MINIREVIEW

CARDIOVASCULAR SIDE EFFECTS
OF NEUROPSYCHIATRIC MEDICATION: AN UPDATE

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ABSTRACT

Neuropsychiatric diseases have a rising incidence and cause a significantly higher risk of morbidity and premature mortality in the general population. Also, cardiovascular diseases (CVDs) are characterized by the highest prevalence in the population and are a major cause of early morbidity, especially through the occurrence of coronary ischemic events. Recently, it has been demonstrated the involvement of neuropsychiatric diseases in the etiology of CVDs. On the one hand, the treatment of these diseases can improve the prognosis of CVD, but on the other hand iatrogenesis may play a very important role in their determinism. Administrating neuropsychiatric medication (NPM) can be very challenging for patients with CVD because of their cardiovascular side effects (CVSEs). NPM and CVDs have a double edged-sword relationship. The purpose of this review is to present the link between the treatment with antidepressants and antipsychotics and the cardiovascular system, and to summarize the current information of the various CVSEs of NPM.

Keywords: cardiovascular disease, neuropsychiatric medication, cardiovascular side effects.

RéSUMÉ

Effets secondaires cardiovasculaires de la médication neuropsychiatrique: données récentes

Les maladies neuropsychiatriques ont une incidence croissante et présentent un risque plus élevé de morbidité et de mortalité prématurée dans la population générale. De plus, les maladies cardiovasculaires se caractérisent par la prévalence la plus élevée dans la population et constituent une cause majeure de morbidité précoce, en particulier par la survenue d’événements ischémiques coronariens. Récemment, l’implication des maladies neuropsychiatriques dans la détermination des maladies cardiovasculaires a été démontrée. D’une part, le traitement de ces maladies peut améliorer le pronostic des maladies cardiovasculaires, mais d’autre part l’iatrogenèse peut jouer un rôle très important dans leur déterminisme. C’est pourquoi l’administration des médicaments neuropsychiatriques peut être très difficile pour les patients atteints de maladies cardiovasculaires en raison de leurs effets secondaires. Dans cet article, nous avons l’intention de présenter le lien entre le traitement antidépresseur et antipsychotique et le système cardiovasculaire, afin de résumer les informations actuelles sur les divers effets
INTRODUCTION

Neuropsychiatric diseases have a rising incidence and cause a significantly risk of morbidity and premature mortality in the general population. Untreated patients with these diseases may die 15-20 years earlier than non-neuropsychiatric patients. On the other hand, cardiovascular diseases (CVDs) are characterized by the highest prevalence in the general population and are a major cause of early morbidity, especially through the occurrence of coronary ischemic events. The prediction of the occurrence of CVD and their complications has become more and more accurate in recent years by identifying and preventing major risk factors. More recently, the involvement of psychiatric illnesses in determining CVDs has been studied. The American Heart Association suggested that depression should be an independent major risk factor for CVD, as dyslipaemia, diabetes, smoking, arterial hypertension (AHT). The treatment of these diseases can improve the prognosis of CVDs, but iatrogenesis may play a very important role in their determinism.

Prescribing NPM is very frequently required in clinical practice, being among the most commonly used treatments. The iatrogenic cause of CVDs is one of the most controversial subjects at the moment. There is a large spectrum of cardiovascular side effects (CVSEs): slowing intraventricular conduction seen on electrocardiogram (ECG) as prolonged baseline QT, ventricular arrhythmias and sudden cardiac death (SCD), effects on blood pressure and heart rate, coagulability disorders, endothelial alteration, hydroelectrolytic disorders, myo(peri)carditis and cardiomyopathy, effects on lipid and glucose metabolism. These CVSEs are associated with most of the antidepressants and antipsychotics.

Furthermore, polypharmacy used to treat a single disease or several coexisting comorbidities is very common, that is why we should be familiar with the side effects, their prevention, early detection and treatment. Also, monitoring and modifying major cardiovascular risk factors is recommended for patients with severe mental diseases.

The purpose of this review is to present the link between the treatment with antidepressants and antipsychotics and the cardiovascular system, and to summarize the current information about this subject. This is an important area of interest because there is a lack of investigation to understand and to determine the various CVSEs of NPM. The main objective of this paper is to promote an interdisciplinary approach for understanding and treating major mental illnesses and CVDs.

This review is based on the evaluation of already published literature. We searched PubMed, Science Direct and references from relevant articles for data of treatment with antidepressants and antipsychotics and their effects on cardiovascular system. We combined different terms of antidepressants, antipsychotics, blood pressure, arrhythmias, sudden death, heart rate, hydroelectrolytic disorders, myocarditis, pericarditis, cardiomyopathy, bleeding, thrombosis, lipid profile disturbances, blood glucose level, diabetes, weight gain, coronary diseases. The literature search was made to identify systematic reviews, meta-analysis, randomized controlled trials, and clinical cases only where there is little information on the subject.
QT PROLONGATION AND ARRHYTHMIAS

Potential mechanism. One of the potential mechanisms of NPM in producing arrhythmias is through inhibition of the delayed rectifier potassium current (IKr) encoded by the human ether a go-go-related gene (hERG). Blocking IKr is known to prolong cardiac repolarization seen on ECG as corrected QT interval (QTc). Clinically, this means ventricular arrhythmias like torsades de pointes (TdP), which can cause SCD. Also, another potential mechanism found only in antipsychotic medication is the inhibition of fast sodium current (INa) encoded by the sodium channel, voltage-gated, type V, alfa subunit (SCN5A) which determines the reduction of the sodium influx in cell, causing altered voltage gradients with Brugada-like syndrome. The effect is the same, SCD8,9.

Risk factors for TdP. Drug induced QT prolongation and TdP have many determinant risk factors: age (> 65 years), female sex, cardiac comorbidities: electrolyte disorders like hypokalemia/hypomagnesemia, bradycardia, other conduction disturbances, myocardial and coronary artery diseases8,10. Patients' factors, such as genetic disease like in type 2 long QT syndrome, hERG mutation or poor metabolizers of cytochrome P450 (CYP)2D6, for example, increased concentration of the drugs and cardiotoxic metabolites11.

Formulas for correcting QT interval for rate. QT interval on the ECG means the depolarization and repolarization of the ventricles and it is measured from the beginning of the QRS complex to the end of the T wave. For the QT correction there have been developed many formulae, but Bazett formula (QTc = QT/RR1/2) is the most frequently used in clinical practice12. American Guidelines recommend to use Hodges formula (QTc = QT + 1.75 (HR-60)) for example, increased concentration of the drugs and cardiotoxic metabolites11.

QT interval. Normal QTc interval values are ≤ 430 ms for men and ≤ 450 ms for women. A QT interval ≥ 500 ms is the cutoff for discontinuing antipsychotic treatment because of the risk of TdP. Also, if QTc interval increases for ≥ 60 ms or ≥ 15% from the baseline, this is an important predictor for TdP14.

There are studies that investigated other alternative markers, except QTc, for estimating the risk of SCD: T peak-T end interval, T wave morphology (flat, asymmetric, notched T wave) or QT dispersion (the difference between the longest and the shortest QT interval in 12 leads)15. Even if for including these markers in clinical practice more investigations are necessary, Okayasu et al demonstrated that the increase of QT interval may be more sensible for predicting arrhythmias due to NPM16.

Antipsychotic drugs. Arrhythmias occur more frequently with the first generation of antipsychotics (FGAs), second generation of antipsychotics (SGAs) having a lower risk of QT prolongation17. Haloperidol (with stronger dopaminergic effects) via the intravenous route showed an increased risk of QT prolongation. Similar arrhythmias have been demonstrated with thioridazine and chlorpromazine (with stronger effects on adrenergic and cholinergic systems), but also clozapine, quetiapine, olanzapine, risperidone – SGAs of last generation18. In some cases, the association between antipsychotics and other medication, such as pantoprazole, ciprofloxacain or antidepressants, increased the torsadogenic risk. In a meta-analysis, Leucht et al observed that the risk of QT prolongation was increased most with sertindole and the lowest risk was with lurasidone20. Slavo et al, in another recent meta-analysis, which compared the appearance of SCD between non-user and users of antipsychotics, demonstrated that the risk was higher with thioridazine, clozapine, risperidone, haloperidol, olanzapine and quetiapine21. Also, the Aritmo projects have shown that the majority of TdP cases were associated with clozapine, olanzapine, quetiapine, ziprasidone, risperidone, haloperidol and fewest with aripiprazole22.

Antidepressant drugs: Tricyclic antidepressants (TCAs) are already known to be associated with prolongation of the QT interval, but lately even some selective serotonin reuptake inhibitors (SSRIs), considered to be safer, demonstrated repolarization disorders. For example, citalopram and its isomer, escitalopram, could cause prolongation of the QT interval. Beach SR et al showed in a meta-analysis that SSRIs caused greater QT prolongation than placebo, and that was dose dependent. Also, the study showed TCAs prolong QT much more than SSRIs. From SSRIs, citalopram prolonged the highest QT. A retrospective study using the Tennessee Medicaid cohort concluded that citalopram used in high doses has the same risk of SCD as the other SSRIs23.
Escitalopram showed in studies the potential of QT prolongation and in the Beach SR et al meta-analysis, QTc increased with 7.3 ms. Also, Tennessee Medicaid cohort demonstrated that high-doses of escitalopram were not associated with higher mortality than other antidepressants\(^{27,21}\). Other SSRIs (fluoxetine, fluvoxamine) have shown a lower risk of QT prolongation\(^{24}\). Sertraline is known as an agent with a good cardiac safety and in the case of paroxetine, vilazodone and vortioxetine no repolarization disorder has been yet reported\(^{13}\). Clinical studies have shown that bupropion, a serotonin and noradrenaline reuptake inhibitor (SNRI) was associated with a very low risk of arrhythmias, and duloxetine did not exhibit repolarization disorders. From SNRIs, venlafaxine is the drug that has shown the highest risk of QT prolongation, but this effect usually appeared in overdose\(^{31}\).

**Heart rate variability (HRV)**

Antipsychotics. Through anticholinergic effect, antipsychotics have been associated with reduced HRV, especially when using clozapine. On one hand, Huang et al in 2013 demonstrated that the antipsychotics with the most important effect on HRV were clozapine, olanzapine and chlorpromazine, but on the other hand, the same Huang in 2016 indicated that quetiapine had an overt decrease in HRV\(^{26,27}\).

Antidepressants. Also, through anticholinergic and adrenergic effect, antidepressants could have this SE. Especially TCAs, less SNRIs demonstrated to have an impact on autonomic nervous activity and decreased the HRV. From SSRIs, paroxetine, through the anticholinergic effect showed the most important reduction of HRV\(^{28}\). Kemp et al showed that almost all SSRIs, except fluoxetine, decreased HRV and paroxetine had a higher impact\(^{29}\).

**Effects on blood pressure**

Antipsychotics. Often orthostatic hypotension (OH) is a CVSE for almost all antipsychotic agents by blocking adrenergic \(\alpha_1\) receptors. From the first generation of antipsychotics “chlorpromazine-like “ drugs were associated with a greater risk of OH\(^{30}\). In Catie study, clozapine, iloperidone, quetiapine had the greatest risk of OH and olanzapine, aripiprazole and lurasidone the lowest risk\(^{31}\). Taking this into consideration patients may pay attention to rise slowly, having a proper fluid ingestion and a sodium containing diet and reduce or stop the antihypertensive medication. After a time of using this drugs tachyphylaxis might occur, reducing the risk of OH. Also, new generation of antipsychotic medication, by acting on dopaminergic receptors, influencing the renin angiotensin system and sympathetic vegetative system, could determine, depending on affinity on a particular receptor, either AHT or arterial hypotension. AHT was associated with clozapine, olanzapine and ziprasidone, while other antipsychotics had a lower risk\(^{32}\). Aripiprazole, one of the newest NPM, displayed AHT as CVSE, most probably because of a high affinity on \(\alpha_1A\) adrenergic receptor\(^{33}\).

Antidepressants. Another SE of antidepressants is AHT, the highest risk is associated with monoamine oxidase inhibitors (MAOIs). SNRIs led to an increased risk of AHT, for venlafaxine it was one of the most common CVSE. On the other hand, clinical experience has shown that SSRIs are rarely associated with AHT\(^{34,35}\). TCAs, mirtazapine, but especially reboxetine (noradrenaline reuptake inhibitor) could cause OH\(^{14}\).

**Hydroelectrolytic disorders**

Hyponatremia was demonstrated to be relatively a common SE of NPM, while hypokalemia appeared only with SGAs\(^{36,37}\). The explanation of hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion\(^{38}\).

Antipsychotics. Bersani et al, in a review, showed that FGAs rather than SGAs had a higher risk of hyponatremia, by worsening polydipsia through dopamine sensitivity\(^{39}\). In a case control study it was suggested that both classes of antipsychotics had the same risk of hyponatremia\(^{40}\). In a very recent review focused only on SGAs it was found that hyponatremia appeared in patients treated with olanzapine, risperidone and aripiprazole. Also, the authors suggested that serum sodium should be evaluated in the first 2 weeks of the initiation of SGAs treatment. Hyponatremia seemed to be reversible if discontinuing the medication. Clozapine was associated more frequently with hypokalemia\(^{41}\).

Antidepressants. The risk of hyponatremia was demonstrated to be lower for TCAs and mirtazapine-antagonist of postsynaptic serotonin receptor, and higher for SSRIs and SNRIs\(^{35}\). Gilboa et al, in a case control study, evidenced that treatment with SSRIs increased the rate of hyponatremia by 50%\(^{42}\). Coupland et al showed that fluoxetine, citalopram and escitalopram had a greater risk of hyponatremia, while paroxetine and sertraline had lower incidences\(^{43}\). From SNRIs, venlafaxine has demonstrated to have a higher risk of hyponatremia\(^{34}\). A recent study showed mirtazapine to be highly associated with hyponatremia, and from serotonin-modulating drugs,
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Cardiovascular side effects

Many frequently used NPM, antidepressants and especially antipsychotics, have been associated with cardiometabolic risk factors, by acting on lipid and carbohydrate metabolisms and developing the metabolic syndrome, thus enhancing the major risk factors for cardiovascular disease. This caused acceleration of atherosclerosis and the onset of ischemic diseases. These drugs have been involved in weight gain, abdominal obesity, dyslipidemias and have increased insulin resistance, hepatic glucose production and the level of blood sugar. It was shown that aripiprazole, a newer SGA, produced an important weight gain, compared with haloperidol. A solution could be combining antipsychotic treatment with statin for improving serum lipid growth.

Antidepressants. Comparing long-term treatment of all classes of antidepressants, the highest risk of weight gain was found with mirtazapine, TCAs and SSRIs. Medium and long-term treatment with paroxetine, mirtazapine, amitriptyline, citalopram and nortriptyline was associated with weight gain. Even short-term treatment with some antidepressants like amitriptyline, mirtazapine and nortriptyline demonstrated weight gain, while bupropion was associated with weight loss. For metabolic disorders, there are only small studies that have been demonstrated the implication of SSRIs in increasing the cholesterol, but not the triglycerides, and paroxetine was shown to produce a significant increase of LDL-cholesterol. The recent pharmacoepidemiological study of Siafis and Papazisis showed that sertraline, mirtazapine and almost all TCAs induced hyperglycemia and were associated with diabetes mellitus, the mechanism involved being the affinity for muscarinic M1, M3, M4, M5 and histaminergic H1 receptors.

Bleeding and thrombosis risk

Antidepressants affect the primary hemostasis by inhibiting serotonin re-uptake, which is involved in platelet aggregation, thus increasing the risk of bleeding. So, as much as serotonin re-uptake is inhibited, the more platelet aggregation is inhibited. By default, among the classes of antidepressants, SSRIs were associated with the highest risk of bleeding. Fluoxetine and fluvoxamine from SSRIs in combination with antivitamin K anticoagulants increased the most the risk of bleeding, so this combination is to be avoided. Also, the new oral anticoagulants that are metabolized via the CYP3A4 pathway, except for dabigatran, interacted with nefazodones, fluoxetine and fluvoxamine, due to the inhibition of the same cytochrome, again increasing the risk of bleeding. Antipsychotics can increase the risk of venous thrombosis and pulmonary thromboembolism. Venous thrombembolism was shown to be higher with SGAs: quetiapine, risperidone, olanzapine, clozapine, but it was found to appear also with FGAs. The mechanisms discussed have been by increasing platelet aggregation and venous stasis, as well as high levels of anti-cardiolipin antibodies, hyperhomocysteinemia and hyperprolactinemia.

Myocarditis and cardiomyopathy

Clozapine is the first SGAs drug and the most valuable treatment to reduce the risk of suicidal behavior in schizophrenic patients. Now, clozapine is approved for schizophrenia drug-resistant at other antipsychotics. The use of clozapine is limited because...
its severe SEs. Besides other CVSEs discussed, there is one life-threatening, early myocarditis and later cardiomyopathy. The potential mechanism of clozapine-induced cardiotoxicity could be explained by oxidative stress, decreased parasympathetic tone and increased adrenergic tone, immunoglobulins or cytokines responses or through the direct toxic effects on myocardial tissue. It might occur in the first 2-8 weeks of treatment or later, unpredictable, dose-independent and it could be reversible when early treatment is discontinued and supportive therapy is used. The clinical symptoms of myocarditis included fever, influenza-like symptoms, nausea, dizziness, sometimes chest discomfort, and patients with cardiomyopathy present heart failure symptoms, but there were reported fatal cases without symptoms. Paraclinically, it was observed the rise in eosinophil cells, presence of inflammatory markers, troponins T and I, creatine-kinase MB, natriuretic peptides, non-specific ECG abnormalities and systolic dysfunction with reduction of the left ventricular ejection fraction. In a prospective study, patients treated with clozapine presented subclinical CVSEs demonstrated by early echocardiographic changes, diastolic dysfunction, high systolic pressure in pulmonary artery, without correlation with the modification of other biomarkers. Also, there are already evidences with high-doses of quetiapine, which is structurally similar with clozapine, that had the same severe SEs. Taking these data into consideration, it seems necessary to develop the diagnostic methods for limiting the risk of life-threatening CVSEs associated with this class of NPM.

**Conclusions**

NPM causes multiple and important CVSEs, so the prognosis of CVDs in treated neuropsychiatric patients is still uncertain. Therefore, it is necessary that clinicians should be aware and evaluate these SEs in order to be able to apply primary and secondary prevention measures for CVDs, to improve the quality of life and to reduce the risk of morbidity. Also, research is still needed to create a safety profile for NPM to make possible the administration of these drugs, even in patients with pre-existing CVDs.

**Author contributions**

O.A.C. and R.R. conceived the original draft preparation. C.S. and E.C.L. were responsible for conception and design of the review. O.A.C. and R.N. were responsible for the data acquisition. O.A.C., A.P.F. and R.R. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed to the published version of the manuscript.

**Compliance with Ethics Requirements:**

The authors declare no conflict of interest regarding this article

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