REVIEW PAPER

QTc Prolongation and Antipsychotic Medications in Psychiatric Patients – A Review

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Abstract

Background: Antipsychotic medications are the cornerstones of the acute and long-term treatment of schizophrenia. Despite their benefits in minimizing the schizophrenia symptoms, they have been associated with the risk of inducing QTc prolongation, which may lead to a serious life-threatening arrhythmia and cause sudden death. Objective: To review the QTc prolongation caused by antipsychotic medications used among psychiatric patients. Methods: Literature search was conducted using databases such as Scopus, Science Direct, Pubmed, and Springer link. The keywords used for the search were “QTc prolongation”, “antipsychotic medications” and “schizophrenia”. The inclusion criteria are articles from 2001 to 2014, articles written in English and articles related to the effects of antipsychotics in causing sudden cardiac death. The inclusion criteria are the articles written in other languages and the article about other adverse effect of antipsychotics. Results: Twenty-seven articles were found to be relevant to this study and twenty of them which discusses about antipsychotic-induced QT interval prolongation have been included in the table of evidence. Conclusion: Antipsychotics regardless of the generations have the potential of causing QT interval prolongation. The risk-to-benefit ratio that accounts for the danger of sudden cardiac death should be evaluated before prescribing an antipsychotic medicine and each individual patient should be assessed on the potential contributing factors to the prolongation of QTc.

Keywords: QTc Prolongation, Antipsychotic, Psychiatric, Schizophrenia

Introduction

Psychotic disorders include schizophrenia, other psychotic disorders, and schizotypal (personality) disorder. They are defined by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms (DSM-5). Psychotic patient is usually out of touch with reality. They may have strange and irrational ideas like thinking that someone can hear their thought or someone is trying to harm them. Their mood may swing from good to bad
mood and vice versa like from getting excited to angry suddenly for no apparent reason. Most of the patients are usually unaware that their condition is actually a disease. The person may also do not concern on their appearance to others (Stanghellini & Raballo, 2015). They may not bath, change the clothes and hard to communicate with. Psychotic illness like patients with schizophrenia will have these kinds of behaviors.

Currently, many available treatments for schizophrenia which include medications, psychological therapies and social support (Bruijnzeel, Suryadevara, & Tandon, 2014). Antipsychotic medications are used to treat these symptoms, though these medications cannot really cure the illness, but at least they can make the symptoms milder. In some cases, they can shorten the course of an episode of the illness as well. It (Bruijnzeel et al., 2014) stated that the antipsychotics available in the world are classified into two major groups which are first generation (conventional) agents and second-generation (atypical) agents. The examples of first-generation antipsychotics (FGAs) are acetophenazine, cyamemazine, perazine, droperidol, haloperidol, chlorpromazine, methotrimeprazine, piperacetazine and mosapramine, while the second-generation antipsychotics (SGAs) include clozapine, amisulpride, zotepine, risperidone, olanzapine, quetiapine, sertindole, ziprasidone, aripiprazole, perospirone and paliperidone. These medications affect the neurotransmitters that involved in communication between nerve cells, particularly dopamine which is thought to be relevant to schizophrenia symptoms (Bruijnzeel et al., 2014).

The introduction of SGAs in the past decade had brought confidence among physicians and patients to the favorable outcomes with antipsychotic therapy in schizophrenia. The newer SGAs are at least as effective as the older FGAs in reducing the symptoms like delusional thinking, hallucinatory experiences and thought disorganization that are the hallmarks of psychosis (Tandon et al., 2008). Moreover, SGAs possess a broader spectrum of efficacy compared to FGAs particularly with regard to negative, cognitive and mood symptoms, and they also have a lower tendency to cause acute and long-term motor side effects. On the other hand, because of having a lower liability for inducing extrapyramidal side effects as compared to FGAs, SGAs are also being termed as ‘atypical’ (Tandon et al., 2008). Subsequently, the expert practitioners and professional organizations around the world considered SGAs to be more effective than FGAs and evenly recommended the use of these newer agents in treating schizophrenia.

However, there are studies stated that FGAs and SGAs has no significant difference in efficacy of treating schizophrenia. A meta-analysis study stated that not all SGAs were superior to FGAs as some may be good in reducing the symptoms but may induce many side effects while the other may moderately treat the symptoms but give lesser side effects (Lin, Rosenheck, Sugar, & Zbrozek, 2014). The study indicated that SGA as a group seemed to be not evidently more superior to perphenazine which is an intermediate potency FGA. The results of the study suggested that a noticeable benefit only for olanzapine over risperidone (both are SGAs) and perphenazine over risperidone amongst all pairwise comparisons, and no medication were found to be superior to perphenazine in pairwise comparisons (Lin et al., 2014). The overall outcomes of first and second-generation antipsychotics in treating symptoms and
improving quality of life of people with schizophrenia remains debated.

The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the electrocardiogram (ECG). In general, the QT interval exemplifies electrical depolarization and repolarization of both the left and the right ventricles. The QRS complex (on the ECG) resembles the time needed for the depolarization of the ventricles, and the T wave is the time for its repolarization. A lengthened QT interval is clinically important as it associated with a dangerous arrhythmia and may cause sudden death (Shah, Aftab, & Coverdale, 2014). QTc is the heart-rate corrected QT interval which improves the detection of patients at increased risk for ventricular arrhythmia (Ozeki et al., 2010).

Though antipsychotic medications were the drugs of choice in minimizing the schizophrenia symptoms regardless of their potency, some of them may induce serious side effects to the central nervous system, endocrine system, normal metabolic pathway and to the cardiovascular system. The effects of these medications to the cardiovascular system are serious as they can lead to sudden cardiac death.

**Objective of Study**

To review the QTc prolongation caused by antipsychotic medications used among psychiatric patients.

**Research Question**

Research question of this study is divided into four essential ‘PICO’ components as stated in a previous paper by Staunton (2007).

<table>
<thead>
<tr>
<th>No</th>
<th>Elements</th>
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<tr>
<td>1</td>
<td>P: Patient and/or problem</td>
<td>Psychiatric patients</td>
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<td>2</td>
<td>I: Intervention or exposure</td>
<td>Antipsychotic medications</td>
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<td>3</td>
<td>C: Comparison intervention</td>
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<tr>
<td>4</td>
<td>O: Outcome</td>
<td>QTc prolongation</td>
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Therefore, the PICO research question for this study is as below:

“What is the prevalence of QTc prolongation with antipsychotic medications among the psychiatric patients?”

**Method**

**Data Sources**

In order to find out the relevant articles for this study, literature search was conducted using databases such as Scopus, Science
Direct, Pubmed, and Springer link. Besides, google scholar and also the literature search feature in Mendeley were also used as the search engine which then will link to the respective databases.

**Inclusion and Exclusion Criteria**

The keywords used for the search were “QTc prolongation”, “antipsychotic medications” and “schizophrenia”. Considered for the inclusion were studies examining the safety, effectiveness and adverse effect of antipsychotic medications, the risk of sudden cardiac death with the usage of antipsychotic and also the risk factors of QTc prolongation. The articles included are those that were published from 2001 to 2014, and only English language articles were included. Those studies that discussed about other side effects of antipsychotics like metabolic syndrome, anxiety disorders and hyperglycemia were excluded.

To complete this review, articles were identified initially through Scopus and PubMed using the following search terms: “antipsychotics” AND “QTc prolongation”, “antipsychotics” AND “sudden cardiac death”, “antipsychotics” AND “side effects”. This review focused on recent randomized-controlled trials, meta-analysis and review articles. Further articles were identified through searching the references of retrieved articles, cited papers and by using the ‘snowball technique’.

**Results**

There are 20 studies included in this review paper, which can be seen in Table 1. In general, the studies can provide useful information for clinical decision making related to the choice of antipsychotic medication. The studies have various types of study design, namely randomized controlled trial, retrospective study, systematic review and review papers.

The first study was a randomized controlled trial among 1017 patients with schizophrenia. This study confirmed that a daily dose of antipsychotics (chlorpromazine equivalents, CP) was associated with a dose-dependent increased risk of QTc prolongation; however, the use of antiparkinsonian drugs, benzodiazepines, and mood stabilizers did not significantly increase this risk.

With regard to individual antipsychotics, CP, haloperidol intravenous injection (HPDiv), and sulpiride were shown to significantly increase the risk of QTc prolongation. CP, HPDiv, and sulpiride were found to significantly lengthen the QTc interval, whereas HPD, bromperidol, olanzapine, quetiapine, risperidone, and zotepine were not. In our sample, antipsychotic doses of more than 1000 and 1500 mg/day of CP equivalents were found to increase the risk of QTc prolongation. In contrast to antipsychotics, mood stabilizers showed no significant risk-increasing effect. However, a recent study suggested that lithium increases the QTc interval significantly. Furthermore, lithium is known to cause T-wave changes that may lead to torsade de pointes when combined with a QTc-lengthening antipsychotic.

The second study was a review paper related to the connections between psychiatric medications and QTc prolongation, with a specific focus on antidepressants and antipsychotics. The nature and measurement of the QT interval, torsades de pointes (TdP) and its consequences, and non-pharmacologic risk factors for QT prolongation and TdP were discussed. The relationship between psychotropic
medications and QT prolongation, with a specific focus on antidepressants and antipsychotics were comprehensively reviewed. Thioridazine was the first antipsychotic medication associated with QTc prolongation and TdP and it continues to present the greatest risk among neuroleptics.

Phenothiazines in general and thioridazine in particular also are over-represented in cases of sudden death compared to antidepressants or other types of antipsychotics (e.g., butyrophenones, thioxanthenes), suggesting that the QTc prolongation seen with phenothiazines may be arrhythmogenic, especially in patients with concomitant risk factors.

Fluphenazine, a high-potency antipsychotic, has been associated with QTc prolongation in patients with schizophrenia. Pimozide and droperidol prolong the QTc and have been clearly associated with TdP. Chlorpromazine, a low-potency phenothiazine like thioridazine, has been shown to block the IKr channel, has been associated with QTc prolongation, and may cause TdP at high doses. In general, low potency typical antipsychotics are thought to carry a greater risk than high-potency agents, and this risk is thought to be dose-related.

Low-potency typicals, IV haloperidol, and ziprasidone may carry the highest risk, though there is limited evidence for actual adverse QTc-related outcomes with ziprasidone. Though limited evidence suggests that some atypical antipsychotics (i.e., olanzapine) may be less likely to prolong the QTc interval, this has not been rigorously studied.

Other than these two studies, the remaining included studies are systematic review ($n = 5$), RCT ($n = 4$), review ($n = 7$), and retrospective study ($n = 2$). The descriptions of findings for each included study are shown within the last column of the Table 1.
### Table 1. Table of evidence

<table>
<thead>
<tr>
<th>No</th>
<th>Author (Year)</th>
<th>Study Type</th>
<th>Title</th>
<th>Objective of study</th>
<th>Findings</th>
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<tr>
<td>1</td>
<td>Ozeki et al (2010)</td>
<td>Randomized Controlled Trial (RCT)</td>
<td>QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia</td>
<td>To determine the potential for antipsychotic drugs to prolong the QTc interval</td>
<td>Second-generation antipsychotic drugs are generally less likely than first-generation antipsychotic drugs to produce QTc interval prolongation.</td>
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<td>2</td>
<td>Beach et al (2013)</td>
<td>Review</td>
<td>QTc Prolongation, Torsades de Pointes, and Psychotropic Medications</td>
<td>To review connections between psychiatric medications and QTc prolongation, with a specific focus on antidepressants and antipsychotics.</td>
<td>Few risk factors for QTc prolongation were displayed by most of the patients in need of psychotropic medications and should be considered to be at low risk for torsades de pointes (TdP).</td>
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<td>3</td>
<td>Ames et al (2002)</td>
<td>Systematic review</td>
<td>Minimizing the risks associated with significant QTc prolongation in people with schizophrenia: a consensus statement by the Cardiac Safety in Schizophrenia Group</td>
<td>This study was designed to help identify and clarify issues associated with cardiac safety in schizophrenia, particularly QTc interval prolongation.</td>
<td>Risk of significant QTc prolongation is dose-related. The route of administration may also have a significant effect on the risk. For example, droperidol appears to have a more marked effect on QTc prolongation when administered by the intramuscular route. In an acute setting, antipsychotics are often administered parenterally and so extra caution must be observed.</td>
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<tr>
<td></td>
<td>Study Authors and Year</td>
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<td>4</td>
<td>Adkins et al (2012)</td>
<td>RCT</td>
<td>Genome-wide association study of antipsychotic-induced QTc interval prolongation</td>
<td>This study aims to detect genetic variants that mediate the effects of five commonly prescribed antipsychotic drugs on QT prolongation (olanzapine, perphenazine, quetiapine, risperidone and ziprasidone). This study suggests that there are genes in common for regulation of the QTc interval and drug-induced QT prolongation. Furthermore, genes not known to affect the regulation of the QTc interval potentially mediate drug-induced QT prolongation. These genes may be of specific interest to personalize treatment for individual patients.</td>
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<td>5</td>
<td>Yang Fu De (2011)</td>
<td>RCT</td>
<td>Sex difference in QTc prolongation in chronic institutionalized patients with schizophrenia on long-term treatment with typical and atypical antipsychotics</td>
<td>To assess the prevalence of prolonged QTc interval in a large population of inpatients with chronic schizophrenia and to explore QTc relationship with demographic variables and prescribed treatments. QTc prolongation was present in 45 of 1,006 patients overall. Fewer men (3.2%, 22 of 689) than women (7.3%, 23 of 317) displayed QTc prolongation. Moreover, QTc intervals were shorter in male than female subjects. Clozapine was found to produce a longer QTc intervals compared to risperidone and typical antipsychotics.</td>
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<td>6</td>
<td>Jennifer Blair et al (2005)</td>
<td>RCT</td>
<td>Electrocardiographic Changes in Children and Adolescents Treated with Ziprasidone: A Prospective Study</td>
<td>To assess the electrocardiographic safety profile of low-dose ziprasidone (≤40 mg/day) among pediatric outpatients treated for up to 6 months. This study demonstrates that treatment with ziprasidone is associated with increases over baseline of the QTc interval in children and adolescents. The baseline-to-peak increase is greater (mean, 28 ± 26 milliseconds) than that demonstrated in studies of adults, which found a mean of 20.6-millisecond (Gordon, 2000) or 11-millisecond (Keck et al., 2003) increases over baseline.</td>
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<td>Author(s)</td>
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<td>7</td>
<td>Fuji et al (2014)</td>
<td>RCT</td>
<td>QT is longer in drug-free patients with schizophrenia compared with age-matched healthy subjects.</td>
<td>The QT interval of patients with schizophrenia not receiving antipsychotics was compared with that of patients with schizophrenia receiving relatively large doses of antipsychotics and healthy volunteers. Patients with schizophrenia displayed longer QT intervals than healthy volunteers even when they were not receiving antipsychotics, although antipsychotics were shown to further prolong the QT interval. The magnitude of the difference in the QT interval between controls and drug-free schizophrenic patients is small. Furthermore, patients with schizophrenia had a higher heart rate than did the healthy volunteers. Whereas a sex difference was observed in the QT interval in the normal controls, no such difference was found in the patients with schizophrenia.</td>
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<td>8</td>
<td>Minns &amp; Clark (2012)</td>
<td>Systematic Review</td>
<td>Toxicology and overdose of atypical antipsychotics</td>
<td>To review the toxicology and general management of poisonings involving the atypical antipsychotic medications. QTc prolongation with antipsychotic drugs is dose related. There are also marked differences between specific agents and their potential for this effect, with ziprasidone and thioridazine causing the most marked QTc prolongation in therapeutic use. Monitoring of QT duration is important. Management of overdose is largely supportive.</td>
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<td>Author(s)</td>
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<td>9</td>
<td>Dargani (2014)</td>
<td>Review</td>
<td>Safety profile of iloperidone in the treatment of schizophrenia.</td>
<td>To describe the safety profile of iloperidone and its clinical implications. QT prolongation is known to be an adverse effect of both first- and second-generation antipsychotics with prolongation being most pronounced in ziprasidone. Mean changes in QTc changes for iloperidone were higher, although not significantly, than that for ziprasidone, with a mean maximum increase of 16.2 ms (iloperidone) versus 12.3 ms (ziprasidone). QTc interval increases were also higher for iloperidone than for risperidone and haloperidol.</td>
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<td>10</td>
<td>Pacher &amp; Kecskemeti (2004)</td>
<td>Review</td>
<td>Cardiovascular Side Effects of New Antidepressants and Antipsychotics: New Drugs, old Concerns?</td>
<td>The primary goal of this review is to shed light on the recently observed clinically important cardiovascular effects of new antidepressants and antipsychotics and discuss the mechanism beyond this phenomenon. The results suggest that the new generation of antidepressants and antipsychotics have clinically important cardiac as well as vascular effects. Clinicians should be more vigilant about these potential adverse reactions and ECG control may be suggested during therapy, especially in patients with cardiovascular disorders.</td>
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<td>11</td>
<td>Narang (2010)</td>
<td>Review</td>
<td>Antipsychotic Drugs: Sudden Cardiac Death Among Elderly Patients</td>
<td>To review the association between sudden death syndrome with taking antipsychotic medications</td>
<td>Sudden cardiac death has become a significant clinical concern when prescribing antipsychotic drugs, especially to older people with dementia. Physicians should always evaluate patients for comorbid conditions, especially heart disease and metabolic abnormalities, and all currently used medications to assure a risk-to-benefit ratio favoring the application of an antipsychotic medication.</td>
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<td>12</td>
<td>Hall et al (2009)</td>
<td>Retrospective study</td>
<td>Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death</td>
<td>To calculate the adjusted incidence of sudden cardiac death among current users of antipsychotic drugs</td>
<td>The rates of sudden cardiac death for both current users of typical antipsychotic drugs and current users of atypical drugs were greater than those for former users. Former users did not have a significantly increased risk of sudden cardiac death as compared with nonusers. The risk of sudden cardiac death increased with an increasing dose among current users of typical or atypical antipsychotic drugs.</td>
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<td>13</td>
<td>Brojmohun et al (2013)</td>
<td>Systematic review</td>
<td>Protected from Torsades de Pointes? What Psychiatrists Need to Know About Pacemakers and Defibrillator</td>
<td>We review practical tips for assessment of the QT interval in patients with paced rhythms, as well as the basic operative principles of cardiovascular implantable electronic devices (CIEDs). We examine the available clinical evidence for the use of CIEDs in patients at risk for TdP.</td>
<td>All physicians should avoid the oversimplified belief that CIEDs provide absolute protection against malignant arrhythmias when prescribing medications with a risk of TdP; rather, the presence of a CIED should serve as a marker of increased cardiac risk and warrants increased vigilance and caution on the part of the prescriber.</td>
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<td>14</td>
<td>Holmes &amp; Zacher (2012)</td>
<td>Review</td>
<td>Second-generation antipsychotics: A review of recently approved agents and drugs in the pipeline</td>
<td>To review the three second-generation antipsychotics, namely iloperidone, lurasidone, and asenapine.</td>
<td>Iloperidone should be used with caution when combined with other drugs that may increase QTc interval due to risk of further QT prolongation. Several limitations to use of this medication include the risk of orthostatic hypotension and QT prolongation. It is noted that iloperidone is associated with mild QT prolongation, which may limit utility in patients with underlying cardiovascular disease.</td>
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<td>15</td>
<td>Armahizer et al (2013)</td>
<td>Systematic Review</td>
<td>Drug-drug interactions contributing to QT prolongation in cardiac intensive care units</td>
<td>To determine the most common drug-drug interaction (DDI) pairs contributing to QTc prolongation in cardiac intensive care units (ICUs).</td>
<td>Many patients are discharged on the medication combinations that they received as an inpatient and there are no data regarding long-term outcomes in these patients. Cardiac death occurs in a large number of patients and it is unknown how many of these deaths are due to unintended and unmonitored QTc prolongation from DDIs. The most common medications related to these DDIs were ondansetron, amiodarone, metronidazole, and haloperidol.</td>
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<td>16</td>
<td>Greenberg (2007)</td>
<td>Review</td>
<td>Ziprasidone for schizophrenia and bipolar disorder: a review of the clinical trials.</td>
<td>To review the use of ziprasidone for schizophrenia and bipolar disorder.</td>
<td>The use of ziprasidone might be associated with a relatively greater risk for prolongation of the QTc interval in the ECG, which could predispose to torsades de pointes, a potentially fatal cardiac dysrhythmia. As these studies demonstrated that prolonged QTc intervals were also associated, to varying degrees, with other antipsychotics, and amid continuing controversy concerning how much of a clinical problem this actually represented, the decisional process eventually culminated in ziprasidone’s approval accompanied with certain warnings about its potential risk.</td>
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<td>17</td>
<td>Hert et al (2011)</td>
<td>Systematic Review</td>
<td>Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care</td>
<td>To review prevalence rates of different physical illnesses as well as important individual lifestyle choices, side effects of psychotropic treatment and disparities in health care access, utilization and provision that contribute to these poor physical health outcomes.</td>
<td>Individuals with severe mental disorders (SMIs) are prone to many different physical health problems. While these diseases are also prevalent in the general population, their impact on individuals with SMIs is significantly greater. Antipsychotics (APs) are associated with a greater risk of QTc prolongation include pimozide, thioridazine and mesoridazine among the conventional APs and sertindole and ziprasidone among the atypical APs.</td>
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<td>18</td>
<td>Shah (2014)</td>
<td>Review</td>
<td>QTc Prolongation with Antipsychotics: Is Routine ECG Monitoring Recommended?</td>
<td>To provide clinically practical guidelines for monitoring QTc intervals in patients being treated with antipsychotics.</td>
<td>The most persuasive evidence for increased risk of QTc prolongation, TdP, and sudden death exists for thioridazine, which has been found to be associated with the largest mean QTc prolongation (35.6 ms) among all of the antipsychotics. QT prolongation, arrhythmias, and sudden death have also been clearly associated with mesoridazine, pimozide, and droperidol. Among the atypical antipsychotics approved by the FDA, ziprasidone has been associated with the greatest concern about the risk of adverse events secondary to QTc prolongation.</td>
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<td>19</td>
<td>Jones et al (2013)</td>
<td>Retrospective study</td>
<td>Risk of Mortality (including Sudden Cardiac Death) and Major Cardiovascular Events in Users of Olanzapine and Other Antipsychotics: A Study with the General Practice Research Database.</td>
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<td>To assess the risks of sudden cardiac death and cardiac mortality among users of the antipsychotic product (olanzapine).</td>
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<td>Previous analyses of clinical trial data have suggested that olanzapine does not increase the risk of QTc prolongations that lead to potentially fatal ventricular arrhythmias, this is supported by findings of the present study that patients treated with olanzapine were not at increased risk of ventricular arrhythmias despite being at increased risk of cardiac mortality in general.</td>
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<td>To review the mechanisms and establish the risk of torsade de pointes and sudden death with antipsychotic drugs.</td>
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<td>Ziprasidone prolongs the QT interval more than haloperidol, olanzapine, quetiapine, and risperidone but less than sertindole and thioridazine. Although it is reassuring that ziprasidone was not associated with cardiac events during premarketing trials, that is not sufficient to guarantee that uncommon but life-threatening arrhythmias will not occur once the drug is in widespread use.</td>
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CP = chlorpromazine equivalents, HPDiv = haloperidol intravenous injection, TdP = torsades de pointes, APs = Antipsychotics, SMIs = severe mental disorders, ECG = electrocardiogram, DDI = drug-drug interaction, QTc = corrected Q-T interval, CIEDs = cardiovascular implantable electronic devices, ICUs = intensive care units.
Discussion

QT interval

Electrocardiogram (ECG) is a test that records electrical activity of the heart. The heart’s electrical activity is translated into line tracing on paper (Shah et al., 2014). On the ECG, the QT interval illustrates the onset of ventricular depolarization to the end of repolarization. Ventricular depolarization results from the movement of sodium ions into the cardiac cells while the following repolarization is due to an outward flow of potassium ions. The movement of potassium ions through two delayed rectifying currents which are rapid (IKr) and slow (IKs) (Fayssoil, Issi, Guerbaa, Raynaud, & Heroguelle, 2011). The prolongation of QT interval may be due to the blockade of either current, preventing the outflow of potassium ions which prolong the action potential (Fayssoil et al., 2011). Accordingly, the duration of ventricular depolarization and repolarization is affected by any alteration in relevant electrolytes balance (Miller & Misher, 2014). As stated in American Heart Association (AHA, 2009), both hypokalemia and hypocalcemia can prolong phase 2 and phase 3 of the action potential, thus lengthening the QT interval (Rautaharju et al., 2009).

Figure 1. Shows ECG and its interpretations
QT segment of the ECG can vary with changes in the heart rate and thus, heart rate-corrected QT interval (QTc) is often used as a more accurate representation of ventricular repolarization (Miller & Misher, 2014). As the heart rate increases, the uncorrected QT interval will shorten. Consequently, it is difficult to determine whether an observed QT change is due to drug repolarization effect or due to a change in the heart rate. Several formulae have been introduced to correct the QT interval. The most commonly used formulae are the formulae derived by Bazett and by Fridericia (Rautaharju et al., 2009). However, according to Beach et al (Beach et al., 2013), there was no studies have been done to ascertain that a particular formula is better in predicting sudden death.

**QTc Prolongation**

QTc prolongation has a huge clinical importance as it is correlated with dangerous arrhythmias especially torsades de pointes (TdP) which may lead to sudden death (Beach et al., 2013). TdP is a specific ventricular arrhythmia which is characterized by polymorphic pattern on the ECG. Patients with TdP maybe asymptomatic but sometimes associated with syncope and dizziness (Ames et al., 2002). A review done by Glassman and Bigger (2001) concluded that all medications which lead to TdP prolong the QTc interval and bind to the potassium rectifier channel, though the relationships are not accurate. They also stated that sudden unexpected death occurred more frequently among population treated with antipsychotic as compared to drug free population (Alexander H Glassman & Bigger, 2001).

Though there are many factors that may play a role in increasing the risk of cardiovascular diseases like smoking, poor diet and sedentary lifestyle, certain antipsychotic drugs may also have an impact on the cardiovascular events and thus increasing the rate of mortality and morbidity (Ames et al., 2002). Ames et al (2002) also stated that people with schizophrenia seem to have a higher risk of getting cardiovascular disease compared to general population, and antipsychotic drug use may play an important role in causing this events (Ames et al., 2002). There are a range of mechanisms proposed by Ames et al (2002) on how antipsychotic drugs influence the cardiovascular functions which include: receptor blockade, conduction disturbances, delayed ventricular repolarization (prolonged QT interval), left ventricular dysfunction and sinus node abnormalities (Ames et al., 2002).

**Individual Antipsychotics**

Both first-generation (FGA) and second-generation antipsychotic (SGA) have an adverse effect of causing QTc prolongation (Dargani & Malhotra, 2014). Nevertheless, there is an apparent variation in the extent to which different agents influence the QTc prolongation by which FGA are more prominent in lengthening the QT interval as compared to SGA (Ames et al., 2002; Narang et al., 2010). Pacher and Kecskemeti (2004) also stated in their study that the new atypical antipsychotics have a better efficacy and lesser side effects than older FGA with the exception of sertindole and ziprasidone that have a significant QTc prolonging effect.

Considering individual antipsychotics, iloperidone which is a SGA prolonged QTc interval at all doses, however no deaths or serious arrhythmias was reported with this drug (Dargani & Malhotra, 2014). A similar finding of QT prolongation caused by iloperidone limits its usage in patient with
underlying cardiac disease (Holmes & Zacher, 2012). A study mentioned that both thioridazine and droperidole were found to cause QTc prolongation even at the dose used for therapy (Pacher & Kecskemeti, 2004). Ziprasidone which is a new atypical drug (SGA) has a fewer side effects as compared to olanzapine and risperidone in causing weight gain, hyperlipidemia and hyperglycemia, however, Ziprasidone was reported to lengthen the QT interval more than haloperidol, olanzapine, quetiapine and risperidone (Pacher & Kecskemeti, 2004). This finding was similar to a randomized controlled trial (RCT) study (Blair et al., 2005) which suggested that treatment with ziprasidone is linked with an increase in baseline of the QTc interval in children and adolescent. Previous reviews were also consistent with the previous study where they concluded that ziprasidone though in therapeutic dose is more likely to prolong QT interval compared to other agents (Greenberg & Citrome, 2007; Minns & Clark, 2012). Thus, a close monitoring on the ECG changes is a must when prescribing this medication.

Among the antipsychotic drugs, thioridazine (FGA) and ziprasidone (SGA) induced the greatest QTc prolongation. The antipsychotics that was categorized in mid-range degree of causing QTc prolongation were chlorpromazine (FGA) and quetiapine (SGA) while haloperidol (FGA) and other SGA like risperidone, clozapine, olanzapine and aripiprazole have a lesser degree of lengthening (Narang et al., 2010). One study also proved that patients treated with olanzapine have no increased risks of CHD and ventricular arrhythmias relative to nonusers with psychiatric illness (Jones et al., 2013).

**Dose of Antipsychotics**

Several researchers have concluded that the risk of QTc prolongation is associated with the dose of the drugs (Ames et al., 2002; Minns & Clark, 2012). Consistently, a study by Jones et al (2013) found that an increase in dose of typical antipsychotic increased the risk of cardiac mortality, but there was no apparent relationship between dose and atypical antipsychotic (Jones et al., 2013). Narang et al (2010) also claimed that cardiac danger was drug dose-related and rise in patients with previous cardiovascular diseases. In contrast, as regard to the type of antipsychotic, they mentioned that both typical and atypical antipsychotic escalated the risk of sudden cardiac death at a higher doses (Narang et al., 2010). Thus the risk of QTc prolongation should be monitored though within the therapeutic dose. On the other hand, the QT interval might be significantly affected by parenteral route of administration, as this route provides a higher bioavailability of drugs (Ames et al., 2002).

**Drug-drug Interaction**

Moreover, drug-drug interaction causes a significant QTc interval prolongation. An adverse effect is expected when a QT-prolonging drug is use concomitantly with other QT-prolonging drugs or with agents that alter the metabolism of the QT-prolonging drug. The examples of drugs that cause QT prolongation other than antipsychotic agents are antiarrhythmics, antibiotics, tricyclic antidepressants, antihistamine and selective-serotonin reuptake inhibitors (Armahizer et al., 2013).

**Age of Patients**

Considering the age of patients, several studies have reported that the risk of sudden cardiac death as a result of QT prolongation increase with an increase in age (Alexander...
H Glassman & Bigger, 2001; Jones et al., 2013; Narang et al., 2010). This might be due to the presence of comorbidities like cardiac disease and more medications intake among elderly (Alexander H Glassman & Bigger, 2001). In contrast, a study reported that the prevalence of QTc prolongation was slightly low among the patients aged 50 and above who was treated with antipsychotics. However, these patients had a low dose of antipsychotic drugs, low frequency of polypharmacy and coadministration of QT-prolonging drugs (Yang et al., 2011).

**Gender of Patients**

A study on sex difference in QTc prolongation concluded that female patients were more prevalent in experiencing QTc prolongation as compared to male patients as well as they have a longer QT interval in normal conditions (Yang et al., 2011). This is supported by a review that suggested that young woman has a longer QT interval which might be due to the effects of testosterone though this effect will diminish in older adulthood (Beach et al., 2013). Conversely, a study done by Ozeki et al. (2010) failed to detect any significant gender difference in the risk of having QTc prolongation. The variance in dose or other risk factors might be the reasons for this events (Ozeki et al., 2010).

**Genetic Factor**

Genetic research of the QT interval plays an important role in investigating antipsychotic-induced QT prolongation. It allows psychiatrists to identify patients with increase susceptibility and thus personalized the treatment for each patient (Tybura et al., 2014). A genome-wide association study of antipsychotic-induced QTc interval prolongation identified that there are a number of genes involved in regulating the QTc interval and drug induced QT prolongation (Adkins et al., 2012). The potential genes that mediate the antipsychotic-induced individual variation in QT prolongation are single-nucleotide polymorphism (SNP) rs4959236 (a member of solute carrier family), nitric oxide synthase 1 adaptor protein gene (NOS1AP) and nucleotide binding protein-like (NUBPL) gene. The solute carrier genes transport a variety of compounds including drugs, environmental toxins and endogenous metabolites across the cell membrane (Koepsell & Endou, 2004). Similarly, a study found that there were a strong association between NOS1AP gene and QT interval duration by affecting cardiac repolarization (Aarnoudse et al., 2007). Therefore, pharmacogenetic studies have a crucial role in identifying drug-induced adverse events and thus improving treatment adherence and efficacy.

**Limitations of study**

The main limitation of this study was that there was less recent studies have been done regarding the antipsychotic medications and its association with QTc prolongation. Besides, time constrain limits the number of articles that can be searched and included in this review. Furthermore, some articles need to be subscribed with payment in order to get the full text, which also contributing to the less number of articles.

**Conclusion**

Patients with antipsychotic medications treatment were exposed to many possible medical complications. Present literature shows that many antipsychotics regardless of the generations have the potential of causing QTc interval prolongation, which in turn has a strong association of triggering sudden cardiac death from fatal arrhythmia.
It is the responsibility of the physicians to examine the risk-to-benefit ratio that accounts for the danger of sudden cardiac death before prescribing an antipsychotic medicine. Each individual patient should be assessed on the potential contributing factors to the prolongation of QTc interval like age, gender, drug interactions and other comorbidities. It is proven that antipsychotic medications still have a significant role particularly in psychotic disease, thus an appropriate assessment on the patient must be done prior to its prescription (Narang et al., 2010). It was also suggested that ECG monitoring should be done routinely especially with those drugs with high risk of causing QTc lengthening (Shah et al., 2014). Further studies which focus on the strategies of reducing the risk factors should be done. It is also recommended that there must an early collaboration between medical disciplines in order to adopt the optimal approach and to manage this issue.

Acknowledgement

In the name of Allah, The most Beneficent, The Most Merciful, Praise and salutations to Prophet Muhammad PBUH. All praises to Allah the Almighty for giving me the health and strength in completing this literature search.

I would like to express my deepest appreciation to all those who provided me the possibility to complete this study. Acknowledgement to my supervisor, Br Syahrir bin Zaini, in stimulating suggestions and encouragement and helped me to coordinate my literature search especially in writing this report.

Special thanks to my coursemates who have been very helpful, supportive and understanding with my condition being a novice learner. Last but not least, my gratitude to my beloved parents who have always supported me physically and spiritually along the way in completing this course. Without them, I will not be the person that I am today. May Allah bless all of you in this world as well as in the hereafter.

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