

## ORIGINAL PAPER

**Co-morbid Hypertension, Diabetes Mellitus or Dyslipidemia  
among Patients Prescribed with Second Generation  
Antipsychotic: A Comparison Study between  
Aripiprazole, Quetiapine and Clozapine  
based on Pharmacy Prescription Database**

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**Abstract**

**Introduction:** Second generation antipsychotic (SGA) was linked to increased risk of metabolic syndrome. The risk varies between different SGA. We aim to study this risk by examining the co-prescription of antihypertensive, antidiabetic and lipid lowering drugs in patients prescribed with either aripiprazole, quetiapine or clozapine. **Methods:** This is a retrospective cohort study based on the prescription records of a teaching hospital. Prescription records between January 1, 2013 and December 31, 2014 for psychiatric unit were extracted. Patients with at least one prescription of any antipsychotic were included. The odds of antihypertensive, antidiabetic and lipid lowering drugs co-prescription in patients with either aripiprazole, quetiapine or clozapine were calculated. **Results:** Of the 1742 study subjects, 88 patients were prescribed with aripiprazole, 175 patients with clozapine and 124 patients with quetiapine. Patients prescribed with quetiapine had higher odds of co-prescribed with antihypertensive (OR = 1.71, 95% CI = 1.11, 2.63), antidiabetic drugs (OR = 1.81, 95% CI = 1.11, 2.95) and lipid lowering drugs (OR = 1.94, 95% CI = 1.19, 3.16). There were higher odds of co-prescription of antihypertensive (OR = 1.54, 95% CI = 1.05, 2.25), antidiabetic drugs (OR = 1.69, 95% CI = 1.10, 2.59) and lipid lowering drugs (OR = 1.90, 95% CI = 1.24, 2.91) in patients with clozapine. However, there were no increase odds of co-prescription of the three agents in patients with aripiprazole. **Conclusion:** We need to monitor the risk of metabolic syndrome in patients treated with SGA. Aripiprazole has lower risk of metabolic syndrome.

**Keywords:** Aripiprazole, Quetiapine, Clozapine, Hypertensive, Diabetes, Hyperlipidemia, Metabolic Syndrome

## Introduction

Second-generation or “atypical,” antipsychotic drugs were introduced in the 1990s with promised enhanced efficacy in schizophrenia<sup>1,2</sup>. The atypical agents differ pharmacologically from first generation antipsychotic agents in their lower affinity for dopamine D2 receptors and greater affinities for other neuroreceptors, such as 5-HT<sup>1A</sup>, 5-HT<sup>2A</sup>, 5-HT<sup>2C</sup>, 5-HT<sup>3</sup>, 5-HT<sup>6</sup>, and 5-HT<sup>7</sup> and alpha adrenergic A1 and A2.<sup>3</sup> Meta-analyses have shown that some second-generation antipsychotics (amisulpride, clozapine, olanzapine, and risperidone) are more efficacious than first-generation antipsychotics<sup>4,5</sup>. Even though, some researchers shared a different view, second generation antipsychotics have become a commonly prescribed drugs in many countries.

Recently, there are substantial concerns about the metabolic side effects of SGAs. Based on the findings of a meta-analysis, four second-generation antipsychotics that have turned out to be more likely than first-generation antipsychotics in inducing substantial weight gain (clozapine and olanzapine)<sup>6</sup>. The metabolic syndrome is a clustering of hyperglycemia/insulin resistance, obesity and dyslipidemia<sup>8</sup>. The understanding of metabolic syndrome helps us to identify patients who are at high risk of developing atherosclerotic CVD and type 2 diabetes. Second, we may be able to understand the pathophysiology that links the components of metabolic syndrome with each other and with the increased risk of CVD. In general, today there is significant agreement the introduction of SGAs has predispose patients to type 2 diabetes mellitus and cardiovascular disease, weight change and utilization of anti-lipidemia medications<sup>8-11</sup>.

In a previous systematic review, it showed that olanzapine and clozapine showing the highest risk of elevation of weight, cholesterol, and glucose. Quetiapine, risperidone, and sertindole had intermediate elevations. Aripiprazole and amisulpride displayed intermediate or low elevations and ziprasidone the lowest elevations<sup>12</sup>. However, there is lacking of evidence to demonstrate the difference risks of metabolic syndrome between different SGA in Asian population especially in Malaysia. In this study, we aims to study the rate of antihypertensive drugs, antidiabetic drugs and lipid lowering drugs among patients prescribed with either aripiprazole, quetiapine and clozapine using a large pharmacist database in one of the teaching hospital in Malaysia. These three SGA were selected in the current study according to the different risk categories of inducing metabolic syndrome based on previous findings<sup>12</sup>.

## Methods

### *Setting and Design*

The study was conducted in University Malaya Medical Centre (UMMC), a referral and a teaching hospital located in Kuala Lumpur, Malaysia. This was a retrospective cohort study among patients from psychiatric unit, UMMC between January 1, 2013 and December 31, 2014. This study was approved by the Medical Ethics Committee, UMMC.

### *Data Sources*

The pharmacy department in UMMC maintained all prescriptions records electronically in Medication Management and Use System Ascribe (Version 10.09) database. From this database, prescription records dated between January 1, 2013 and December 31, 2014 for psychiatric unit were extracted using IBM's Cognos Business

Intelligence PowerPlay. The information extracted from the database includes patients' gender, age, ethnicity and drug's generic name for every individual. The prescription of coverage was 100% for the above-mentioned study period.

All drugs in the database were coded according to British National Formulary (BNF) classification. All subjects with at least one prescription of antipsychotic (ATC code = N05A) was selected. The data of the subjects with prescription of the three atypical antipsychotic, namely aripiprazole, quetiapine and clozapine was extracted. The outcome measures were the co-prescription of antihypertensive drugs, antidiabetic drugs and lipid lowering drugs.

### **Statistical Analyses**

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS version 22, IBM Corporation). The odds of co-prescription of antihypertensive drugs, antidiabetic drugs and lipid lowering drugs were calculated and analysed with using Chi-Square analysis. All statistical analyses were tested with alpha less than 5% using two-tailed.

### **Results**

For the study period, 1742 patients were prescribed with at least once with antipsychotic. The mean age of the study subjects included in this study was  $43 \pm 15$  years old with majority were Chinese (44.8%) followed by Indian (25.3%) and Malay (24.4%). 62% of them are female (Table 1).

**Table 1.** Socio-demographic characteristics of the study subjects (N=1742)

Characteristics	
Age, mean (sd)	43.12 (15.63)
Gender, n (%)	
Male	661 (37.9)
Female	1081 (62.1)
Ethnic, n (%)	
Malay	425 (24.2)
Chinese	780 (44.8)
Indian	440 (25.3)
Others	97 (5.6)

Of all the study subjects, 88 patients were prescribed with aripiprazole, 175 were prescribed with clozapine and 124 subjects were prescribed with quetiapine during the two years study period. Those who prescribed with quetiapine had higher odds of co-prescribed with antihypertensive (OR = 1.71, 95% CI = 1.11, 2.63), antidiabetic drugs (OR = 1.81, 95% CI = 1.11, 2.95) and lipid lowering drugs (OR = 1.94, 95% CI =

1.19, 3.16). There were also higher odds of co-prescription of antihypertensive (OR = 1.54, 95% CI = 1.05, 2.25), antidiabetic drugs (OR = 1.69, 95% CI = 1.10, 2.59) and lipid lowering drugs (OR = 1.90, 95% CI = 1.24, 2.91) among patients with clozapine. However, there were no increase odds of co-prescription of the three agents in patients with aripiprazole (Table 2).

**Table 2.** Analysis of co-prescription of antihypertensive drugs, antidiabetic drugs and lipid lowering drugs among patients prescribed with either aripiprazole, quetiapine or clozapine.

Prescription	Anti-hypertensive n (%)	OR	95% CI	<i>p</i> *	Anti-diabetic n (%)	OR	95% CI	<i>p</i> *	Lipid lowering n (%)	OR	95% CI	<i>P</i> *
Aripiprazole												
Yes	13 (14.8)	0.88	0.48, 1.61	0.68	15 (17.0)	1.69	0.95, 3.02	0.07	11 (12.5)	1.22	0.64, 2.35	0.5
No	272 (16.7)				179 (10.8)				173 (10.5)			
Quetiapine												
Yes	30 (24.2)	1.71	1.11, 2.63	0.01	22 (17.7)	1.81	1.11, 2.95	0.02	22 (17.7)	1.94	1.19, 3.16	0.0
No	255 (15.8)				172 (10.6)				162 (10.0)			
Clozapine												
Yes	39 (22.3)	1.54	1.05, 2.25	0.03	29 (16.6)	1.69	1.10, 2.59	0.02	30 (17.1)	1.90	1.24, 2.91	<0.0
No	246 (15.7)				165 (10.5)				154 (9.8)			

OR = odds ratio

CI= confident interval

\* Chi Square analysis

## Discussion

This is the first study looking into the co-prescription of antihypertensive drugs, antidiabetic drugs and lipid lowering drugs in patients prescribed with second generation antipsychotic. In the findings, we showed that patients prescribed with quetiapine or clozapine had higher odds of being co-prescribed with any of the three agents. In contrast, there were no increase odds of being prescribed with either antihypertensive drugs, antidiabetic drugs or lipid lowering drugs in patients on aripiprazole.

Patients with mental illness including schizophrenia, bipolar disorder and depression have higher risk for cardiovascular disease (CVD) such as obesity, smoking, diabetes, hypertension and dyslipidemia<sup>13</sup>. In addition, antipsychotic medication can induce weight gain or worsen CVD risk factors<sup>14</sup>. As a result, it is important to determine the different risk of metabolic syndrome induced by different type of antipsychotic. In the current study,

we demonstrated that not all the second generation antipsychotic carry the same risk of association with hypertension, diabetes and dyslipidemia.

Clozapine and quetiapine were shown to have higher odds of being prescribed with antihypertensive, antidiabetic or lipid lowering drugs. In CATIE study, quetiapine showed to had higher risk of hypercholesterolemia than risperidone and was close to that observed with olanzapine<sup>4</sup> as well as elevations in triglycerides<sup>4, 10</sup>. This suggests that quetiapine has a greater metabolic effect than risperidone.

The actual mechanism of atypical antipsychotic inducing metabolic syndrome is not fully understood. However, the association of obesity or overweight with atypical antipsychotic is well-established. Overweight and obesity, along with increases in adiposity in general, are established risk factors for insulin resistance, hyperglycaemia and dyslipidaemia<sup>15</sup>. A number of studies suggest that the effect of antipsychotic treatment on insulin

resistance, rather than insulin secretion, is more important causative factor for hyperglycemia in patients treated with atypical antipsychotics<sup>6, 15</sup>.

Although changes in insulin resistance occur mostly secondary to adiposity<sup>16, 17</sup>, there is some patients may experience glucose dysregulation independent of weight gain or increase adiposity<sup>18-21</sup>. This suggested that the possibility of a direct effect of certain antipsychotic medications on insulin sensitivity or secretion. One possible mechanism for antipsychotic drug effects would involve drug effects on glucose transporter function. Studies showed that clozapine, olanzapine and chlorpromazine, can inhibit glucose uptake via interactions with glucose transporter proteins, whereas other agents, such as haloperidol, had less effect on glucose transport<sup>22, 23</sup>. These findings suggest that differing effects on glucose transport can be hypothesised to explain the different adiposity-independent antipsychotic drug effects on insulin sensitivity. Changes in noradrenaline and adrenaline turnover and plasma concentrations during clozapine treatment<sup>24, 25</sup> may also be relevant to understanding drug effects on glucose metabolism. This could independent of changes in adiposity. Increases in noradrenaline and adrenaline could be linked to reduce beta-cell function and increase glucose release from hepatocytes.

In the current study, our findings showed that patients prescribed with aripiprazole has no increased risk of being co-prescribed with either antihypertensive drugs, antidiabetic drugs or lipid lowering drugs. This is in concordance with the result of a systematic review, assessing the risk for weight gain, dyslipidemia, glucose abnormalities, and diabetes mellitus in adult patients receiving treatment with

aripiprazole<sup>26</sup>. Twenty-two peer-reviewed articles were included in the systematic review. Compared with other atypical antipsychotics, aripiprazole was either less likely to have an impact or had a comparable impact on weight gain and dyslipidemia. In addition, there was less risk of diabetes mellitus with aripiprazole compared with most other atypical antipsychotic agents<sup>26</sup>. In a case series study, 31 patients were followed up with extensive evaluation of metabolic syndrome for three months. The results showed that there was a significant reduction in fasting glucose, fasting insulin, insulin resistance index, and serum lipids levels (cholesterol, triglycerides, low-density lipoprotein (LDL), LDL/HDL, Chol/HDL, and non-HDL cholesterol)<sup>27</sup>.

There are several limitations in the current study. First, the pre-existing medical conditions were not determined for the study subjects which could bias the result. Second, the diagnosis of the study subjects was not available in the Medication Management and Use System Ascribe (Version 10.09) database. The risk of metabolic syndrome could be differed between types of mental illnesses. Lastly, there are many other risk factors of metabolic syndrome were not included in the current study such as life style, smoking, alcohol consumption, diet habit and family history. These are important and potential confounders for the study.

## Conclusion

The risk of metabolic syndrome is high among patients prescribed with second generation antipsychotic. However, the risk could be varied between individual drugs. The odds of having hypertension, diabetes mellitus and dyslipidemia were higher among patients prescribed with quetiapine or clozapine as compared to aripiprazole. As

such, it is important to monitor the risk of secondary metabolic syndrome in patients prescribed with atypical antipsychotic.

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