ventricular arrhythmia torsade de pointes [27]. While it may resolve spontaneously, it also poses a risk of sudden cardiac death by precipitating ventricular fibrillation [28]. Extensive retrospective cohort studies have approximated that individuals treated with second-generation antipsychotics (SGAs) face a heightened risk, ranging from 1.5 to 2.5 times, of experiencing sudden cardiac death (SCD) or ventricular arrhythmias compared to individuals diagnosed with schizophrenia who do not use antipsychotic medications [29]. Haloperidol has been observed to be associated with sudden cardiac death (SCD), especially when administered intravenously. However, this association should be viewed in the context of its frequent use in high doses for quickly calming acute mania or schizophrenia, or for managing acute delirium in the elderly and patients who already have a substantially elevated baseline risk of SCD due to electrolyte imbalances or concurrent treatments that prolong the QT interval [29]. In contrast, a randomized clinical trial conducted from 2011 to 2017 found no notable alterations in the QT interval among patients receiving treatment for delirium with either haloperidol or ziprasidone [30]. Another study demonstrated that QT prolongation manifests at an individual level among patients [31]. Data obtained from various cases facilitated the categorization of psychotropic medications, including antipsychotics, into three risk categories. The first category (Class A) includes drugs such as aripiprazole, olanzapine, perphenazine, and zuclopenthixol, which pose no risk of QTc prolongation or torsades de pointes. Amisulpride, chlorprothixene, clozapine, flupentixol, levomepromazine, paliperidone, quetiapine, risperidone, and sulpiride were classified as Class B medications, associated with a propensity for QTc prolongation. The third group, denoted as Class C drugs, encompasses medications with potential QTc prolongation, documented cases of Torsades de Pointes (TdP), or other life-threatening arrhythmias. This category includes haloperidol, pimozide, sertindole, and ziprasidone [32]. Based on this understanding, it can be inferred that a personalized assessment of factors contributing to QT prolongation is essential when prescribing an antipsychotic medication.

Atrial fibrillation

Another potentially hazardous arrhythmic adverse effect associated with antipsychotics that warrants discussion is atrial fibrillation, the most prevalent form of arrhythmia [33], capable of precipitating severe events such as ischemic stroke [34]. Possible underlying mechanisms contributing to this adverse effect include direct blockade of cardiac ion channels, direct sympathetic stimulation, drug-induced hypotension leading to reflex sympathetic tone increase, and an anticholinergic effect(blockade of M1 receptors) [35]. The risk of atrial fibrillation occurrence is notably elevated with certain atypical antipsychotics, which exhibit greater binding affinity to cardiac muscarinic receptors [36]. Sometimes antipsychotic drug-induced atrial fibrillation requires restoring the sinus rhythm [37]. Instances of severe atrial fibrillation (AF) induced by antipsychotics, whether administered in toxic or therapeutic doses, have been documented in patients without prior cardiovascular issues. To begin with, a case reported in 2011 depicted a 21-year-old woman who ingested 10 mg of olanzapine in a suicide attempt [38]. At first, her ECG showed a standard sinus rhythm, while four hours later, atrial fibrillation with large fibrillatory waves occurred. She had no previous history of arrhythmias. Another case involving the use of clozapine and olanzapine featured a 49-year-old woman who was hospitalized due to treatment-resistant schizophrenia [39]. While undergoing treatment with high doses of clozapine and olanzapine, the patient experienced multiple episodes of atrial fibrillation. Cessation of both medications resulted in the absence of similar

episodes during subsequent treatment with risperidone, quetiapine, and haloperidol. Paliperidone has also been associated with the occurrence of atrial fibrillation, as evidenced in a patient undergoing multi-drug therapy [40]. The drug was implicated in causing this condition, as it was the sole medication introduced just four days prior to the incident. Instances of atrial fibrillation emerging in patients undergoing antipsychotic therapy highlight the importance of commencing treatment with low doses and closely monitoring patients for the development of arrhythmias.

Heart rate changes

In addition to arrhythmias, antipsychotics can impact heart rate. Tachycardia provoked by antipsychotic medications is most frequently observed with the use of low-potency first-generation antipsychotics (FGAs), such as chlorpromazine, and certain second-generation antipsychotics (SGAs), such as clozapine [24]. Tachycardia associated with antipsychotics can arise from various mechanisms, including the anticholinergic effects of the medications, orthostatic hypotension (described above) resulting from α1-adrenoceptor blockade, as well as indirect effects such as myocarditis and neuroleptic malignant syndrome [41]. In a study conducted from 2015 to 2020, analysing 636 Medical Emergency Team (MET) calls occurring in 449 psychiatry inpatients, a positive association between the use of antipsychotic medications and severe tachycardia (heart rate ≥130 per min) was found [41]. A patient admitted to a psychiatric ward and receiving any antipsychotic medication had a 4.1 times higher likelihood of encountering severe tachycardia and necessitating a MET call compared to patients not prescribed antipsychotics. This association remained consistent even after controlling for factors such as age, temperature exceeding 38°C, use of anticholinergic medications, and hypoglycemia.

In addition to inducing tachycardia, antipsychotic medications can also lead to a decreased heart rate. Documented evidence suggests that antipsychotic medications, including risperidone, quetiapine, amisulpride, olanzapine, and notably, clozapine, have been associated with instances of bradycardia, despite clozapine being typically associated with a higher likelihood of inducing tachycardia [42]. Instances of bradycardia induced by risperidone leading to cardiac arrest have predominantly affected elderly individuals, as seen in an 82-year-old woman with a heart rate of 43 beats/min and a 69-year-old man with a heart rate of 39 beats/min [43]. Upon initiating resuscitation and providing patient support, discontinuation of the medication was warranted. In another case, an elderly male patient receiving 225mg/day of quetiapine for severe psychotic symptoms experienced suspected cardiac abnormalities, which improved upon dose reduction [44]. A similar scenario occurred in a 45-year-old male treated with 400-800 mg/day of amisulpride, who developed bradycardia that significantly improved upon discontinuation of the drug [45]. Interestingly, this patient did not experience bradycardia upon switching from amisulpride to risperidone, suggesting that antipsychotic-induced bradycardia may be influenced by various factors. However, contrary to the presented data, findings from other studies indicated no association between the use of antipsychotics and the occurrence of bradycardia whatsoever [46].

Myocarditis

Another potentially life-threatening adverse effect of antipsychotic medications is myocarditis. As previously mentioned, clozapine is the drug most commonly associated with this adverse effect. Myocarditis occurs in approximately 3% of patients undergoing treatment with clozapine [47] and typically manifests within the initial weeks of treatment [48]. It has been found that simultaneous use of sodium valproate elevates the risk of clozapine-induced myocarditis [49]. Mechanisms associated with clozapine-induced myocarditis include catecholaminergic activation, stimulation of cardiomyocyte apoptotic pathways, immunomodulation, and proinflammatory mechanisms (involving cytokine release syndrome and an IgE-mediated - type I hypersensitivity reaction), as well as free radical-induced oxidative stress and impairment of enzymes essential for cellular metabolism, leading to decreased myocardial energy production [50]. The majority of cases describe individuals diagnosed with clozapine-induced myocarditis as having hypereosinophilia, suggesting that an IgE-mediated reaction is the most common mechanism [51]. It is noteworthy that eosinophilia may also be present in patients treated with clozapine who do not develop myocarditis [52]. Patients with myocarditis typically exhibit symptoms such as dyspnea, fever, and tachycardia. Elevated cardiac markers and C-reactive protein (CRP) levels are commonly observed. Additionally, crepitations may occasionally be detected upon lung auscultation [53]. Myocarditis can progress to cardiac death, as documented in numerous cases. Regrettably, patients developing myocarditis often exhibit minimal warning signs, aside from episodes of tachycardia and mild chest discomfort, despite being already monitored in the unit [48]. However, clozapine is not the sole antipsychotic associated with documented cases of drug-induced myocarditis. For instance, in an 18-year-old patient previously treated with methylphenidate for an extended period, the addition of quetiapine was deemed a probable contributor to

myocarditis leading to acute ST-elevation myocardial infarction (STEMI) [54]. Subsequently, a decision was made to discontinue both medications, resulting in the complete recovery of the patient within 8 weeks. Two deceased patients, later attributed to olanzapine, both exhibited myocardial necrosis and elevated levels of eosinophilic granulocytes [55]. Although the cause of death could not be definitively determined, myocarditis was suspected. However, these cases are considered exceptional, as other scientific evidence indicates no correlation between olanzapine and myocarditis [56]. This information provides a more optimistic outlook compared to the numerous documented cases of clozapine-induced myocarditis.

Other cardiotoxic effects

Apart from myocarditis, two different types of clozapine-induced cardiotoxicity have been described in the literature: clozapine-associated cardiomyopathy and subclinical clozapine-associated cardiotoxicity [57]. Nowadays, cardiomyopathy is divided into subcategories, including hypertrophic, dilated and restrictive [58], dilated cardiomyopathy being the type caused by antipsychotic medication [24]. Dilated cardiomyopathy is characterized by the enlargement of the left ventricle and impaired contractile function [59]. Most instances of clozapine-induced cardiomyopathy occur over a longer duration compared to the time required for myocarditis to develop, and such occurrences are relatively rare. Additionally, cardiomyopathy generally exhibits a lower mortality rate than myocarditis, with one study reporting rates of 12.7% for myocarditis and 7.8% for cardiomyopathy [60]. However, studies present inconsistent findings regarding the severity of both cardiotoxic effects [60, 61]. The occurrence of severe adverse events, including fatalities, is minimal and likely underreported, a factor clinicians should consider when assessing the risk-benefit balance [62]. Subclinical clozapine-associated cardiotoxicity is more common than clozapine-associated cardiomyopathy and myocarditis, and early detection could enhance patient outcomes by preventing cardiac dysfunction. Symptoms of cardiomyopathy are nonspecific and challenging to identify promptly; they may include tachycardia, dyspnea, palpitations, chest pain, and fatigue, resembling those of heart failure. Nonetheless, many cases remain asymptomatic [63]. The underlying mechanism of this event remains largely unknown [64]. There have been instances of drug-induced cardiomyopathy related to drugs other than clozapine. For example, a 37-year-old woman experienced dilated cardiomyopathy, characterized by sinus tachycardia with left bundle branch block morphology and cardiomegaly, likely attributed to high doses of quetiapine. This diagnosis was made as her condition could not be explained by acute myocarditis or ischemic heart disease, and no family history of heart disease was evident [65].

Other possible cardiovascular complications

The literature contains cases of heart failure arising from antipsychotic treatment. Typically, the emergence of severe adverse effects signals the need to discontinue treatment [29]. However, in the case of a 51-year-old man receiving clozapine, treatment continued with cardiology consultation despite a diagnosis of heart failure [66]. The patient presented with episodes of tachycardia and chest pain, with an electrocardiogram (ECG) showing partial right bundle branch block (RBBB). Following the initiation of ramipril and bisoprolol, the patient's cardiac function improved, and cardiologists determined that clozapine treatment could be continued with regular ECG monitoring.

Apart from causing QT prolongation, torsades de pointes (TdP), arrhythmias, and bradycardia, antipsychotics can lead to cardiac arrest through other mechanisms. Certain antipsychotics have been associated with unmasking a specific type of ECG abnormality known as Brugada syndrome [67]. Brugada syndrome, first described in 1992 by Pedro and Josep Brugada [68], is linked to a heightened risk of sudden cardiac death in individuals with structurally normal hearts [69], particularly in males [70]. Additionally, some cardiac manifestations induced by antipsychotics that result in cardiac death may have genetic underpinnings, although the role of genetics in this context remains poorly understood [71]. It is noteworthy that while therapeutic doses of antipsychotics can be fatal for patients, many instances of sudden cardiac events are also attributable to unintentional poisoning [72].

A summary of important adverse effects caused by antipsychotics is provided in table 2.

Two faces of clozapine

As previously noted, clozapine is highly effective but associated with numerous dangerous adverse effects. Therefore, its initiation requires careful consideration by clinicians. It is important to review the appropriate timing and procedures for starting clozapine treatment, as well as the necessary monitoring protocols. Clozapine is regarded as a prototype for other (SGAs) and has demonstrated significantly greater efficacy compared to conventional antipsychotics [73]. Its particularly complex receptor-binding profile likely contributes to both its effectiveness and the variety of adverse effects associated with its use. These adverse effects often outweigh the benefits of clozapine, leading to other SGAs becoming the first-line treatment for schizophrenia [74]. While their

Table 2.

Adverse effect	Mechanism	Medication[11]
Orthostatic hypotension	α1[12] antagonism	FGA[13]
QT-interval prolongation	Kir[14] inhibition in the myocardium	Haloperidol, pimozide, sertindole, ziprasidone
Atrial fibrillation	blockade of cardiac ion channels, sympathetic stimulation, hypotension, anticholinergic effect(M1[15] blockade)	Clozapine, olanzapine
Tachycardia	M1 antagonism, orthostatic hypotension(α1 antagonism)	FGA, clozapine
Bradycardia	Not fully known	SGA[16]
Myocarditis	Proinflammatory mechanism – IgE-mediated	Clozapine
Cardiomyopathy	Not fully known	Clozapine

11 Medication most likely to cause this adverse effect
12 α1-adrenoceptor
13 First generation antipsychotics
14 Rectifier potassium channel
15 Muscarinic acetylcholine M1 receptor
16 Second generation antipsychotics

antipsychotic efficacy may not match that of clozapine, they are less problematic for long-term use [9].

When diagnosing a patient with schizophrenia, clozapine is not recommended until two other SGAs used in monotherapy have proven ineffective. Besides treatment-resistant schizophrenia, clozapine may also be considered for patients who are highly suicidal [11]. When initiating clozapine treatment in an inpatient setting, it is recommended to start with 12.5 mg once or twice daily on the first day. The dosage should then be increased daily by 25–50 mg until the minimum therapeutic dose is reached, provided it is well-tolerated. The minimum plasma trough level of clozapine associated with a good therapeutic response is generally considered to be 350 ng/mL, while levels exceeding 600 ng/mL are linked to a higher risk of dose-dependent side effects, such as seizures. Therapeutic drug monitoring is unnecessary if the patient is responding well to the therapy. However, it is recommended in cases where clinical improvement is not observed or if there is a possibility of non-adherence to the treatment. Throughout therapy, careful monitoring is essential to prevent adverse events. This study will specifically emphasize cardiovascular monitoring [11].

Before starting clozapine, biochemical tests for brain natriuretic peptide (BNP), troponin, C-reactive protein (CRP), electrolytes, and creatine kinase should be conducted. Additionally, an ECG is recommended. During the first two weeks of treatment, blood pressure, temperature, and pulse should be monitored, and cardiac symptoms such as chest pain, edema, or shortness of breath should be assessed. During the first two months of clozapine treatment, CRP, BNP, troponin, and creatine kinase levels should be monitored. If clozapine treatment continues beyond eight weeks, annual ECGs are recommended, with echocardiography as needed [11].

The decision to stop clozapine treatment may be influenced by issues related to its effectiveness, patient adherence, tolerability, or the onset of severe adverse effects. In non-emergency situations, clozapine dosage should ideally be gradually reduced over a period of six months, if feasible. During this tapering process, cross-titration to an alternative antipsychotic should be considered based on the patient's treatment history, tolerability, and side-effect profile [11].

If myocarditis or cardiomyopathy occurs, discontinuation of clozapine is typically recommended, although this decision may vary depending on the specific clinical circumstances and information available [75].

Important drug interactions

As demonstrated by this study, antipsychotic medications can lead to significant cardiovascular issues in individuals. It is important to note that, given the general prevalence of schizophrenia and other psychiatric disorders, many psychiatric patients are likely to already suffer from cardiac diseases. It is important to note that, due to the general prevalence of schizophrenia and other psychiatric disorders, many psychiatric patients are likely to also suffer from cardiac diseases. Treating these patients can be particularly challenging due to frequent cardiac-psychiatric drug interactions. Antiarrhythmics are especially problematic in this context [76]. Cardiotoxicity is the most prevalent issue in cardiac-psychiatric interactions involving antiarrhythmics. As

previously mentioned, antipsychotics can be cardiotoxic on their own; thus, combining them with antiarrhythmics can be potentially fatal. Specifically, the use of quetiapine or risperidone with amiodarone, dronedarone, flecainide, procainamide, propafenone, or sotalol is contraindicated [77].

Another significant adverse effect exacerbated by drug interactions is prolongation of the QT interval. A study conducted in 2021 involving 832 elderly psychiatric patients indicated that the drug combinations most likely to increase this adverse effect include escitalopram with risperidone (11.5%), escitalopram with olanzapine (11.1%), and fluoxetine with olanzapine (8.7%) [78]. It is noteworthy that among this cohort of patients, 180 individuals had pre-existing cardiovascular disease. Of these, 75.1% were recommended to undergo regular ECG monitoring. Another study on this topic demonstrated that the interaction causing QT interval prolongation between antipsychotics and antidepressants is mediated by P-glycoprotein (P-gp). The findings indicated a higher incidence of QT prolongation when P-gp substrate antipsychotic drugs such as quetiapine and sulpiride were combined with SSRIs that inhibit P-gp. Conversely, no correlation with QT prolongation was found in patients using antipsychotics that are not substrates for P-gp [79].

Finally, it is notable that medications used for COVID-19 treatment may increase the risk of QT prolongation and Torsades de Pointes (TdP) [80]. The use of hydroxychloroquine, chloroquine, or azithromycin is contraindicated with haloperidol, ziprasidone, zuclopenthixol, chlorpromazine, and levomepromazine. Lopinavir and ritonavir potentially interact with most antipsychotics. Although the pandemic has subsided, clinicians should remain vigilant about these interactions in clinical practice.

Brighter side of the antipsychotics

On a more optimistic note, there is a hypothesis suggesting a potential link between atypical antipsychotic drugs and the reduction of mortality risk from ischemic heart disease. This hypothesis posits that blocking the 5-HT2A receptor could contribute to this outcome by preventing serotonin from enhancing platelet aggregation [81]. Serotonin is known to be associated with various cardiovascular effects, including vasodilation or vasoconstriction [82], hypotension or hypertension [83], and bradycardia [84] or tachycardia [85]. Consequently, it is proposed that elevated blood serotonin levels and platelet activation may increase the risk of sudden cardiac events, and blocking 5-HT2A receptors could potentially mitigate this risk to some extent.

What is more, when comparing the cardiovascular side effects of recently developed antipsychotics, including brexpiprazole, cariprazine, lurasidone, pimavanserin, and roliperidone, roliperidone exhibited the lowest occurrence of cardiovascular effects and metabolic influences, such as hypotension, QTc prolongation, weight gain, and metabolic syndrome. This suggests a potential therapeutic approach to mitigate the drawbacks of second-generation antipsychotics (SGAs). However, additional clinical trials are necessary to assess both safety and efficacy [86].

In terms of treatment, clinicians now have access to various methods that enhance its effectiveness. One increasingly utilized approach is therapeutic drug monitoring(TDM), which was previously discussed in the context of clozapine treatment. Patients metabolize drugs at different rates, leading to varying concentrations in the plasma for the same dosage. Despite the varying recommendation levels for specific antipsychotics, TDM is highly advised for certain specific indications [87]. These indications represent complex clinical scenarios, where the supporting evidence for TDM ranges from case reports to clinical trials. Extensive evidence from patients with chronic schizophrenia indicates that treatment for nearly half of these patients will require interventions beyond dose titration, such as adjusting the target dose or switching antipsychotics [87]. Rather than relying on a trial-and-error approach, TDM can offer critical insights to guide the decision-making process. Critically, TDM plays a significant role in preventing adverse effects. As previously stated, maintaining clozapine plasma levels within the range of 350 to 600 ng/mL is key to minimizing adverse effects in most patients [11]. In addition to clozapine, TDM is advised for dose titration and specific indications when initiating treatment with drugs such as fluphenazine, haloperidol, olanzapine, perazine, and perphenazine. For other antipsychotics, TDM is recommended with a lower level of clinical confidence [87]. However, this approach still offers considerable potential for improving antipsychotic treatment.

Summary

In summary, antipsychotic medications can potentially induce various adverse effects, yet these effects typically should not serve as an absolute contraindication to their use. Despite the capacity of certain drugs, such as clozapine, to precipitate severe complications in patients, their therapeutic efficacy often warrants continued utilization by clinicians. It is imperative to acknowledge that severe adverse effects commonly manifest in patients undergoing multidrug therapy or harboring multiple individual risk factors. Moreover, the emergence of third-generation antipsychotics offers promise in mitigating the burden associated with older antipsychotic agents. Essential to clinical practice is the conscientious consideration of potential adverse effects when

prescribing such medications, recognizing each patient as a unique individual with distinct medical history. Through such personalized approach, it is conceivable that many adverse effects associated with antipsychotic drugs could be mitigated, thereby facilitating the provision of less burdensome therapies and optimizing patient outcomes.

Conflict of interest

The authors have declared no conflict of interest.

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Corresponding author

Alicja Gładysz
e-mail: alicjagladysz2001@gmail.com
Institute of Heart Diseases, Medical University of Wroclaw

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