Review Article

Interventional Cardiology

Atypical Antipsychotic Medications Disrupt the Cardio-Metabolic and Cardio-Immune Axes

B Rostama, M May, KL Houseknecht*

Department of Biomedical Sciences, College of Osteopathic Medicine, University of New England, Biddeford, Maine, USA

*Author for correspondence:
E-mail: khouseknecht@une.edu

Received date: March 12, 2020
Accepted date: March 27, 2020
Published date: April 03, 2020

Abstract:

Antipsychotic medications, including atypical antipsychotics (AA), are widely prescribed and are associated with significant cardiometabolic side effects. It has been known for some time that AA cause drug-induced tachycardia, weight gain, dyslipidemia and hyperglycemia, and AA use in older adults is associated with increased risk of mortality, largely due to MI or stroke. The pharmacological mechanisms underlying these diverse adverse events are largely unknown. AA drugs are also associated with increased risk of infections, in patients across age ranges and regardless of diagnosis. Emerging evidence indicates that AA medications may have anti-inflammatory and immune dysregulatory properties, which may contribute to medication efficacy for schizophrenia and psychosis and increase susceptibility to infection. The role of antipsychotics in modulating the cardio-immune axis is largely unknown. In this review, we will highlight new data which shed light on potential mechanisms and implications for prescribing and patient care.

Keywords: Antipsychotic; Risperidone▪Olanzapine▪Cardiac▪Immune▪Inflammation

Introduction

Prescribing of psychotropic medications is increasing worldwide, and in the United States 1 in 6 adults have been prescribed one or more of these medications [1]. This increase in use is largely due to off-label prescribing for diverse indications, most notably in vulnerable populations including pediatric patients, older adults, and people with neurodevelopmental disorders. Antipsychotic medications were developed and approved by the United States Food and Drug Administration (FDA) for the treatment of psychosis associated schizophrenia and bipolar disorder but are now highly prescribed for non-psychotic conditions. Antipsychotic drugs (APDs), including atypical antipsychotics (AA), are associated with increased mortality and with metabolic and endocrine side effects including rapid weight gain, dyslipidemia, and insulin resistance, all of which contribute to cardio metabolic risk. Antipsychotic use has also been linked to an increased risk of death due to infection. In this review, we will highlight emerging mechanistic evidence linking AA medications to rapid onset dysregulation of immune/inflammatory pathways and implications for cardiac health.

Pharmacology of atypical antipsychotic medications

Antipsychotic medications were originally designed and FDA approved for the treatment of the positive symptoms of schizophrenia and bipolar disorder [2]. First generation, or "typical" antipsychotics (TA; e.g. chlorpromazine, haloperidol) were designed to potently and preferentially antagonize dopamine receptors. Dopaminergic antagonism is thought to be the primary mechanism underlying efficacy for schizophrenia, based upon the dopamine hypothesis that positive symptoms are associated with overactivity in the mesolimbic dopamine pathway. TA are efficacious for the treatment of psychosis,

however they are associated with significant side effects including severe and often irreversible extrapyramidal effects. These side effects include rigidity, bradykinesia, dystonias, tremor, akathisia and tardive dyskinesia.

The severity of side effects seen with TA medications led to the development of second generation or more commonly known AA. AA also target dopaminergic receptors, however the pharmacology is distinct from TA in that they display broader affinity for dopamine receptor subtypes, and overall are less potent dopaminergic antagonists than TA. Rational drug design strategies were employed to maintain, yet lessen, dopaminergic antagonism (via partial antagonism, inverse agonism, or partial agonism) in order to maintain antipsychotic efficacy while lessening/minimizing extrapyramidal side effects. While development of newer AA drugs has been successful in reducing extrapyramidal side effects, the broader pharmacological profile of AA, which includes antagonism of serotonin, histamine, alpha-adrenergic, and muscarinic receptors has resulted in increased metabolic liability (across the drug class) as well as sedation (histamine receptors), hypotension (alpha-adrenergic receptors), and dry mouth/constipation (muscarinic receptors) [3,4].

In summary, AA medications are a class of diverse chemical structures, each with a range of activities at multiple neurotransmitter receptors, including receptors outside of the nervous system. This is important to remember when considering drug associated side effects and their underlying pharmacology. AA broadly antagonize G-protein coupled receptors (GPCRs) including dopamine, serotonin, muscarinic, histamine, and alpha-adrenergic receptors, with varying degrees of potency, resulting in unique efficacy and side effect profiles [5]. However, the broader systemic inhibition of GPCRs is not without consequence, as many cells, including cardiomyocytes [6-9] and immune cells [10,11] express these GPCRs and the effects of their broad inhibition by AA has not been investigated.

Cardio metabolic side effects of AA medications

Atypical antipsychotic medications are associated with a constellation of metabolic and endocrine side effects which increase overall cardiovascular risk. Metabolic side effect profiles vary across the AA class, with the greatest metabolic liability (weight gain, dyslipidemia, hyperglycemia) reported for clozapine and olanzapine, although most drugs in the class, including newer drugs such as aripiprazole, carry some degree of metabolic side effect risk [12,13].

Antipsychotic-induced weight gain

The prescribing of AA continues to expand to new off-label indications, thereby impacting more patients across age ranges [4,14-18]. Among patients with severe mental health disorders, cardiovascular disease is the leading cause of death [19,20]. AA are associated with rapid and significant weight gain, often called antipsychotic-induced weight gain (AIWG), and the resulting obesity and cardiometabolic effects contribute to the 15-20 year decreased life expectancy observed in patients with mental illness [21,22]. These effects are more pronounced in female patients, and pediatric patients are especially susceptible to their adverse cardio -metabolic side effects [23-26]. AA medications cause hyperphagia as a consequence of the dysregulation of dopamine reward pathways, but also via antagonism of histamine and serotonin receptors [27-29].

Beyond appetite control, neurotransmitter receptor antagonism by AA can also directly affect AIWG, for example by the induction of adipogenesis and inhibition of metabolic rate via the antagonism of α1-adrenergic receptors [30]. Increasingly, oral hypoglycemic medications such as metformin and lipid lowering drugs (statins) are currently given concomitantly with AA to manage AIWG associated metabolic side effects, as lifestyle interventions for weight control are proving difficult for some patients with mental illness [30-33]. Cardiometabolic side effects of AA should be closely monitored clinically and the severity of adverse reactions taken into consideration when switching to AA with lower risk profiles.

Atypical antipsychotic-induced insulin resistance and hyperglycemia

Consumption of AA medications contributes significantly to the development of insulin resistance, hyperglycemia, and increased risk of type-2 diabetes (3-5 fold) [34]. These effects are due to AIWG as well as direct effects on the regulation of glucose metabolism. AA have shown to have dose-dependent effects on whole-body insulin sensitivity and insulin release from pancreatic β-cells [31,32]. AA also directly influence hepatic glucose metabolism, leading to hyperglycemia [22]. The effects of AA on insulin resistance and hyperglycemia are acute in nature, occurring prior to AA-associated weight gain [35]. The indirect effects of AA on hyperglycemia have been attributed to neurotransmitter antagonism in the central nervous system, with increased sympathetic nervous system signaling inducing gluconeogenesis, particularly from the liver [22,34] Concomitant use of metformin with AA appears to be beneficial in moderating weight gain and

improving insulin sensitivity [36,37].

Atypical antipsychotics cause dyslipidemia

AA medications can cause dose-dependent dyslipidemia, and hyperlipidemia may be inversely correlated to severity of psychotic symptoms [38] AA increase circulating triglycerides, free fatty acids, LDL, and lipoprotein-associated phospholipase-A2, and reduce HDL [38-41]. AA increase the expression of SREBP1/2 transcription factor proteins, the master regulators of cholesterol biosynthesis, upregulating their many downstream lipogenic gene targets [42,43]. AA also promote resident stem cells to differentiate into adipocyte lineages, as observed with satellite cells in muscle tissues, but potentially in other stem cell depots as well [44]. Although AA are strongly associated with dyslipidemia, the degree of severity varies across the drug class. Thus, it is particularly important to monitor changes in the profile of circulating lipids if patients switch AA drugs [45].

Antipsychotic-induced arrhythmia

Antipsychotic medications carry a class label warning for QT prolongation, and most are known for the potential induction of Torsades de Pointes tachycardia and arrhythmias. Antipsychotics also have the potential for drug associated myocarditis (especially clozapine) and sudden cardiac death, particularly in elderly patients. [46-49]. AA directly affect the electrophysiology of the heart and the cardiac risks are often dose-dependent [50,51]. AA antagonism of cardiomyocyte N^+ channels and inwardly rectifying K^+ channels are implicated in prolonged QT interval and sudden cardiac death adverse effects, respectively [52]. Clinicians are advised to carefully evaluate patients for predispositions and risks of cardiovascular side effects through history and preventative evaluations, and monitoring of symptoms after prescription. The effectiveness of psychiatric therapy should be weighed together with potential cardiovascular effects for modification of AA treatment regimens. [49,52,53].

Atypical antipsychotics cause autonomic dysfunction

AA medications have significant effects on autonomic nervous system function with impact on insulin resistance and metabolic syndrome including hyperglycemia, non-alcoholic fatty liver disease (NAFLD), obesity, and inflammation pathways [54]. AA effects on cardiac function also occur via instability and dysregulation of autonomic tone, with increased stress on the heart and risk of mortality [55]. The dysregulated autonomic effects can present as reduced heart rate variability, atrial fibrillation, neuroleptic malignant syndrome, sympathovagal imbalance, and sinus tachycardia [56,57]. AA can impair autonomic nervous system function by binding and inhibiting numerous targets in both the central and peripheral nervous systems, including adrenergic and cholinergic receptors, and hERG potassium ion channels [19].

AA have been linked to reduced heart rate variability directly and indirectly via AIWG, and reduced deceleration capacity, increasing the risk for cardiac mortality [58-60]. AA-induced loss of dopaminergic inhibition of the sympathetic nervous system may also be indicated in neuroleptic malignant syndrome [61]. AA-induced autonomic dysregulation is dose-dependent, and the associated increased risk of atrial fibrillation has been linked to AA that possesses high affinity for M2 muscarinic receptors [62].

AA with higher affinity for M2 muscarinic receptors reduce heart rate variability by reducing parasympathetic signaling, exacerbated by anti-cholinergic medications [63]. While evidence indicates AA drugs reduce parasympathetic tone and increase sympathetic tone [20,64,65], countervailing evidence also exists [66,67], illustrating the need for further research to distinguish between these differences. Long-acting injectable AA appear to have a lower impact on autonomic dysregulation and decreased heart rate variability than oral AA, and the impact of AA on autonomic disruptions may be mitigated by angiotensin converting enzyme inhibitors [67,68].

Antipsychotic drugs impact blood pressure

The effects of antipsychotic medications on blood pressure are complex, and the effects are due to their diverse and complex pharmacology. Orthostatic hypotension is a common side effect of antipsychotic medications, believed to be due to robust alpha-adrenergic antagonism [69]. Furthermore, AA associated hypotension is exacerbated by autonomic dysfunction, which is also a risk factor for patients with metabolic syndrome, diabetes, and schizophrenia. Complications of orthostatic hypotension include syncope, stroke, myocardial infarction, and death. Orthostatic hypotension in older adults is also linked to increased risk of falls and fractures in patients taking AA medications [70].

Some antipsychotic medications can also cause hypertension (HTN), the leading cause of major cardiovascular events including stroke, myocardial infarction, and aneurysms. The underlying etiology of HTN is complex, and drug-associated weight gain, dyslipidemia, and insulin resistance can contribute to HTN in patients taking psychiatric medications. Additionally, blood pressure is regulated by dopamine signaling, primarily via dopaminergic receptors in the kidney [71,72]. Briefly, dopamine D1, D3, and D4 receptors interact with the renin-angiotensin system, while D2 and D5 receptors interact with sympathetic nervous system regulation of blood pressure. As antipsychotic medications are potent dopamine receptor antagonists (D2 and/or D4 antagonists), they are able to negatively impact blood

pressure regulation. Among AA medications, clozapine, which antagonizes both dopamine D2 and D4 receptors, has been shown to significantly increase HTN and cardiovascular morbidity [73]. Data on drug-associated HTN are more limited for other AA medications, thus additional studies are needed to further assess the risk of HTN or hypotension across the class of AA medications.

Atypical antipsychotic drugs cause endocrine disruption

AA can also cause endocrine dysregulation including hyperprolactinemia, hypogonadism, and suppression of growth hormone [4,74-78]. Hyperprolactinemia stems from the AA-induced, dopamine-mediated disinhibition of lactotropic neurons of the adenohypophysis, and can have a cascade of effects such as hypogonadism, hypercoagulation, amenorrhea, gynecomastia, and bone loss among others [79-83]. Risperidone has the highest incidence of drug-associated hyperprolactinemia [77], while aripiprazole, especially when administered via long-acting intramuscular injections, appears to have a diminished or negative hyperprolactinemic effect [84-87]. Paliperidone has been reported to have a dose-dependent suppressive effect on the levels of adrenocorticotropin and corticosterone by modulation of the hypothalamic-pituitary axis [88]. Other AA-mediated endocrine effects require further analysis and indicate individual patient monitoring, but cortisol and leptin levels may be directly affected [89-91].

Immunomodulatory properties of AA medications

Patients with psychiatric illnesses including schizophrenia often have altered immune function profiles [92-95], and the severity of symptoms often correlate with the neuroimmune/neuroinflammation levels [96]. Animal models, patient case-reports, and *ex-vivo/in-vitro* studies indicate that multiple AA decrease certain inflammatory cytokines and prostaglandins [97-99], promote anti-inflammatory pathways, and alter immune cell and immune system phenotypes, all of which may contribute to their efficacy [100-106].

Even with consideration of their obesogenic side-effects taken into account, anti-inflammatory effects of AA can be observed [107]. Direct effects of AA on primary and immune cell lines show suppression of inflammatory cytokine release, and gene expression changes promoting quiescence [108-110]. Depending upon the AA and the patient profile, case reports and preclinical models indicate AA use may be linked to increased infections [98,111,112]. Certain markers of immunosuppression are known side-effects of AA in patients, and they may be indicators of a larger systemic problem of AA use. Agranulocytosis is often an effect associated with clozapine [113]. However, neutropenia, leukopenia, and monocytopenia, in addition to agranulocytosis, have been reported as a result of many other AAs, including aripiprazole, quetiapine, and risperidone [114-120]. In a preclinical murine model of risperidone treatment, AA-induced myeloid dysplasia in the bone marrow, steatosis of the thymus, and global immunosuppression initiated after five days of treatment. Several immune function pathways were severely disrupted, and likely led to the lowered circulating cytokine levels described (Figure 1) [98].

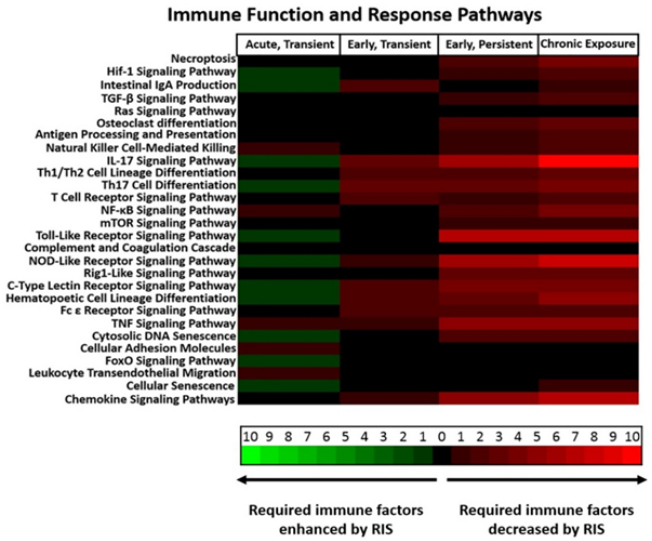

Figure 1: Risperidone treatment causes immune dysregulation in healthy animals. Cytokines that have been measured during risperidone treatment in a preclinical model are integral to several immune function pathways in the KEGG database. The number of altered cytokines present at wild-type levels at each effect stage (acute/transient effect, early/transient effect, early/persistent effect, or chronic effect) were tabulated in vehicle-treated (red) and risperidone-treated (green) mice. Chronic exposure measurements reflect the total cytokines that were altered at both 5 days and 4 weeks. Absence of altered cytokines in an effect category are colored black (λ=0 nm). The intensity of red reflects the number of immune markers significantly decreased during risperidone treatment, and consequently the strength of function in vehicle-treated mice relative to function in risperidone-treated mice, and vice versa regarding green intensity showing an expected enhancement of pathway function. Twenty-six immune function pathways were altered by risperidone treatment, and twenty-one of these were depressed after only five days of treatment. This image was adapted from May et al. [98].

The cardio-immune axis

There is a lifelong, intimate balance in the cardio-immune axis that maintains cardiac homeostasis, which can damage heart function when there are immune perturbations [121,122]. The interactions between cardiomyocytes, cardiac interstitial cells, and resident cardiac macrophages with peripheral cytokines and immune cell infiltrates that make up the homeostatic physiology are susceptible to drug-induced immunosuppression [123-126]. Long-term AA treatment can lead to drug-induced fevers, sterile myocarditis and/or cardiomyopathy, which in turn contribute to the arrhythmia

and tachycardia discussed above [127,128]. Autopsy findings in AA-treated patients and preclinical models include cardiac fibrosis, hypertrophy, and atherosclerosis [129-131]. Histopathologic findings in the heart include chronic inflammatory lesions featuring eosinophilic infiltrates during clozapine; aripiprazole, quetiapine, and olanzapine treatment [132-135]. The cellular makeup of infiltrates leading to chronic inflammatory pathologies during risperidone or ziprasidone treatment has never been described.

The most extensive body of literature reporting inflammatory and immune dysfunction in patients centers on clozapine, which is considered of limited clinical utility due to its side effect profile. More recent studies describe parallel findings for other, more widely used APDs, however. For example, Kelly *et al*. reported that the rates of myocarditis, cardiomyopathy, and atherosclerosis were not significantly different between patients treated with clozapine and those treated with risperidone [136]. In addition to clozapine, changes in cytokine levels have now been reported in patients, preclinical models, or in vitro for olanzapine, risperidone, ziprasidone, quetiapine, and aripiprazole, including global immunosuppression during short-term risperidone treatment in a preclinical model [98,137-142].

Proteomic analysis of cardiac tissues during risperidone treatment showed an increase in several proteins with the potential to facilitate inflammation or infiltration of inflammatory cells (i.e., the plasminogen activator receptor PLAUR, Gc globulin, cyclophilin A, alpha 7 integrin, and CD14). Paradoxically, a small number of proteins with similar features (i.e., NOTCH2, DOCK2, and connexin 43) were significantly decreased during treatment, suggesting a complex dynamic attempting to regulate inflammatory processes occurs in the heart [98,143]. This analysis also showed an increase in proteins associated with the pathophysiology of cardiomyopathy (lamin A/C, myosin heavy chain 7, and SLC25A4) and atherosclerosis (apolipoprotein M, afadin, cyclophilin A, and PLAUR) [143]. Taken together, these findings provide insight into potential mechanisms that lead to the clinical findings of myocarditis, cardiomyopathy, myocardial infarction and atherosclerosis in patients treated with APDs over and above their promotion of weight gain.

Summary and Implications for Clinical Care

In summary, APD are widely prescribed medications that are associated with significant metabolic, endocrine and cardiovascular side effects (Figure 2).

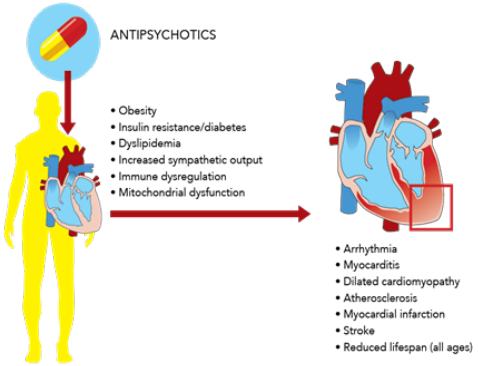

Figure 2: Antipsychotic medications increase cardiovascular disease risk by direct and indirect mechanisms. Atypical antipsychotic drugs (AA) are associated with increased obesity, insulin resistance, hyperglycemia, dyslipidemia and altered autonomic function, all of which are risk factors for cardiovascular disease. Both AA and first generation antipsychotics are associated with cardiac arrhythmia. Other drug- associated effects are more acute and may be due to direct effects on cardiac function, including effects on cardiac mitochondrial function and expression of mitochondrial and immune system genes in the heart. Taken together, AA medications exert myriad effects on the cardiovascular system which culminate in accelerated development of cardiovascular disease in patients of all ages.

Side effects are especially pronounced in vulnerable populations including children and older adults. Emerging evidence of the anti-inflammatory and immunosuppressive properties of these medications has important implications for antipsychotic efficacy as well as increased susceptibility to infection. Furthermore, pre-clinical proteomic data indicate that drug associated changes in cardiac proteomic signature relating to mitochondrial and immune functions precede overt cardiac pathology and weight gain, suggesting AA medications accelerate cardiovascular disease directly.

Additional studies are needed to determine the extent to which these effects translate clinically, however clinical evidence is consistent with increased cardiovascular risk for patients prescribed AA. Care should be taken in prescribing AA medications, especially in the case of non-psychotic and vulnerable populations and patient screening protocols for weight gain, hypertension and glycemic endpoints should be followed [144,145]. Furthermore, co-therapies such as metformin should be considered to offset AA-associated insulin resistance and hyperglycemia, known factors which increase cardiovascular disease risk [37]. As psychiatry and cardiovascular disease are both treated with polypharmaceutical therapeutic regimens, it is important for clinicians to be aware of drug interactions between AA medications and medications used to treat cardiovascular disease as interactions can result in changes in pharmacokinetic and/or pharmacodynamic properties [146].

Conclusion

Finally, AA associated immunosuppression may have myriad consequences for patient outcomes including increased susceptibility to infections, impaired adaptive immunity, and impaired surgical outcomes. More data are needed to better understand AA-associated effects on the immune system and the impact on overall patient outcomes.

Conflict of Interest

All authors declare no financial or proprietary conflict of interest related to this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit.

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