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REVIEW
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Atypical antipsychotics and oxidative cardiotoxicity: review of literature and future perspectives to prevent sudden cardiac death

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ABSTRACT Oxidative stress is considered the principal mediator of myocardial injury under pathological conditions. It is well known that reactive oxygen (ROS) or nitrogen species (RNS) are involved in myocardial injury and repair at the same time and that cellular damage is generally due to an unbalance between generation and elimination of the free radicals due to an inadequate mechanism of antioxidant defense or to an increase in ROS and RNS. Major adverse cardiovascular events are often associated with drugs with associated findings such as fibrosis or inflammation of the myocardium. Despite efforts in the preclinical phase of the development of drugs, cardiotoxicity still remains a great concern. Cardiac toxicity due to second-generation antipsychotics (clozapine, olanzapine, quetiapine) has been observed in preclinical studies and described in patients affected with mental disorders. A role of oxidative stress has been hypothesized but more evidence is needed to confirm a causal relationship. A better knowledge of cardiotoxicity mechanisms should address in the future to establish the right dose and length of treatment without impacting the physical health of the patients.

Second-generation (atypical) antipsychotics are used in the treatment of mental disorders (schizophrenia, bipolar disorder, major depressive disorder). Since marketed, clozapine was widely used because of its efficacy in drug-resistant schizophrenia and freedom from extrapyramidal effects. After clozapine, other antipsychotics were introduced (olanzapine, quetiapine, risperidone) with similar effects and the same safer profile and soon became the mainstay of the treatment of schizophrenia.[1] The therapeutic effect of second-generation antipsychotic agents is related to dopaminergic D2 receptor antagonism and to the blockage of serotonin receptors. Major cardiovascular adverse effects (tachycardia, bradycardia, hypertension, hypotension, syncopal episodes) and electrocardiographic abnormalities (prolonged QT interval) are reported in patients suffering from mental disorders and treated with antipsychotics.[2–8] An increased risk of sudden death has been also reported but the risk of underreporting is concrete because of the lack of a systematic post-mortem examination.[9–13] In addition, individuals with schizophrenia are known to be at greater risk of cardiac death, in part linked to inadequate lifestyles that predispose to cardiovascular disease, in part due to poor compliance with health care.[14–16] However, many typical and atypical antipsychotic drugs have been reported in the literature to significantly increase the risk of sudden cardiac death in patients with psychiatric disorders,[17] and this has led to restrictions in clinical practice or the withdrawal of these molecules from the market. A retrospective cohort study showed that the incidence of sudden cardiac death in subjects taking antipsychotics is increased (dose-related increase) compared to non-users of antipsychotics, regardless of the pharmacological class.[18]

Sudden antipsychotic cardiac death appears to be

linked to arrhythmic mechanisms, dilated heart disease, and myocarditis.[19–21] In the pathogenesis of the aforementioned cardiological alterations, an involvement of oxidative stress has been suggested, with an increase in reactive oxygen (ROS).[22] ROS modulates multiple cellular signaling pathways in physiological conditions. However, when the production of intracellular ROS is excessive it causes damage to the molecular components of the cell, favoring the pathogenesis of various diseases with particular reference to cardiovascular ones.

Despite the large use, factors underlying cardiovascular disease in patients treated with antipsychotics are still far to be completely understood and need to be deeply studied.[23–27] Growing interest is aimed at understanding the contribution of antipsychotic therapy in the genesis of cardiac toxicity in schizophrenic patients.

The purpose of the present study is to review the scientific literature on the topic and propose a possible explanation of antipsychotics-related cardiotoxicity.

LITERATURE ANALYSIS

Relevant scientific articles were identified from PubMed, Cochrane Central, Scopus, Web of Science, Science Direct, EMBASE up to January 2020 using the following keywords: “atypical antipsychotics”, “cardiomyopathy”, “myocarditis”, “oxidative stress”, and “sudden cardiac death”. The main keywords were individually searched in association with each of the others.

The resulting 527 references were screened to exclude duplicates, which left 67 articles for further consideration. In addition, non-English papers were excluded and the following inclusion criteria were used: original research articles, reviews and mini-reviews, documents and guidelines promulgated by scientific societies and international organizations, and book chapters.

The papers not suitable for the review were excluded, a hand search was performed through the reference lists of the included articles. These publications were carefully evaluated considering the main aims of the review. An excel data extraction form was used to extract pivotal data, including publication year, first author, types of scientific articles, the topic of the study. This evaluation left 106 scientific papers, distributed as original research articles, reviews, and mini-reviews (Figure 1). These reports were published between 1981 and 2020.

The features of included papers were described in Tables 1–3. The table was organized by dividing the main topics of the present review into three subgroups: the relationship between heart disease and use of antipsychotic drugs, the relationship between

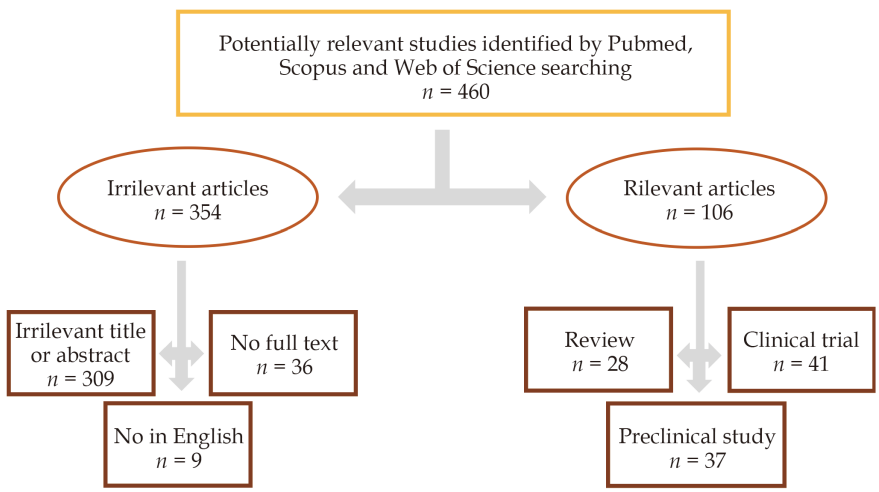

Figure 1 Relevant scientific articles were identified from PubMed, Cochrane Central, Scopus, Web of Science, Science Direct, EMBASE up to January 2020 using the following keywords: “atypical antipsychotics”, “cardiomyopathy”, “myocarditis”, “oxidative stress", "sudden cardiac death". The main keywords were individually searched in association with each of the others. The resulting 527 references were screened to exclude duplicates, which left 67 articles for further consideration. In addition, non-English papers were excluded and the following inclusion criteria were used: original research articles, reviews and mini-reviews, documents and guidelines promulgated by scientific societies and international organizations, and book chapters.

Table 1 Baseline characteristics of the studies with the correlation between use of antipsychotics and heart disease.

Authors	Year	Types of study designs	Methods	Aim of the study
Ariyarajah, *et al.*[115]	2010	Observational study (Case series)	Tree cases series of patients with schizophrenia, treated with clozapine	Cardiac magnetic resonance diagnostic role in clozapine-induced myocarditis
Belhani, *et al.*[87]	2006	Preclinical study	Eight groups of six New-Zealand White rabbits were treated for three months: group I: controls (saline); group II: amisulpride; group III: haloperidol; group IV: levomepromazine; group V: olanzapine; group VI: risperidone; group VII: levomepromazine + haloperidol; group VIII: levomepromazine + risperidone	Evaluate the hypothesis that myocardial lesions can be induced by neuroleptic drugs
Bellissima, *et al.*[116]	2018	Review	Reviewed of 359 cases of clozapine-induced myocarditis through individual case reports, case series, summated case series, spontaneous pharmacovigilance reporting and reviews	Identify and prevent myocarditis associated with clozapine therapy
Bugge, *et al.*[49]	2016	Observational study (Case report)	Case report of a schizophrenic patient treated with clozapine	Description of a case of perimyocarditis and parenchymal lung disease caused by clozapine treatment
Chow, *et al.*[24]	2014	Observational study (Multicentre cross-sectional cohort study)	100 schizophrenic patients treated with clozapine, without a history of cardiac pathology; 21 schizophrenic patients (controls) treated with non-clozapine antipsychotics; 20 controls without schizophrenia	Evaluation of prevalence of subclinical cardiomyopathy in the three groups analysed
Coulter, *et al.*[4]	2001	Observational study	WHO database on antipsychotics side-effects	Examine the relation between antipsychotic drugs and myocarditis and cardiomyopathy
Curto, *et al.*[2]	2016	Review	Reviewed of 88 articles about clozapine and cardiac desease	Analise the correlation between clozapine and cardiac desease
De Berardis D, *et al.*[20]	2018	Review	Reviewed of 93 articles about clozapine and myocarditis	Analise the correlation between clozapine and myocarditis
Fineschi, *et al.*[13]	2004	Observational study (Case report)	Case concerns the sudden death of a 29-year-old male during clozapine therapy	Clozapine-induced hypersensitivity myocarditis
Gareri, *et al.*[117]	2008	Review	Current knowledge on clozapine use in elderly patients	Study the safety of clozapine in elderly patients
Hussein, *et al.*[118]	2015	Observational study (Case-control)	19 patients diagnosed with schizophrenia, schizoaffective, and bipolar disorder; 10 healthy volunteers	Investigate the effect of short-term (two months) treatment with atypical anti-psychotics on coronary heart disease risk factors, in psychiatric patients
Jerrell, *et al.*[119]	2010	Observational study (Retrospective cohort design)	2,231 schizophrenic adults assemed atypical or conventional antipsychotic medications	Examine the risk of cerebro- and cardiovascular disorders associated with antipsychotic treatment among adults with schizophrenia
Katta, *et al.*[120]	2016	Observational study (Case report)	Case concerns the sudden death of a 54-year-old male during clozapine therapy	Clozapine-induced hypersensitivity myocarditis
Khan, *et al.*[12]	2017	Observational study (Cohort study)	503 patients with treatment-resistant schizophrenia maintained on clozapine during the study (between January 2009 and December 2015)	Incidence of sudden death and time to myocarditis in patients treated with clozapine
Kontoangelos, *et al.*[121]	2014	Observational study (Case report)	Case report of a schizophrenic patient treated with clozapine	Myocarditis is a recognized complication associated with clozapine
Korkmaz, *et al.*[122]	2019	Observational study (Cross sectional study)	40 schizophrenic adults treated with antipsychotics; 40 healthy volunteers	Scrutinize the changes that occur in left ventricle in adults treated with antipsychotics
Lang, *et al.*[123]	2008	Observational study (Case report)	Case report of a 50-year-old man treated with clozapine	Investigate treatment options after clozapine in treatment resistant schizophrenia
Lee, *et al.*[3]	2003	Observational study (Case report)	Case report of a 84-year-old man treated with olanzapine	Description of a case of cardiac side effects caused by olanzapine treatment
Mackin, *et al.*[42]	2008	Review	A revision on common side effects associated with psychotropic drugs	Description of the common effects of psychotropic drugs on the cardiovascular system
Marti, *et al.*[124]	2005	Observational study (Case report)	Case report of a 29-year-old man schizophrenic patient treated with risperidone	Description of a case of sudden cardiac death attributed to risperidone therapy
Merrill, *et al.*[48]	2005	Review	Review current literature on adverse cardiac events associated with clozapine	Study the association between clozapine and adverse cardiac events

Continued

Authors	Year	Types of study designs	Methods	Aim of the study
Papazisis, *et al.*[9]	2012	Observational study (Case report)	Case report of a 60-year-old man treated with quetiapine	Description of a case of sudden cardiac death attributed to quietapina therapy
Patel, *et al.*[62]	2019	Review	Review current literature on life-threating cardiovascular side effects associated with clozapine, edited until 2019	Examine the proposed aetiologies, diagnostic approaches and subsequent management strategies of cardiotoxicity associated with clozapine use
Peters, *et al.*[125]	2014	Observational study (Case report)	Case report of a 62-year-old woman treated suffering from bipolar affective disorder was treated with a mixture of olanzapine, amisulpride, biperiden, benperidol and lithium carbonate	Description of a case of tako tsubo cardiomyopathy in a patient treated with a mixture of olanzapine, amisulpride, biperiden, benperidol and lithium carbonate
Pillinger, *et al.*[11]	2019	Observational study (Case-control study)	14 schizophrenic patients treated with antipsychotic; 17 controls	Role of antipsychotics in fibro-inflammatory myocardial process that contribute to the excess cardiovascular mortality associated with schizophrenia
Polcwiartek, *et al.*[126]	2015	Review	Examination of preclinical, clinical, and epidemiological studies on cardiac safety of aripiprazole	Assess aripiprazole's cardiac safety in patients at high risk for torsade
Polcwiartek, *et al.*[127]	2016	Review	Review current literature about cardiovascular safety of antipsychotics, edited until 2016	Discuss side effect of antipsychotics and current guidelines regarding routine electrocardiogram monitoring
Ray, *et al.*[18]	2009	Observational study (Retrospective cohort study)	44,218 users of typical antipsychotics; 46,089 users of atypical antipsychotics; 186,600 matched nonuser controls	Role of typical and atypical on dose-related increased risk of sudden cardiac death
Roden, *et al.*[90]	2004	Review	Review literature about drug-induced (including antipsychotic) prolongation of the QT interval and torsade de pointes, edited until 2004	Summarize the current knowledge about molecular and clinical predictors of drug-induced prolongation of the QT interval and torsade de pointes, consider how new molecular predictors of a drug's activity might be incorporated into drug-development programs and clinical practice, and suggest a general approach to drugs that are suspected of causing this problem
Salvo, *et al.*[17]	2016	Observational study (Meta-analysis)	Meta-analysis of observational studies: two cohort (740,306 person-years) and four case-control (2,557 cases; 17,670 controls) studies	Estimate the risk of sudden cardiac death or sudden unexpected death related to individual antipsychotics
Serrano, *et al.*[128]	2013	Observational study (Two cross-sectional studies)	125 patients treated with clozapine; 59 patients with other antipsychotics; 88 patients treated with clozapine; 61 patients treated with atypical antipsychotics; 23 patients treated with typical antipsychotics; 11 patients treated with atypical and typical antipsychotics; 36 patients treated with other drugs	Examine the risk of cardiomyopathy and hyponatraemia in patients treated with antipsychotics
Sicouri, *et al.*[129]	2008	Review	Review current literature about arrhythmic liability of antipsychotic and antidepressant drugs capable of inducing long QT and/or Brugada syndrome phenotypes	Provide an update on the ionic and cellular mechanisms thought to be involved in, and the genetic and environmental factors that predispose to, the development of cardiac arrhythmias and sudden cardiac death among patients taking antidepressant and antipsychotic drugs that are in clinical use
Smolders, *et al.*[130]	2017	Observational study (Case report)	A case of a 37-year-old woman treated with high doses of quetiapine	A case of cardiomyopathy due to quetiapine
Türe, *et al.*[50]	2019	Observational study (Case report)	A case of a 15-year-old female taking clozapine in a suicide attempt	A case of atrioventricular total cardiac block associated with the taking of clozapine in a suicide attempt
Unsal, *et al.*[26]	2013	Observational study (Case-control study)	116 patients with schizophrenia; 88 healthy patients	Describe higher cardiovascular risk in schizophrenic patients taking antipsychotics
Vang, *et al.*[8]	2016	Observational study (Case-series)	Two schizophrenic death men under olanzapine treatment	Describe correlation between fatal eosinophilic myocarditis and olanzapine
Vieweg, *et al.*[131]	2003	Review	Review literature about antipsychotic drug and QT interval, edited until 2002	Examine the risk of QT interval prolongation and antipsychotics administration
Wassef, *et al.*[54]	2015	Observational study (Case report)	A case of an 18-year-old man taking quietapine	A case of myocarditis induced by quietapine

Continued

Authors	Year	Types of study designs	Methods	Aim of the study
Wu, *et al.*[10]	2015	Observational study (Case-crossover study)	17,718 patients with incident ventricular arrhythmia and/or sudden cardiac death treated with antipsychotic drug (control time windows of 7, 14, and 28 days)	Describe higher ventricular arrhythmia and/or sudden cardiac death risk in schizophrenic patients taking antipsychotics
Zhu, *et al.*[132]	2019	Review	Review current literature about adverse cardiac effects associated with antipsychotics	Examine adverse cardiac effects associated with antipsychotics and suggest the application of preventive measures

Table 2 Baseline characteristics of the studies with the correlation between use of antipsychotics and oxidative stress.

Authors	Year	Types of study designs	Methods	Aim of the study
Abdel Wahab, *et al.*[69]	2014	Preclinical study	Histological hallmarks and biochemical markers of myocarditis, proinflammatory cytokines and parameters of oxidative stress were assessed in rats treated with coadministration of captopril and clozapine	Investigate the protective effect of captopril against clozapine-induced myocarditis in rats
Abdel Wahab, *et al.*[74]	2014	Preclinical study	Rats treated with clozapine were assessed in echocardiographic, histopathological and immunohistochemical parameters, including markers of cardiotoxicity, oxidative stress, inflammation and apoptosis	Investigate a possible mechanisms of clozapine-induced cardiotoxicity in a rat model
Arumugan, *et al.*[79]	2012	Preclinical study	Rat with experimental autoimmune myocarditis and treated with edaravone were assessed on echocardiographic study and histopathological markers	Determined whether edaravone protects against cardiac remodelling in dilated cardiomyopathy
Arumugan, *et al.*[133]	2012	Preclinical study	Western blotting, histopathological staining and immunohistochemical analyses to measure the myocardial expressions of AMPK signaling and oxidative stress related parameters werw carried out in normal and vehicle or edaravone-treated experimental autoimmune myocarditis rats, respectively	Involvement of MAPK, AMPK signaling in the progression of experimental autoimmune myocarditis and if it can be blocked by the treatment with antioxidant edaravone
Auger, *et al.*[134]	2018	Preclinical study	Two groups of mice were treated once a week, for 22 weeks, with intraperitoneal injection of risperidone; two other groups received intraperitoneal injection of the vehicle of risperidone following the same schedule. Mice of one risperidone-treated groups and of one of vehicle-treated groups were fed a diet with curcumin, while mice of the two other groups received the standard diet	Investigate the potential capacity of curcumin, to attenuate the risperidone-induced metabolic dysfunction
Breier, *et al.*[65]	1994	Observational study	Double-blind, parallel groups design	Compare the effects of clozapine and haloperidol on plasma levels of norepinephrine
Dogan, *et al.*[135]	2018	Observational study (Case-control)	Thirteen schizophrenic patients using atypical antipsychotic drugs and 30 healthy controls	Determine the changes in oxidative status and thiol disulfide homeostasis in schizophrenic patients using atypical antipsychotic drugs
Elman, *et al.*[66]	1999	Observational study (Case-control)	10 schizophrenic patients treated with clozapine; 7 schizophrenic patients treated with fluphenazine; 7 schizophrenic patients treated with placebo	Compare the effects of clozapine on plasma levels of norepinephrine respect to norepinephrine levels of patients treated with fluphenazine or placebo
Fehsel, *et al.*[136]	2005	Observational study (Case-control)	5 Olanzapine-treated patients; 14 polymedicated schizophrenic patients; 19 healthy subjects; 8 septic shock patients	Examined cellular effects of clozapine on blood cells of treated patients with and without clozapine-induced agranulocytosis
Haak, *et al.*[76]	2003	Observational study (Case series)	Four cases of patients with schizophrenia, treated with clozapine	Role of clozapine in the development of inflammation
Heiser, *et al.*[95]	2010	Preclinical study	Measure formation of reactive oxygen in the whole blood of rats treated with haloperidol, clozapine and olanzapine	Examine reactive oxygen formation after treatment with antipsychotics by using electron spin resonance spectroscopy and test the protective capacity of vitamin C
Hendouei, *et al.*[137]	2018	Observational study	100 patients with chronic schizophrenia treated with clozapine or risperidone or perphenazine	Comparison of serum level of glutathione, protein carbonyl, lipid peroxidation, superoxide dismutase and Ferric reducing ability of plasma in the three groups analysed

Continued

Authors	Year	Types of study designs	Methods	Aim of the study
Li, *et al.*[27]	2019	Preclinical study	Quetiapine-treated mice hearts showed were evaluated in inflammatory infiltration and fibrosis marker. Pharmacologic blockade of necroptosis using its specific inhibitor Necrostatin-1 was assessed in its ability to attenuate quetiapine-induced myocardial injury in mice	Study a novel cell death type, quetiapine-induced necroptosis, which accounted for quetiapine cardiotoxicity and propose therapeutic strategies
Nikolić-Kokić, *et al.*[138]	2018	Preclinical study	Adult male Wistar rats were treated with clozapine, ziprasidone, and sertindole. Histopathological analysis of the heart was performed and expression and activity of antioxidant enzymes were determined	Examine the role of atipycal antipsychotics on rat heart morphology and determine whether redox imbalance plays a role in development of histopathological changes
Padurariu, *et al.*[139]	2010	Observational study (Case-control)	35 schizophrenic patients treated with different antipsychotics; 10 healthy control	Evaluate the specific activity of some peripheral antioxidant defences (SOD and GPX) and the level of MDA (lipid peroxidation maker), in schizophrenic patients treated with antipsychotics, and compared with age-matched healthy subjects
Vidović, *et al.*[140]	2013	Observational study (Case-control)	30 schizophrenic patients with atypical antipsychotic therapy; 60 control subjects	Describe an increased oxidative stress and changed lipid profile in schizophrenic patients treated with atypical antipsychotic therapy
Wang, *et al.*[64]	2008	Preclinical study	Male Balb/C mice were administered clozapine: one group was administered clozapine plus propranolol. Saline-treated mice served as controls. histopathological examination on heart section, plasmatic catecholamines and myocardial TNF-alpha were determined	Examine whether clozapine administration cause myocarditis in association with an increase in catecholamines
Williams, *et al.*[72]	2003	Preclinical study	Mice were administered clozapine and the extent of covalent binding was assessed by Western blotting	Evaluated whether clozapine undergoes bioactivation by murine cardiac tissue, in comparison to hepatic tissue

cardiovascular pathologies and oxidative stress, and the relationship between antipsychotics and cardiac oxidative stress. In each subgroup, the type of scientific article, the methods used and the purpose of the work were indicated.

Oxidative Stress and Cardiac Injury

Superoxide anion (O_2-), hydroxyl radical (OH-), hydrogen peroxide (H_2O_2), singlet oxygen, carbon-centered radicals, peroxynitrite (ONOO-), nitric oxide (NO), and nitrogen dioxide radicals are the free radicals identified in the human heart. Under basal conditions, the production of free radicals is low. However, the maintenance of intracellular redox homeostasis is fundamental to guarantee the physiological cardiac functions (development and maturation of cardiomyocytes, the release of intracellular calcium, and the coupling of cardiac excitation/contraction).[28] The physiological intracellular levels of ROS are maintained by an antioxidant defense system which includes superoxide dismutases, catalase, the glutathione peroxidase/reductase system, and the peroxiredoxin/thioredoxin system. When pathological conditions occur (e.g., myocardial ischemia), hyperproduction of O_2- is observed from multiple cellular sources, the cellular antioxidant defense system is depleted and the free radicals scavenging enzyme system superoxide dismutase, glutathione peroxidase, chloramphenicol acetyltransferase is significantly reduced.[29] ROS can cause severe oxidative damage, especially to DNA, lipids, and proteins. Lipids are the class of biological molecules most susceptible to attack by oxygen free radicals. Oxidation takes place on the fatty acids present in cell membranes or lipoproteins, producing toxic substances for cells and tissues. Furthermore, as far as proteins are concerned, these, following the oxidation of the –SH groups of some amino acids (His, Arg, Lys, Pro) and the liberation of iron by the degradation of the porphyrin rings by ROS, lose their physiological structure and therefore functionality. In DNA, the oxidative phenomena concern the purine and pyrimidine bases;[30] one of the most studied markers of DNA damage from oxidative damage is represented by 8-OHdG.[31] The excessive production of ROS determines the activation of cell death, with consequent apoptosis or myocardial necrosis.[32] In the pathogenesis of cardiac

Table 3 Baseline characteristics of the studies with the correlation between oxidative stress and heart disease.

Authors	Year	Types of study designs	Methods	Aim of the study
Abu-Elsaad, *et al.*[141]	2018	Preclinical study	Histopathological examinations of stained heart sections on lipid profile, oxidative stress, and cardiac function biomarkers in rats received high-carbohydrate/high-fat diet concurrently with luteolin	Test luteolin protective effect against high-carbohydrate/high-fat diet-induced cardiac dysfunction in rats
Akao, *et al.*[142]	2003	Preclinical study	Study the H_2O_2-induced response (loss of mitochondrial membrane potential and cell death) in cultured cardiac myocytes	Describe cardiac cellular responses after oxidant stress and identify target for intervention in the prevention of cell death
Brown, *et al.*[143]	2010	Review	Review of articles about cardiac mitochondria involved in the genesis of arrhythmia, edited until 2010	Discuss the correlation between arrhythmia and cardiac mitochondrial alterations, in order to prevent arrhythmias by preserving mitochondrial membrane potential in the face of oxidative stress
Doroshow, *et al.*[59]	1981	Preclinical study	CDF1 mice were pretreated with a pharmacologic dose of n-acetyl-l-cysteine before doxorubicin administration	Investigate the effect of N-acetylcysteine. administration on the toxicity of doxorubicin
Esposito, *et al.*[85]	2009	Review	Review of articles about the role of nitroso radicals in circulatory shock, edited until 2009	Analyse the involment of oxidative and nitrosative stress in cardiovascular pathologies
Fineschi, *et al.*[144]	2010	Review	Review of articles about stress-induced cardiomyopathy, edited until 2010	Examine correlation between alterations in catecholamine system functions stress-related and acute and chronic cardiovascular disorders
Finkel, *et al.*[86]	1992	Preclinical study	Study the effects of pro-inflammatory cytokines on the contractility of mammalian heart and evaluate if the nitric oxide synthase inhibitor NG-monomethyl-L-arginine blocked these negative inotropic effects	Examine if the direct negative inotropic effect of cytokines is mediated through a myocardial nitric oxide synthase
Frangogiannis, *et al.*[82]	2002	Review	Review of articles about processes regulating the inflammatory response following myocardial ischemia and reperfusion, edited until 2001	Summarize current understanding of the cellular and molecular mechanisms regulating the inflammatory response following myocardial ischemia and reperfusion
Gong, *et al.*[98]	2018	Preclinical study	Evaluation of serum glucose and insulin levels, lactate dehydrogenase and creatine kinase, the expression of pro-inflammatory cytokines and activation of nuclear factor-κB in Tmbim1 knockout mice	Examine if down regulation of Tmbim1 enhance high fat diet-induced cardiomyopathy by increasing inflammation and oxidative stress
Ishiyama, *et al.*[83]	1997	Preclinical study	20 rats with autoimmune miocarditis were adserum level of ministered aminoguanidine and evaluated in serum level of creatine kinase-muscle/brain, and himmunohistochemical exam for inducible nitric oxide synthase and nitrotyrosine	Investigate the role of nitric oxide in the development of myocardial damage and the effects of aminoguanidine, an inhibitor of inducible nitric oxide synthase, on experimental autoimmune myocarditis
Javadi, *et al.*[145]	2017	Preclinical study	Assess the efficacy of natural molecules (e.g. apigenin, berberine and quercetin) along with some plant extracts in experimental autoimmune myocarditis animal models	Evaluations of inflammatory and immunological mechanism and oxidative stress in experimental autoimmune myocarditis
Joseph, *et al.*[97]	2016	Preclinical study	Evaluations of heart rhythm and calcium homeostasis in a transgenic mouse model of cardiac lipid overload, the peroxisome proliferator-activated receptor-γ	Examine the hypothesis that the increase in ventricular ectopy during cardiac lipid overload is caused by increased mitochondrial oxidative stress
Karagueuzian, *et al.*[146]	1982	Review	Summarize current knowledge on oxidative stress-mediated arrhythmogenesis, and discuss how myocardial fibrosis promotes ventricular arrhythmias	Propose a sinergic antifibrotic therapy, to reduce the risk of sudden cardiac death caused by arrhythmias
Killian, *et al.*[147]	1999	Preclinical study	Identify in patients started clozapine treatment the cases of myocarditis and cardiomyopathy in Australiafrom voluntary reports to the Australian Adverse Drug Reaction Committee	Investigated the cardiovascular complications for clozapine
Kishimoto, *et al.*[148]	2003	Experimental study	Nine patients (six in myocarditis, three in acute dilated cardiomyopathy) were treated with high-dose intravenous Ig (1–2 g/kg, over two days)	Examine the effects of intravenous Ig by the analyses of inflammatory cytokines and oxidative stress
Koponen, *et al.*[149]	2008	Review	An update of the prevalence and mechanisms for sudden cardiac death in schizophrenia from 1966 and 2007	Describe the sudden cardiac death related antipsychotics

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Authors	Year	Types of study designs	Methods	Aim of the study
Krexi, *et al.*[150]	2016	Retrospective observational study	110 cases of sudden cardiac death in relation to a stressful event	Sudden death occurred in the absence of structural heart disease may reflect the proarrhythmic potential of high catecholamines on the structurally normal heart
Li, *et al.*[94]	2007	Preclinical study	Normal cardiomyocytes or traumatic cardiomyocytes were cultured with normal plasma or traumatic plasma and apoptosis was determined by caspase-3 activation	Study the molecular mechanisms responsible for cardiomyocyte apoptosis induced by trauma
Li, *et al.*[151]	2013	Preclinical study	In a coxsackievirus B3 murine myocarditis model effects of carvedilol and metoprolol was assessed in myocardial histopathological changes, cardiac function, texpression of 4-HNE, superoxide dismutase and glutathione peroxidases activities	Determine whether levels of lipid peroxides are elevated in the myocardium and whether carvedilol reduces the lipid peroxidation level and increases antioxidant enzyme activities in viral murine myocarditis model
Marian, *et al.*[152]	2006	Experimental study (Randomised controlled trial)	42 subjects with hypertrophic cardiomyopathy, one half treated with antioxidant N-acetylcysteine and the others with placebo	Analyse the protective cardiac effect of N-acetylcysteine
Matsui, *et al.*[58]	1999	Preclinical study	Sprague-Dawley rats were treated with doxorubicin, carvedilol, doxorubicin, +carvedilol, or atenolol +doxorubicin. Cardiac performance and myocardial lipid peroxidation were assessed	Test if carvedilol protects against doxorubicin-induced cardiomyopathy
Melendez, *et al.*[91]	2010	Preclinical study	Adult male Sprague-Dawley rats were infused with IL-6 and compared with vehicle-infused, aged-matched controls. Left ventricular function, myocardial interstitial collagen volume fraction and isolated cardiomyocyte size were assessed	Examine if elevated levels of IL-6 mediate myocardial remodeling
Mito, *et al.*[153]	2011	Preclinical study	Rats with autoimmune myocarditis were divided randomly into a treatment (curcumin) and vehicle group. Myocardial protein expression of inducible nitric oxide synthase, the catalytic subunit of nicotinamide adenine dinucleotide phosphate reduced oxidase and myocardial endoplasmic reticulum stress signaling proteins were assessed	Examine the mechanism of curcumin in experimental autoimmune myocarditis
Miyamoto, *et al.*[154]	2004	Preclinical study	Histopathology and thioredoxin expression in spontaneous myocarditis in inbred strains of mice was assessed	Investigate the role of thioredoxin and redox-regulating system in spontaneously developed myocarditis
Nimata, *et al.*[77]	2005	Preclinical study	Rats with experimental autoimmune myocarditis treated with ederavone and untreated rats were compared in histological markers	Determine if the free radical scavenger edaravone protects against acute experimental autoimmune myocarditis in rats by the radical scavenging action associated with the suppression of cytotoxic myocardial injury
Octavia, *et al.*[155]	2012	Review	Review of articles about the role of oxidative stress in heart failure, edited until 2012	Discuss the importance of nicotinamide adenine dinucleotide phosphate oxidase-dependent reactive oxygen generation in the various subtypes of heart failure and its implications
Pacher, *et al.*[93]	2005	Review	Review of articles about the role of peroxynitrite or matrix metalloproteinases and poly (ADP-ribose) polymers in the experimental therapy of various forms of myocardial injury, edited until 2005	Discuss the role of nitrosative stress and downstream mechanisms, including activation of matrix metalloproteinases and poly (ADP-ribose) polymers, in various forms of heart failure
Pacher, *et al.*[156]	2008	Review	Review of articles about the pathophysiological relevance of the peroxynitrite-poly (ADP-ribose) polymers pathway in various forms of heart injury and systemic pathology, edited until 2008	Examine the correlations between peroxynitrite-peroxynitrite-poly (ADP-ribose) polymers pathway and oxidative DNA damage in heart injury and systemic pathology
Raucci, *et al.*[157]	2019	Review	Review current literature about the role of HMGB1 in heart desease	Summarizes recent findings on HMGB1 biology and heart dysfunctions and discusses the therapeutic potential of modulating its expression, localization, and oxidative-dependent activities

Continued

Authors	Year	Types of study designs	Methods	Aim of the study
Shimada, *et al.*[158]	2015	Preclinical study	Rats with experimental autoimmune myocarditis were treated with N-acetylcysteine and N(G)-nitro-l-arginine methylester (inhibitor of nitric oxide)/ N(G)-nitro-d-arginine methylester (an inactive enantiomer)	Investigate the effects of N-acetylcysteine, a potent antioxidant, on experimental autoimmune myocarditis in rats
Shimazaki, *et al.*[159]	2010	Preclinical study	Rats with experimental autoimmune myocarditis and treated with edaravone were studied in echocardiographic parameters and inflammation and oxidative stress parameters	Determine if edaravone ameliorate the progression of experimental autoimmune myocarditis by inhibiting oxidative and endoplasmic reticulum stress and cardiac apoptosis
Shinoda, *et al.*[89]	2016	Preclinical study	Neonatal rat cardiomyocytes werw treated with haloperidol, and exposed to angiotensin II. Hypertrophy, σ1R expression, mitochondrial Ca (2+) transport and ATP levels were assessed	Examine if sudden cardiac failure induced by haloperidol is mediated by chronic haloperidol inhibition of cardiac σ1R
Shin, *et al.*[75]	2002	Review	Review literature about the role of chemokines (MCP-1, IL-8) in the pathogenesis of vascular disease, edited until 2002	Supports the pivotal role of chemokines in the pathogenesis of vascular disease and suggest delineating the patterns of gene expression (MCP-1, IL-8) to identify molecular targets for the prevention and treatment of atherosclerosis
Singh, *et al.*[159]	2008	Observational study (Randomized cross-sectional study)	Two groups of fifty schizophrenic patients treated by haloperidol and olanzapine, respectively for at least six months	Examine the correlations between serum antioxidants parameters and antipsychotics
Skrzypiec-Spring, *et al.*[160]	2018	Preclinical study	Carvedilol in 3 doses (2, 10, and 30 mg/kg) was given daily to 3 study groups of rats with experimental autoimmune myocarditis	Evaluate the effects of carvedilol administration in acute myocarditis and its impact on matrix metalloproteinases' activation
Sovari, *et al.*[78]	2013	Preclinical study	Wild type mouse and ACE8/8 (an animal model of cardiac renin-angiotensin system activation were treated with different antioxidant therapies	Determine the source of reactive oxygen and if reactive oxygen played a role in the arrhythmogenesis
Sugiyama, *et al.*[102]	2016	Preclinical study	Induce oxidative stress in NOS1AP knockout mice to evaluate electrocardiographic and echocardiographic parameters	Evaluate the relationship between oxidative stress and ventricular tachyarrhythmia/heart failure in genetic variations at NOS1AP
Sukumaran, *et al.*[161]	2011	Preclinical study	Experimental autoimmune myocarditis was induced in rats by immunization with porcine cardiac myosin. The rats were divided into two groups and treated with either telmisartan (10 mg/kg per day) or vehicle for 21 days and expression of inflammatory cytokines and oxidative stress markers was evaluated	Investigation of telmisartan (angiotensin II type 1 receptor antagonist) protects against experimental autoimmune myocarditis by suppression of inflammatory cytokines and oxidative stress
Tse, *et al.*[99]	2016	Review	Literature review on investigation the effects of reactive oxygen on cardiac ion channel function, remodeling and arrhythmogenesis	Study the relationship between increased oxidative stress cardiovascular pathologies such as diabetes and hypertension associated with arrhythmias
Turillazzi, *et al.*[57]	2017	Observational study (Case-control)	Biochemical and immunohistological markers of oxidative/nitrosative stress were evaluated in subjects who had died from high doses of cocaine, compared to the control group	Examine the hypothesis that cardiac toxicity by acute exposure to high dosage of cocaine could be mediated by unbalanced myocardial oxidative stress
Wu, *et al.*[162]	2018	Preclinical study	A model of experimental autoimmune myocarditis on which Toll-like receptors 4 activation or inhibition was performed to induce chronic inflammation	Examine the role of mitochondrial dynamics in Toll-like receptors 4 activation-mediated dilated cardiomyopathy
Yang, *et al.*[163]	2015	Review	Scientific evidence on the mechanisms linking metabolic derangement and cardiac excessive oxidative stress that predisposes to ventricular arrhythmias and sudden cardiac death	Report the association between cardiac oxidative stress and malignant arrhythmias providing novel therapeutics to prevent sudden cardiac death
Yuan, *et al.*[164]	2004	Preclinical study	Rats with experimental autoimmune myocarditis induced by porcine myosin and treated with carvedilol, racemic carvedilol, metoprolol, or propranolol was assessed in echocardiographic study and inflammatory and oxisative stress parameters	Investigate whether carvedilol exert protective effect against experimental autoimmune myocarditis by suppression of inflammatory cytokines and its antioxidant properties

Continued

Authors	Year	Types of study designs	Methods	Aim of the study
Varga, *et al.*[55]	2015	Review	Review literature about mitochondrion-mediated cardiotoxicity, edited until 2015	Discuss the mechanisms of mitochondrion-mediated cardiotoxicity of commonly used drugs and some potential cardioprotective strategies to prevent these toxicities
Wang, *et al.*[64]	2008	Preclinical study	Examine expression of pro-inflammatory cytokines, activation of nuclear factor κB, markers of oxidative stress and apoptosis pathway in platelet-activating factor receptor-knockout mice	Explore if platelet-activating factor receptor could modulate myocardial I/R injury in mice by inflammation and oxidative stress
Zhang, *et al.*[35]	2010	Observational study (Case-control)	92 schizophrenic patients treated with typical and atypical antipsychotics; 50 control subjects	Evaluate antioxidant enzymes and lipid peroxidation in schizophrenic patient treated with antipsychotics
Zhang, *et al.*[34]	2015	Experimental study (Randomised controlled trial)	41 schizophrenic patients treated with risperidone; 37 schizophrenic patients treated with haloperidol; 30 control subjects	Compare antioxidant enzyme activity and nitric oxide levels in schizophrenic patients treated with typical and atypical antipsychotics, respectively

pathologies, a fundamental role is played by mitochondrial-derived ROS, which derives from electron transfer into the mitochondrial respiratory chain complexes and from the action of mitochondrial proteins. Mitochondria are one of the main drivers of intracellular oxidant production and other relevant sources are nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX family of enzymes). Besides, other enzymes contribute to intracellular ROS production, including xanthine oxidase, nitric oxide synthase (NOS), cyclooxygenases, cytochrome P450 enzymes, and lipoxygenases.

Several data in the literature suggest that this type of ROS is involved in the pathogenesis of numerous cardiac pathologies, such as myocardial infarction, heart failure, and diabetic cardiomyopathy.[28] Specifically, in cardiac infarction, hypoxia induces a decrease in adenosine triphosphate (ATP) with consequent loss of depolarization of the mitochondrial membrane with activation of anaerobic glycolysis, lactate formation, and cytosolic calcium accumulation.[33] These cellular damages are finally further implemented by the reperfusion of hypoxic cells, causing an increase in cellular necrosis. Otherwise, in heart failure, the cellular modifications related to ROS occur in a more dilated time span. The basis of these modifications is the interaction between the increase in angiotensin II and the increase in myocardial stress, with consequent cardiac remodeling, contractile dysfunction, and the onset of arrhythmias.[34] The role played by NADPH oxidase (NOX) seems to be relevant in the failure, which can uncouple the NO synthase and promote O_2-.[35] Also, angiotensin II-mediated ROS increase activates nuclear factor kappaB induced hypertrophy pathway.[32]

Instead, diabetic heart disease is linked to the accumulation of fatty acids in cardiomyocytes with a consequent reduction in the use of carbohydrates as an energy substrate especially during periods of high demand for ATP and, consequently, increased formation of ROS with mitochondrial damage and promotion of apoptosis of cardiomyocytes. The peroxisome proliferator-activated receptor, a nuclear hormone receptor which modulates the metabolism of glucose and fatty acids, is involved in this heart disease.[36]

Finally, oxidative stress, in association with the increase in inflammation products, promotes endothelial dysfunction through the inactivation of NO, an important molecule with a vasodilator and anti-atherogenic role. NO inactivation is promoted by NADPH oxidase and uncoupled NOS.[37]

In light of these data, there is growing interest in the literature about the role played by ROS in the pathogenesis of cardiovascular diseases and the possible experimental use of antioxidant molecules in the treatment of heart diseases.

Cardiovascular Complications from Antipsychotics

Atypical antipsychotic therapy is notoriously associated with cardiovascular pathologies and an increase in sudden cardiac death.

Second-generation antipsychotic drugs have a significant influence on the development of metabolic syndrome, which is known to be a risk factor for cardiovascular disease. Furthermore, a correlation is known with myocarditis,[8] dilated heart dis-

ease,[10] and QT tract prolongation, which represents an important risk factor for the development of malignant arrhythmias and sudden cardiac death.[38] In addition to this, subjects affected by schizophrenia, regardless of the therapy taken, have additional cardiovascular risk factors on a dysmetabolic basis, such as type 2 diabetes mellitus, reduced glucose tolerance, insulin resistance, and obesity.[5]

As for the adverse effects of the dysmetabolic type, as previously mentioned, atypical antipsychotics can cause weight gain, especially olanzapine and clozapine, and related metabolic disorders such as insulin resistance, type 2 diabetes mellitus, dyslipidemia, and diabetic ketoacidosis.[16]

It is also known that obese and diabetic subjects have an increased incidence of atrial fibrillation, ventricular ectopia, and long QT.[39] Besides, diabetes mellitus and obesity are associated with an increased risk of sudden cardiac death, which is often caused by ventricular arrhythmias. As regards the electrocardiographic changes induced by antipsychotics, it has been observed that the use of these drugs is associated with prolongation of the QTc, that is, prolonged cardiac repolarization.[40] QTc is defined on the electrocardiogram as the period between the onset of the Q wave (ventricular depolarization) and the cessation of the T wave (ventricular repolarization) corrected for heart rate. It is known to be an indicator of potential proarrhythmic toxicity as it can lead to a specific polymorphic ventricular arrhythmia known as torsade de pointes which can develop into malignant arrhythmias such as ventricular fibrillation and sudden cardiac death. The most common mechanism of antipsychotic mediated QTc prolongation appears to be blockage of the hERG channel in the myocardium which prevents outward movement of potassium responsible for ventricular depolarization.[41] The risk increases in the presence of underlying heart diseases associated with abnormal repolarization, electrolyte abnormalities, and co-treatment with other drugs (diuretics, antidepressants, mood stabilizers).[42] For this reason, treatment with antipsychotics should only be undertaken if there is a concrete therapeutic advantage and some authors propose the application of stratification measures for patients at greater risk of developing this condition before starting therapy.

Among antipsychotics, there was an increased risk of QTc prolongation for typical antipsychotics; in particular droperidol and thioridazine are associated with an increase in QTc in a dose-dependent manner.[43] However, there are data in the literature that also describe it for atypical antipsychotics. Clinical studies have reported a clear association of the aforementioned electrocardiographic alteration and sertindole and risperidone, in a dose-dependent manner,[42] although among the atypical antipsychotics, ziprasidone is the riskiest,[44] so much so that it has been proposed to take an electrocardiogram at the start of therapy.[45]

Preclinical studies have reported a dose-dependent prolongation of the QT interval with other atypical antipsychotics as well, namely clozapine and olanzapine.[42] Finally, antipsychotic therapy, although rarely, can be associated with severe complications such as myocarditis and evolving cardiomyopathies towards decompensation. This is especially true of clozapine,[45] an atypical antipsychotic used for resistant schizophrenia and prevention of suicide risk.[46] In addition to myocarditis, cases of cardiomyopathy have been described, albeit more rarely.[47] This is also more frequent with clozapine with a later onset than myocarditis (the average onset was reported in a study after 12 months) and associated with high mortality.[48] Specifically, clozapine, in therapeutic doses, can also be associated with the occurrence of serious cardiovascular side effects, very rare but described in the literature as dilated cardiomyopathy, pericarditis and concomitant myopericarditis associated with parenchymal lung disease.[49] Finally, complete atrioventricular blockage by ingestion of massive drug doses of clozapine has been described,[50] which can be fatal if not promptly recognized and managed.

For this reason, the United States Food and Drug Administration has included potentially fatal events and cautious use of clozapine in patients with pre-existing cardiac diseases and with severe cardiac conditions among the adverse effects of clozapine.[11]

A retrospective study of all adverse drug reactions reported voluntarily to the Australian Adverse Drug, identified an incidence of suspected myocarditis ranging between 0.7% and 1.2% of patients treated with clozapine, with an average age of 30

years; the disease developed on average two weeks after starting therapy with a mortality rate of 10.3%.[51]

Myocarditis is an uncommon, dose-independent, potentially lethal adverse effect; probably underestimated due to the often, atypical clinical manifestation and the poor compliance of these patients with medical treatment. In fact, the clinical presentation can be very variable, ranging from subclinical forms to fulminant heart failure.

Sudden death after clozapine intoxication due to eosinophilic myocarditis was first described in 1992,[52] but the same was also reported in subsequent several clinical cases with the use of therapeutic doses of the drug.[53]

Although with extremely rare incidence, cardiomyopathy has also been described with quetiapine, an atypical antipsychotic structurally similar to clozapine, suggesting a pharmacological class effect.[54] According to the WHO's program for international drug monitoring, myocarditis and cardiomyopathy induced by the use of quetiapine are typically present mimicking myocardial infarction with acute ST-segment elevation on electrocardiogram. As well as for clozapine, the mechanism of quetiapine-induced cardiotoxicity is still undefined.

The use of antipsychotics is burdened by an increased risk of sudden cardiac death; in fact, in subjects taking antipsychotics, the risk of sudden cardiac death has more than doubled in consideration also of weight gain, dyslipidemia, and type 2 diabetes mellitus related to antipsychotic treatment.[15] To these risk factors, additional environmental cardiovascular risk factors are added, such as smoking, alcohol abuse, poor diet, a sedentary lifestyle, and stress, which are often present in individuals suffering from schizophrenia.

Sudden cardiac death in patients taking antipsychotics has a multifactorial nature, resulting from a complex interaction between the aforementioned environmental factors, any pre-existing cardiac substrates, both structural and genetic, and the pathological action of these drugs at the cardiac level. However, the underlying molecular mechanisms are still to be understood also concerning the causal weight of a possible heritable component that can make individuals taking antipsychotics more susceptible to sudden cardiac death.

OXIDATIVE STRESS IN ANTIPSYCHOTIC-RELATED CARDIOMYOPATHIES

Marketed drugs have been often associated with cardiovascular major adverse events and safety concerns due to a significantly increased risk of cardiac fibrosis, myocardial infarction, and myocardial inflammation. Despite efforts in the preclinical phase of the development of drugs, cardiotoxicity remains a great concern due to the lack of sufficient knowledge of the mechanism of cardiotoxicity. Linkage with the entity of intracellular ROS and RNS reaction has been evocated to explain drug-induced myocardial injury.[55] Oxidative and nitrative modifications of key mitochondrial proteins have a central role in drug-induced cardiotoxicity.[56] The oxidative stress resulting from increased free radical generation in cardiomyocytes produces an energetic imbalance, impairment of mitochondrial function, activation of stress-related signaling pathways, p53 accumulation, and cellular loss.[57] By the way, it has been supposed that administration of antioxidants (vitamin C and vitamin E, carvedilol, L-carnitine, N-acetylcysteine, coenzyme Q10, dexrazoxane) is associated with a decrease in ROS-induced cardiomyocytes damage and can play a role in reducing drug-induced cardiotoxicity.[58,59]

An analysis of the literature highlights the need to acquire more data on the pathogenesis of heart disease induced by atypical antipsychotics through post-mortem studies. Conversely, numerous preclinical studies on animal models have been carried out to understand the pathogenesis of heart disease associated with individual antipsychotics. To clarify the role played by oxidative stress in the origin of pathologies affecting the heart induced by atypical antipsychotic drugs, it appears useful to analyze the cardiac pictures related to them individually (Figure 2).

Myocarditis

Myocarditis is mainly described in patients taking clozapine, although it has also been reported in association with the use of other second-generation antipsychotics.

Clear evidence about dose-related clozapine cardiotoxicity is still far to be demonstrated. The mechanism by which clozapine induces cardiotoxicity remains unclear but numerous hypotheses have been

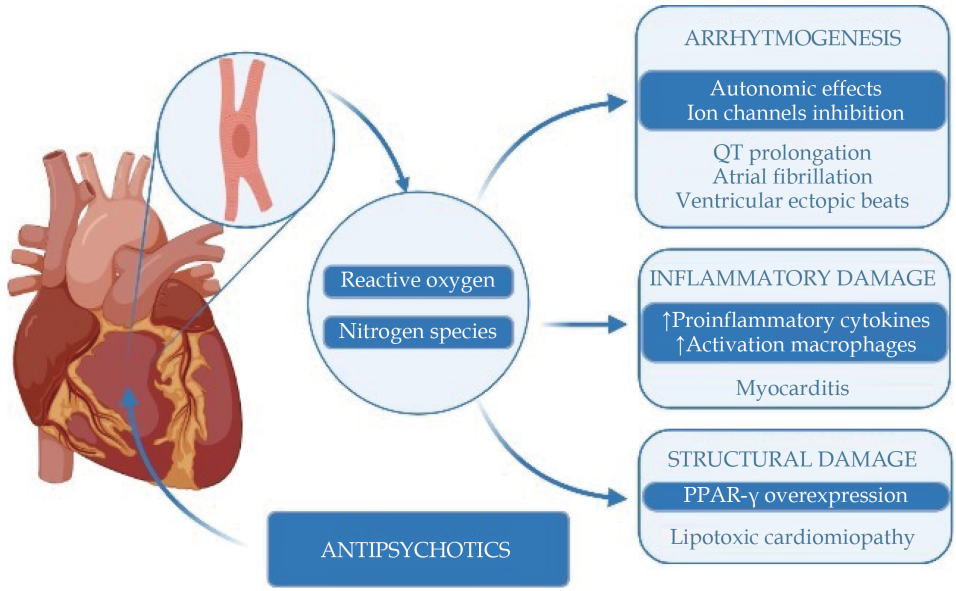

Figure 2 Antipsychotic drugs appear to be linked to arrhythmic mechanisms, dilated heart disease, and myocarditis. In the pathogenesis of the aforementioned cardiological alterations, an involvement of oxidative stress has been suggested, with an increase in reactive oxygen and nitrogen species.

proposed. An immunoglobulin E-mediated hypersensitivity (type I allergy) has been proposed for the first time by Killian, *et al.*[60] as a mechanism of cardiac toxicity in clozapine-treated patients. The results of necropsy showed mainly lymphocytic and mixed infiltrates with myocytolysis, consistent with an acute pharmacological reaction.[61] Then, eosinophilic myocarditis was described in the sudden death of patients treated with clozapine, and a hypereosinophilic action of clozapine was proposed as the main mechanism of cardiotoxicity.[13,20,62,63] Finally, a role of pro-inflammatory cytokines, catecholamines, and oxidative stress was proposed.[64–66] Bioactivation of clozapine in the myocardial tissues is associated with the generation of a chemically reactive nitronium ion metabolite which stimulates cellular injury, lipid peroxidation, and formation of free radical. When bound with a protein of the myocardium, this nitronium ion produces an antigenic complex that stimulates an immune response, and activates macrophages releasing proinflammatory cytokines.[67,68]

To support the importance of oxidative stress in clozapine-associated myocarditis, there is a study conducted by Abdel-Wahab, *et al.*[69] This study aimed to study the protective effect of captopril against clozapine-induced myocarditis in rats and the possible mechanisms underlying this effect. Administration of the angiotensin converting enzyme inhibitor reduced the histological signs and biochemical markers (creatine phosphokinase–MP isoenzyme and lactate dehydrogenase) of myocarditis, as well as reduced the oxidative stress parameters (NO and DNA degradation products) in a dose-dependent manner, suggesting how the cardio-interpretive effect exerted by captopril, in the presence of clozapine-induced myocarditis, is also mediated by the reduction of oxidative stress.

A clinical study reported that the erythrocyte concentration of selenium, an antioxidant molecule, was reduced in schizophrenic patients taking clozapine compared to those who did not take it and compared to patients with mood disorders and healthy controls. This evidence suggests that reduced antioxidant activity may contribute to the development of cardiological complications related to clozapine, including myocarditis.[70]

High levels of tumor necrosis factor-alpha (TNF-α) in association with an increase in catecholamines have also been described in antipsychotic-related myocarditis and dose dependence has been demonstrated. TNF-α hyperproduction is related to the attraction of leukocytes and the generation of further free radicals and cytotoxic proteins.[71–76] High levels of myeloperoxidase were observed in experimental studies with clozapine-treated animals and were in-

dicated as a sensitive marker of neutrophil migration and myocardial injury.[74] Histopathological examination of the heart of mice treated with clozapine showed a significant dose-related increase in myocardial inflammation. The latter correlated with plasma catecholamine and TNF-α levels. Furthermore, this effect was significantly reduced in mice treated with propranolol, compared to controls, suggesting a potential immune-mediated mechanism of action of clozapine.[64]

A preclinical study was conducted to investigate the influence of clozapine, ziprasidone, and sertindole on rat heart morphology and determine whether redox status plays a role in the development of cardiac histopathological changes induced by antipsychotic.[67] The results showed that all three drugs induced cardiac histopathological changes related to a picture of toxic myocarditis. In particular, clozapine increased the activity of superoxide dismutase 1 while ziprasidone reduced the activity of glutathione reductase. Sertindole did not exert any marked effect on the function of antioxidant enzymes in the heart even though myocardial degeneration was observed. In conclusion, treatment with clozapine or ziprasidone induced pathophysiological changes in the rat heart, which seemed to be associated with disturbances in antioxidant capacity. Finally, an antioxidant molecule (edaravone) is effective in reducing myocardial damage in animal models of acute autoimmune myocarditis in association with a reduced state of oxidative stress.[77]

Cardiomyopathy and Cardiac Injury

Heart disease is another adverse effect associated with antipsychotics, although the pathophysiological mechanisms underlying the processes of myocardial remodeling in association with a pro-arrhythmic condition with increased risk of sudden death are not clear in this context too.

A preclinical study supports the importance of mitochondrial oxidative stress in the presence of heart disease characterized by an increase in angiotensin II levels, proposing the use of mitochondrial antioxidants in the prevention of evolving arrhythmias towards sudden cardiac death in the presence of the renin-angiotensin axis.[78] An increasing amount of data in the literature indicate that cardiac mitochondria are involved in the genesis of arrhythmia. In fact, the energetic state of the mitochondrial network can alter the potassium flows through the ATP-sensitive potassium channels (essential for cell survival in the face of oxidative stress), creating the electrical conditions to favor fatal arrhythmias. For this reason, the cardiac mitochondrial network has emerged as a key target for strategies that seek to reduce arrhythmias through the maintenance of mitochondrial integrity in the face of metabolic stress, preserving the integrity of the membrane potential.

Preclinical data also clearly show that edaravone, a new free radical scavenger, improves the evolution of dilated cardiomyopathy and cardiac remodeling by modulating oxidative stress.[79]

Cardiomyopathy related to taking atypical antipsychotics can, at least in part, be due to cardiomyocyte apoptosis, known to be important in the pathogenesis of patients with severe heart failure from various etiologies.[80] Experimental studies on mice proposed a programmed cell necrotic death (necroptosis) as a possible explanation for the cardiotoxicity of quetiapine. Myocytes treated with quetiapine showed disruption of the cellular membrane, mitochondria swelling with reticulum expansion and generation of oxygen reactive species. These effects are reversed by the administration of necrostatin-1, a TNF inhibitor,[27,81] suggesting a close correlation between inflammation, oxidative stress, and cell death.

Treatment with clozapine has been also associated with an increased cardiac level of total nitrite, a stable end product, an indirect marker of NO. Increased formation of NO produced by inducible NOS has a negative inotropic effect and contributes to the progression of myocardial damage potentially leading to cardiac fibrosis.[82–91] Besides, hyperexpression of peroxynitrite in cardiac samples was observed at an immunohistochemical study which was involved in direct oxidative damage to lipids, proteins, cardiac cells, and myocytes and in the nitration of tyrosine residues of pro-apoptotic proteins in cardiomyocytes.[92,93] In fact, increased NO formation is associated with lipid peroxidation, inactivation of enzymes, and depletion of reduced glutathione and it confirmed that antipsychotic cardiotoxicity is related to increased oxidative stress and weakened antioxidant defense.[94,95]

Metabolic Syndrome

The use of atypical antipsychotics is associated with the development of the metabolic syndrome. It has been proposed that the metabolic alterations induced by these molecules and the increase in arrhythmic risk related to lipid accumulation in cardiomyocytes involve oxidative stress.[96] Cardiac lipid accumulation gives rise to non-ischemic cardiomyopathy called lipotoxic cardiomyopathy.

A preclinical study used a transgenic mouse model of cardiac lipid overload with cardiac overexpression specific to the peroxisome proliferator-activated receptor gamma, a paradigm of metabolic syndrome in humans.[97] Lipotoxic cardiomyocytes have been shown to exhibit increased ROS production and impaired calcium homeostasis with increased ventricular ectopy. This arrhythmic effect is improved by the inhibition of mitochondrial ROS through the use of a mitochondrial antioxidant molecule suggesting a potential role of mitochondrial antioxidants in the prevention of arrhythmia and sudden cardiac death in obesity and diabetes mellitus.

The role of metabolic stress concerning oxidative stress in the development of these cardiomyopathies is also highlighted in the preclinical study conducted by Gong, *et al*.[98] Here it was shown that the knockout mice of BAX transmembrane inhibitor motif-containing 1, a suppressor of BAX-mediated cell death and associated with the regulation of ROS, present promotion of metabolic disorders and cardiac dysfunctions induced by the diet rich in fats with increased proinflammatory cytokines and oxidative damage.

In the light of these data, a clear relationship seems to emerge between metabolic/inflammatory alterations and oxidative stress, key elements for the development of structural and arrhythmogenic heart diseases that can lead to fulminant fatal events.

Sudden Cardiac Death

As for sudden cardiac death linked to antipsychotics, this is probably caused by an arrhythmic mechanism, but other mechanisms may be involved, including autonomic effects, inhibition of other ion channels or other acute cardiotoxicities, such as myocarditis associated with the use of clozapine.

In the literature, numerous data are supporting the involvement of oxidative stress in pathological conditions involved in the genesis of sudden cardiac death.

Ventricular arrhythmia is the main cause of sudden cardiac death. A relationship between metabolic disorder and excessive oxidative stress has been proposed with cardiac ion channel dysfunction, which predisposes to ventricular arrhythmias and sudden cardiac death.

ROS production has been hypothesized to play a significant role in arrhythmic substrate production.[99] In particular, an abnormal mitochondrial function can lead to an altered function or expression of the cardiac ion channels responsible for the generation of the cardiac action potential with the possibility of generating re-entry phenomena implicated in the development of malignant arrhythmias.

It is also known that an altered redox state is implicated in cardiovascular pathologies such as atherosclerosis, diabetes mellitus and myocardial ischemia, all conditions that can create a structural substrate for increasing sudden cardiac death.[100] In particular, in myocardial ischemia and heart failure, the efficiency of the mitochondrial electron transport chain is compromised with a consequent increase in ROS production.[101] The aforementioned pathological conditions are notoriously arrhythmogenic and predispose to sudden cardiac death and this could be linked to an altered intracellular electrical and ionic hemostasis consequent to the increase in ROS production.

To support the importance of oxidative stress in the genesis of heart disease associated with sudden cardiac death, some data are emerging from preclinical studies. Doxorubicin (molecule that increases oxidative stress) injection knockout mice for the neuronal nitric oxide synthase-1 adaptive (NOS1AP) protein compared to wild types showed significantly higher mortality, QTc prolongation, and reduced contractile function, as well as the development of spontaneous ventricular tachyarrhythmias. The administration of the antioxidant N-acetyl-L-cysteine significantly reduced the mortality of knockout NOS1AP mice and prevented the prolongation of the QT interval and the reduction of systolic function, suggesting a fundamental role of oxidative stress in the

development of ventricular tachyarrhythmias and heart failure, which can cause sudden cardiac death.[102]

POST-MORTEM STUDIES

Several post-mortem studies have been carried out on subjects who used antipsychotics in life to highlight a correlation between the increase in mortality from cardiovascular causes observed on schizophrenics and the use of antipsychotics, typical and atypical (Table 4).

As can be seen in Table 4, epidemiological/observational studies and a cohort study have been carried out to assess cardiovascular risk in subjects taking antipsychotics with a descriptive methodology.[8,18,103–107] In fact, databases were analyzed from hospitals, mainly psychiatric, or from national registers, where the causes of death (cardiac and non-cardiac) were reported in the appropriate death certificates.

However, in the literature, there are few systematic necropsy studies aimed at analyzing this aspect. The post-mortem investigation described by Kelly, *et al.*[104] analyzed a sample of sixty-two deceased subjects treated at life with atypical antipsychotics (clozapine and risperidone), highlighting that 11% of the patients treated with clozapine and 7% of those treated with risperidone had died of cardiovascular causes. Also, three cases of cardiomyopathy were described in the group of subjects taking clozapine and two cases in those taking risperidone. Besides, three cases of myocarditis have been described only in subjects taking clozapine.[104] A post-mortem diagnosis of myocarditis has also been described by Vang, *et al.*[8] This study included two case reports relating to the death of two young men, both who took olanzapine at therapeutic doses, who died suddenly. In both cases, an autopsy, histological and toxicological tests were carried out, which made it possible to make diagnoses of death of eosinophilic myocarditis. Another epidemiological study carried out using a database on autopsy data of all deaths occurring over a 26-year period (1984–2009) in adults receiving care in one large psychiatric hospital in New York, revealed the presence of twenty-two deaths from cardiovascular disease on one hundred cases of sudden death. The twenty-two deaths from cardiovascular death were divided as follows: fifteen deaths due to acute coronary syndrome, two deaths due to heart failure, two deaths due to aortic dissection, two deaths due to myocarditis, and one death due to commotio cordis.[103] Also, Ifteni, *et al.*[106] used a register of autopsy data from Maryland hospital databases from 1989 to 2013. This study included a cohort of 7,198 schizophrenic patients hospitalized in psychiatric facilities. Of these, fifty-seven patients died of sudden death during hospitalization and fifty-one patients underwent autopsy. On autopsy, 62.8% of deaths were attributed to cardiovascular causes, such as myocardial infarction (52.9%), myocarditis (5.9%), and dilated cardiomyopathy.

However, it should be noted that no studies have analyzed the correlation between antipsychotic-induced cardiac death and oxidative stress in humans. In this regard, numerous preclinical studies previously exposed have highlighted the link between cardiac damage induced by oxidative stress/inflammation and antipsychotics. Concerning this, numerous molecules have been analyzed at the murine level; the alterations highlighted in the various studies conducted included an increase in TNF-α, an increase in catecholaminergic tone, an increase in the ROS and nitrate pathways, the presence of DNA degradation products, and lipid peroxidation, as well as alteration of endogenous antioxidant systems.

Specifically, animal models of myocarditis associated with the use of clozapine have shown an increase in TNF-α and free radicals, effects that were reduced with the use of propranolol, suggesting that the increase in catecholaminergic tone could mediate the inflammatory increase and oxidative stress in this pathology.[64] The scarcity of post-mortem studies suggests the need for research in this sense, to be able to highlight whether oxidative stress can at least partially mediate cardiotoxicity due to antipsychotics also in human subjects. In this sense, the increase in TNF-α can be assessed in humans through immunohistochemistry investigations on cardiac histological sections previously treated with anti-TNF-α.[57] Furthermore, an index of cardiac damage from oxidative stress is represented by the increase in the levels of malondialdehyde, an indicator of lipid peroxidation, and the reduced glutathione/oxidized glutathione ratio, both

Table 4 Post-mortem studies carried out on subjects who used antipsychotics in life to highlight a correlation between the increase in mortality from cardiovascular causes observed on schizophrenics and the use of antipsychotics, typical and atypical.

Authors	Year	Type of article	Case	Drug	Death diagnosis	Investigations
Kelly, *et al.*[104]	2009	Descriptive epidemiological study	People with schizophrenia who had received clozapine (n = 62) or risperidone (n = 42). Use of a database on autopsy data about cardiac desease	Clozapina; risperidone	7 of the 62 (11%) in the clozapine treated group died of cardiovascular disease; 3 of the 42 (7%) in the risperidone group died of cardiovascular disease; 3 of the 62 (5%) patients died of cardiomyopathy in the clozapine group; 2 of the 42 (5%) patients of risperidone groups died of cardiomyopathy; 3 of the 62 (5%) died of myocarditis in the clozapine group	Autopsy; histological examination
Kelly, *et al.*[105]	2010	Descriptive epidemiological study	136 deaths; use of an administrative database of schizophrenia patients treated in Maryland, con clozapine (n = 1 084) con risperidone)(n = 602) between 1994 and 2000	Clozapina; risperidone (Control)	43 cardiovascular disease	Revision of an administrative database; identifications of cardiovascular desease in death certificates; no autopsy were done; no histological examination
Vang, *et al.*[8]	2016	Case reports	2 cases: a 39-year-old man with known substance abuse and schizophrenia; 36-year-old man diagnosed with schizophrenia, found dead unexpectedly	Case 1: olanzapine 40 mg/day; pregabalin; venlafaxine; oxazepam Case 2: olanzapine 20 mg/day +5 mg; aripiprazole 30 mg/day; mirtazapine 30 mg/day	Eosinophilic myocarditis	Autopsy; histological examination; toxicological investigation
Manu, *et al.*[103]	2011	Descriptive epidemiological study	100 cases of sudden death; utilizzo di un database on autopsy data of all deaths occurring over a 26-year period (1984–2009) in adults receiving care in one large psychiatric hospital in New York	First and second generation: antipsychotics; antidepressants; mood stabilizers; benzodiazepine; methadone; psychostimulants	Cardiovascular diseases (22); acute coronary syndrome (15); heart failure (2); aortic dissection (2); myocarditis (2); commotio cordis (1); upper airway obstruction (5); pulmonary emboli (4); thrombotic strokes (3)	Autopsy; histological examination
Ifteni, *et al.*[106]	2014	Descriptive epidemiological study, autopsy data	cohort of 7,189 schizophrenia patients admitted to a free-standing, psychiatric teaching hospital from 1989 to 2013	Antipsychotics	57 patients died suddenly and unexpectedly; 51 autopsies performed. Causes of sudden death were most commonly cardiovascular disorders (62.8%), including myocardial infarction (52.9%), pneumonia (11.8%), airway obstruction (7.8%), myocarditis (5.9%), and dilated cardiomyopathy, hemopericardium, pulmonary embolus, hemorrhagic stroke and brain tumor (2.0% each)	Autopsy findings using data extracted from their medical records and the post-mortem examination report
Ray, *et al.*[165]	2009	Retrospective cohort	1,870 sudden cardiac deaths. Cohort: 44,218 and 46,089 baseline users of single typical and atypical drugs; and 186,600 matched nonuser controls. Study data were obtained from computerized files of Tennessee Medicaid from 1990 to 2005	Antipsychotics	1,870 sudden cardiac deaths	Revision of a database (computerized files of Tennessee Medicaid)
Jones, *et al.*[107]	2013	Descriptive epidemiological study	General Practice Research Database was used to identify cohorts of antipsychotic users and nonusers with psychiatric illness (patients registered in database from January 1995 to January 2011)	183,392 antipsychotic users (20,954 olanzapine users) and 193,920 psychiatric nonuses	Cardiac mortality (number of events): nonuser psychiatric (1,289). User psychiatric: atypical (1,200); typical (1,180); olanzapine (206)	Evaluate cardiac mortality, including coronary heart disease, and life-threatening ventricular arrhythmias using death certificate data and records from national registry of hospital admission

of which can be assessed in humans through biochemical analyzes, respectively of chromatographic and spectrophotometric type.[108,109]

In addition to this, to highlight the presence of a correlation between oxidative stress and heart disease induced by antipsychotics, it would be useful to carry out immunohistochemical investigations aimed at assessing the presence of oxidative stress markers, such as inducible NOS, 8-OHdG, NOX2, and finally the pathways of apoptotic death by TUNEL assay.[57]

CONCLUSIONS

Cardiotoxicity of atypical antipsychotics represents a major concern in clinical practice due to its large use in mental disorders. Major cardiovascular adverse events and sudden unexpected deaths are reported, but the mechanism of myocardial injury is not completely known. An increase in myocardial oxidative stress and inflammatory cytokines may play an important role in cellular death and DNA damage. Post-mortem examination is still crucial for research and must be seen as an opportunity for early detection of patients at risk for an unexpected death, and discovery of preventive measures.[110,111] Post-mortem studies carried out show increased cardiac death in subjects taking antipsychotics compared to the general population, reporting cases of myocarditis, cardiomyopathy, and sudden cardiac death. However, the pathogenesis of cardiac toxicity induced by these molecules is still unclear. A potential role of oxidative stress in cardiotoxicity caused by antipsychotics has been proposed in numerous preclinical studies, but post-mortem data from subjects taking atypical antipsychotics during life is extremely lacking. It would be desirable to carry out biochemical and immunohistochemical investigations on cardiac tissue of subjects who died of cardiac death related to antipsychotics, to verify whether oxidative stress can at least partially mediate the cardiotoxicity associated with the use of these molecules. If the mechanism of cardiac toxicity of antipsychotics is clarified in the future clinicians will be able to better establish the dose and length of treatment improving mental disease without impacting the physical health of the patients reducing mortality.[112–114]

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