Interactions between Antipsychotics and Non-Psychotropic Medications

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Schizophrenia is a psychotic disorder that exists at the more extreme end of a spectrum of diseases, and significantly affects daily functioning. Cardiovascular adverse effects of antipsychotic medications are well known, and include changes in blood pressure and arrhythmias. Sudden cardiac death is the leading cause of death worldwide, and antipsychotic medications are associated with numerous cardiac side effects. A possible link exists between antipsychotic medications and sudden cardiac death. Common prescribing patterns that may influence cardiovascular events include the use of multiple antipsychotics and/or additional drugs commonly prescribed to patients on antipsychotics. The use of antipsychotics with other medications can significantly increase the risk of cardiac adverse effects (AEs), including sudden cardiac death.

Keywords: schizophrenia ; antipsychotics ; cardiac events ; QTc prolongation ; polypharmacy

1. Introduction

Schizophrenia is a psychotic disorder that exists at the more severe end of a spectrum of diseases, and is characterized by positive symptoms, such as hallucinations or delusions; negative symptoms, such as blunted affect and anhedonia; and cognitive impairments that grossly affect daily functioning [1][2][3]. Altered dopamine, glutamate, and serotonin signaling in the corpus striatum, hippocampus, midbrain, and prefrontal cortex have been indicated in the process of psychosis [4]. According to the dopamine hypothesis of schizophrenia, the positive symptoms of the illness, otherwise known as hallucinations and delusions, are due to the excessive activation of D_2 receptors in the mesolimbic pathway [5]. As such, antipsychotic treatment options have some degree of action at the D_2 receptor, primarily antagonism [2][4]. Conversely, low levels of dopamine in the nigrostriatal pathway are thought to cause motor symptoms via the extrapyramidal system, and low levels of dopamine in the mesocortical pathway are thought to cause the negative symptoms of schizophrenia, such as avolition and flat facies [5].

Antipsychotics can also antagonize alpha-adrenergic receptors. The antagonization of the alpha-1 receptors is thought to improve the positive symptoms, and the antagonization of the alpha-2 receptors helps relieve both the negative and cognitive symptoms [6]. However, this can have cardiac-related adverse effects, such as tachycardia and orthostatic hypotension [7]. Antipsychotics can also antagonize cholinergic receptors, such as the muscarinic receptors, leading to an elevated resting heart rate, QT prolongation, and the induction of polymorphic ventricular tachycardia, also called torsade de pointes [7][8]. Over 60 antipsychotic medications have been developed over time for the symptomatic treatment of psychosis, 20 of which are available for use in the United States [2][4]. Choosing which antipsychotic medication to use can be challenging [2].

The adverse effects (AE) of antipsychotic medications include extrapyramidal, metabolic, sedative, and cardiovascular effects, such as changes in blood pressure and arrhythmias [2]. Arrhythmias can lead to a condition known as sudden cardiac death (SCD), and the most common of these is ventricular fibrillation [9]. Hypertension can lead to arrhythmias; more importantly, chronic hypertension can lead to ventricular arrhythmias, such as ventricular fibrillation [10]. Hypertension causes the hypertrophy of the cardiac muscles, the proliferation of fibrous tissue, and increased intercellular coupling [11]. This leads to dysfunctional electrical properties in the cardiac tissues and the propensity for various arrhythmias [11]. The most common of these arrhythmias is atrial fibrillation [12]. Chronic hypertension can lead to left ventricular hypertrophy and ultimately heart failure, leading to supraventricular arrhythmias and ventricular arrhythmias [12].

Age and the onset of menopause can lead to an increase in antipsychotic adverse effects. With the onset of menopause, estrogen levels drop, which studies have shown to lead to the worsening of hallucinations and delusions during this time [13]. This may necessitate the need for increased dosages of antipsychotic doses, which can lead to increased adverse

effects. Age also plays a role in the probability of adverse effects, especially cardiac adverse effects. The elderly often also have cardiovascular diseases and other comorbid conditions, and thus may be more likely to be taking multiple medications, making polypharmacy an issue [14].

Medications blocking alpha-1-adrenergic and beta-adrenergic receptors help protect against ventricular arrhythmias. However, activating the cardiac D1 receptors can trigger these arrhythmias [15][16]. SCD can be defined as abrupt, unexpected death due to cardiac causes within an hour of symptoms starting, if witnessed, or one day if not [9][17]. SCD is generally related to structural heart diseases, such as ischemic heart disease and hypertrophic cardiomyopathy, or to electrophysiologic conditions, such as long QT syndrome and ventricular fibrillation [9][17]. As sudden cardiac death is the leading cause of death worldwide [9], and antipsychotic medications have known cardiac side effects [2], a review of the possible link between the use of antipsychotic medications and sudden cardiac death is worthwhile. This is especially important as polypharmacy with multiple antipsychotics or multiple other medications is common among those taking antipsychotics.

2. Interactions between Antipsychotics and Non-Psychotropic Medications

2.1. Opioids

Opioids are commonly used analgesic agents that bind to opioid-specific receptors on neuronal cell membranes to inhibit the transmission of pain signals. All opioids can cause vasodilation and bradycardia, resulting in hypotension, edema, or syncope. However, opioids alone will not alter cardiac function, except for meperidine. Meperidine can significantly decrease cardiac output by depressing myocardial contractility [18].

Some opioids can prolong the QTc interval, which increases the risk of ventricular arrhythmias and sudden cardiac death [18]. Methadone is the opioid with the most significant effect on the QTc interval [18]. It blocks the delayed rectifier potassium channels (IKr) encoded by the human ether-à-go-go-related gene (hERG) to delay repolarization [19]. Methadone can cause QT prolongation in a dose-dependent manner [20]. Methadone-induced torsade de pointes cases have been reported in patients receiving high doses (>200 mg/day), or even following recent dose increases [20]. However, the incidence of severe QTc prolongation in individuals taking methadone is relatively low, at 6.0%; this risk increases if other risk factors are present, including chronic use, female sex, advanced age, congestive heart failure, and concomitant QTc-prolonging medication use [21].

Buprenorphine has a less profound effect on the QTc interval than methadone, and has little impact on IKr channels [19]. It has been suggested that buprenorphine is the safer option for treating opioid use disorder in heroin users and those with, or that have experienced, methadone-induced torsade de pointes [20]. However, due to unknown mechanisms, high-dose transdermal buprenorphine can significantly increase QTc interval [22]. Additionally, buprenorphine can substantially prolong the QTc interval when combined with antiretroviral agents [23].

2.2. Antibiotics

Azithromycin is a macrolide antibiotic used to treat various infections, including respiratory tract infections, urinary tract infections, and sexually transmitted diseases. Azithromycin is thought to cause QTc prolongation by blocking IKr channels, which regulate the outward flow of potassium ions during repolarization [24]. In a research comparing the incidence of severe cardiac arrhythmias and all-cause mortality in US veterans taking azithromycin vs. amoxicillin, azithromycin was associated with a 1.48-fold increased risk of death, and a 1.77-fold increased risk of severe cardiac arrhythmia, during the first five days of treatment. However, this research is limited by potential bias, as the patients prescribed azithromycin may have had more serious infections than the patients prescribed amoxicillin [25]. Additionally, clinical trials in healthy individuals taking azithromycin did not prolong QTc interval [26]. Still, a meta-analysis investigating cardiovascular risk associated with macrolides demonstrated an increased risk of sudden death and ventricular arrhythmia associated with azithromycin [27].

Similarly, levofloxacin is a commonly used antibiotic belonging to the fluoroquinolone class, which is thought to cause QTc prolongation by a similar mechanism as azithromycin. In the same research comparing the incidence of AEs in levofloxacin to amoxicillin, levofloxacin was associated with a 2.43-fold increased risk of serious cardiac arrhythmia and a 2.49-fold increased risk of death during treatment days 1–10 when compared to amoxicillin. The same potential bias also limits this study, since patients prescribed levofloxacin may have had more serious infections than patients prescribed amoxicillin [25]. Additionally, multiple clinical trials in healthy individuals taking levofloxacin did not demonstrate QTc prolongation [28][29].

In addition to QTc prolongation, the association of fluoroquinolones and macrolides with heart failure has also been studied. A randomized cohort research assessing cardiac outcomes in patients taking macrolides, fluoroquinolones, or beta-lactams for community-acquired pneumonia found that levofloxacin and moxifloxacin had a lower risk of heart failure compared to beta-lactam monotherapy [30]. Erythromycin, a macrolide antibiotic, was associated with the highest risk of heart failure; as a hepatic CYP 3A4 isozyme inhibitor, erythromycin can also increase the risk of sudden cardiac death [30] [31]. This is an important hepatic enzyme responsible for the metabolism of 50% of available drugs [32]. The inhibition of CYP 3A4 blocks the metabolism of many antipsychotics, and many other medications, allowing them to be present longer to exert their effects on the body. It is important to know that there are polymorphisms among CYP enzymes making the metabolizing of medications either faster or slower in patients with these particular polymorphisms [33]. This should be noted when prescribing medications that work on the CYP3A4 enzyme. The recent development of pharmacogenetic interventions may help clinicians identify these polymorphisms in patients and, therefore, avoid the side effects caused by them or by any other drugs that affect the metabolism of drugs using these pathways [34]. These interventions are not widely used at this time; however, they do offer an exciting avenue for research and possible clinical interventions in the future.

2.3. Other Antimicrobials

Chloroquine and hydroxychloroquine are antimalarial agents that have also been used to treat autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). However, multiple cardiac complications have been described in association with chloroquine and hydroxychloroquine use, including increased risk of QTc prolongation, torsade de pointes, heart blocks, and cardiomyopathy. Populations at increased risk for cardiac events when taking chloroquine and hydroxychloroquine include the female sex, advanced age, NSAID users, and SLE patients [35].

Highly active antiretroviral therapy (HAART) is a medication regimen used to treat HIV, and commonly includes at least three antiretrovirals—protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and nucleoside reverse transcriptase inhibitors. Treatment with HAART is associated with a risk of QTc prolongation, likely due to protease inhibitors [23]. Protease inhibitors have been associated with IKr channel inhibition, leading to QTc prolongation [36]. The use of HIV medications in the presence of risk factors carries a greater risk of QTc prolongation. Using the HAART regimen with buprenorphine, which has a minimal effect on QTc prolongation in isolation, can cause a statistically significant increase in QTc prolongation [23]. Some studies, however, have noted that other factors, such as age, gender, and other comorbidities, may be responsible for the QTc prolongation and adverse cardiac events seen in those using HAART, especially regarding protease inhibitors [37]. It is important to note that ritonavir, a protease inhibitor used in HAART, is also a CYP 3A4 inhibitor [32]. As stated in a previous section on antibiotics, inhibition of this enzyme can lead to the decreased metabolization of some medications, including some antipsychotics. This can lead to the drug being present in the body for a longer time duration, prolonging the exertion of its effects.

2.4. Illicit Drugs

Antipsychotic use in people that also use illicit drugs is common, and the possible AEs should be examined. Cocaine is associated with multiple cardiovascular complications, including myocardial infarction, cardiac arrhythmias, aortic dissection, stroke, and sudden cardiac death [38]. Cocaine is a dopamine and norepinephrine reuptake inhibitor that increases sympathetic activation, leading to coronary vasoconstriction, tachycardia, and hypertension. It also promotes platelet aggregation, leading to thrombus formation, accelerated atherosclerosis, left ventricular hypertrophy, and stroke [39].

3,4-methylenedioxymethamphetamine (MDMA or “ecstasy”) is a serotonin agonist and a dopamine and norepinephrine reuptake inhibitor that causes sympathetic hyperstimulation [39]. Repeated use of MDMA causes left ventricular dilation and diastolic dysfunction, resulting in cardiomyopathy [38]. MDMA can also cause myocardial infarction, QT prolongation, arrhythmia, and sudden cardiac death [39].

Synthetic cannabinoids act on the endocannabinoid system, which has significant roles in cognitive processes, memory, motor control, pain sensation, and appetite. This drug can cause various adverse effects, including hypertension or hypotension, bradycardia or tachycardia, agitation, psychosis, nausea, seizures, and vomiting. It can also significantly impact the heart’s supraventricular and ventricular conduction system, resulting in arrhythmias. Supraventricular arrhythmias associated with synthetic cannabinoids include sinus tachycardia, atrial fibrillation, sinus bradycardia, supraventricular tachycardia, and asystole. Ventricular arrhythmias associated with synthetic cannabinoid use include left bundle branch blocks, QT prolongation, atrioventricular block, and ventricular fibrillation. The arrhythmia mechanism is poorly understood, but is dose-dependent and involves multiple ionic currents [40].

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