



## Effect of atypical antipsychotics on blood glucose levels and HbA1c in patients of schizophrenia and bipolar disorder.

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### Article received on:

11/06/2020

### Accepted for publication:

11/08/2020

**ABSTRACT... Objectives:** To evaluate the effect of atypical antipsychotics on serum glucose levels and HbA1C in patients of schizophrenia and bipolar disorder. **Study Design:** Quasi-experimental study. **Setting:** Department of Neurology and Sir CJ Institute of Psychiatry LUMHS Jamshoro/Hyderabad. **Period:** Dec 2018-Dec 2019. **Material & Methods:** Total 360 participants of age more than 15 years of either gender presenting with psychiatric illness i.e. schizophrenia and bipolar disorder and prescribed same brand of antipsychotic drugs were included in the study. Fasting blood glucose (FBS), random blood glucose (RBS) and glycosylated hemoglobin (HbA1c) were measured at baseline and 6<sup>th</sup> months after treatment with atypical antipsychotic agents. SPSS version 23 was used to analyze data. **Results:** A total of 360 patients were enrolled in the study duration, among them 338 patients were followed up till 6 months, while 22 patients were lost to follow up. The mean age of the study sample was reported as 39.33±8.83 years. At baseline mean FBS, RBS and HbA1c were reported as 92.52±9 mg/dl, 143.21±14.91, 5.83±0.37 which significantly increase after treatment with antipsychotics at 6 months (p<0.05). About 23.6% developed diabetes mellitus and 21.3% developed hyperglycemia at the end of 6 months. **Conclusion:** Non-diabetic treatment naïve schizophrenia and bipolar disorders patients have higher chances developing side-effects on the glucose regulations after initiation of antipsychotic therapy. Overall, the early identification and diagnosis of antipsychotic-induced diabetes mellitus and hyperglycemia requires proper evaluation, reporting, and physician and patient awareness.

**Key words:** Atypical Antipsychotics, Bipolar Disorder, Diabetes Mellitus, Glucose Levels, Glycosylated Hemoglobin, Hyperglycemia, Schizophrenia.

**Article Citation:** Bughio AH, Ansari SJ, Kumar R, Sheikh MH, Devrajani T. Effect of atypical antipsychotics on blood glucose levels and hba1c in patients of schizophrenia and bipolar disorder. Professional Med J 2021; 28(2):158-164. <https://doi.org/10.29309/TPMJ/2021.28.02.5189>

## INTRODUCTION

Antipsychotic drugs are treatments for symptoms of psychosis such as perceptual disturbance, delusions, disorganized behavior and the disorder of thought. Psychosis is prevalent in bipolar disorder and schizophrenia, as well as in dementia, major depressive disorder and few personality disorders.<sup>1</sup>

In Pakistan recently there has been a rise in the use of antipsychotics, particularly atypical antipsychotics, with little polypharmacy. The overall use of antipsychotics increased by 4.3 fold in Pakistan. Olanzapine and risperidone were the most prescribed antipsychotics.<sup>2</sup> The use of atypical antipsychotics is associated with

the severe disruption in whole blood glucose and lipid metabolism. This partially occurs through central nervous system and result in impaired insulin action through brain.<sup>3</sup> Unfortunately, several studies have linked the patient on antipsychotic treatment with the occurrence of insulin resistance, impaired glucose tolerance and type 2 diabetes<sup>1,4,5</sup> but the cause behind this correlation is not established. Research suggested that schizophrenia patients had higher diabetes levels than the normal population.<sup>6,7</sup> It indicates that genetic or environmental factors may also be essential to psychiatric patients in increasing insulin resistance.<sup>8,9</sup>

Patients with schizophrenia are more likely than

the general population to develop diabetes, which contributes to a high risk of cardiovascular complications. Individuals with schizophrenia are two to three times more likely to die from cardiovascular disease than the general population.<sup>9,10</sup> The risk of diabetes and hence cardiovascular disease is particularly increased by some of the new atypical antipsychotic drugs.<sup>11</sup> Therefore, the aim of current study is to see the effect of atypical antipsychotics on HbA1c and serum glucose level of patients with schizophrenia and bipolar disorder.

## MATERIAL & METHODS

It was a quasi-experimental study conducted at Sir C. J Institute of Psychiatry Hyderabad from Dec 2018-Dec 2019. Sample size was estimated using Open Epi sample size calculator by taking statistics for FBS (mg/dl) at baseline as  $93.8 \pm 2.12$  and after use of antipsychotic at 6 months as  $94.5 \pm 1.77(12)$ , power of test 90% and 95% confidence level. The estimated sample size was 328 patients, by inflating the sample size by 10% for loss to follow up total 360 patients were enrolled in the study. Patients of age more than 15 years of either gender presenting with psychiatric illness i.e. schizophrenia and bipolar disorder and prescribed same brand of antipsychotic drugs (either Olanzapine, Clozapine, Quetiapine or Risperidone) were included in the study using non-probability consecutive sampling technique. Patients with known history of cardiovascular events and diabetes, lactating and pregnant females, patients on medications which likely to interrelate with antipsychotic medicines were excluded from the study.

Ethical approval was sought out before conduct of study from institutional ethical review board. Written informed consent was obtained from legally effective person for all the eligible patients. Fasting blood glucose (FBS), random blood glucose (RBS) and glycosylated haemoglobin (HbA1c) were measured at baseline and 6<sup>th</sup> months after treatment with atypical antipsychotic agents, to check whether hyperglycaemia was drug induced or not. After 6 months, FBS greater than 100 mg/dl and RBS greater than 170 mg/dl was considered as hyperglycaemia positive

whereas HbA1c more than more 6.5% were deemed as diabetes.

SPSS version 23 was used to enter and analyze data. Mean and SD were reported for all quantitative variables. Frequency and percentage were reported for all qualitative variables. Paired t-test was used to assess the mean difference in FBS, RBS and HbA1c level. Chi-square test was used to assess the association between different atypical antipsychotic drugs and hyperglycemia and diabetes mellitus.  $P < 0.05$  was taken as statistically significant.

## RESULTS

A total of 360 patients were enrolled in the study duration, among them 338 patients were followed up till 6 months, while 22 patients were lost to follow up. Therefore, analysis was carried out for 338 patients.

The mean age of the study sample was reported as  $39.33 \pm 8.83$  years ranging from 16 to 69 years. About 241 were males (71.3%) and 97 were females (28.7%). Out of 338 patients, 122 had positive family history of diabetes mellitus (36.1%).

At baseline mean FBS, RBS and HbA1c were reported as  $92.52 \pm 9$  mg/dl,  $143.21 \pm 14.91$ ,  $5.83 \pm 0.37$  which significantly increase after treatment with antipsychotics at 6 months by 6.2%, 7.6% and 4.2% respectively ( $p < 0.05$ ). The mean FBS, RBS and HbA1c were reported as  $98.27 \pm 15.88$  mg/dl,  $154.12 \pm 28.20$  and  $6.08 \pm 0.74$  at 6 months shown in Figure-1.

As compared to baseline, insignificant change was observed in FBS and RBS in quetiapine treated group at the end of 6<sup>th</sup> month ( $p > 0.05$ ), whereas HbA1c showed statistically significant increase at the end of 6<sup>th</sup> month ( $p < 0.05$ ). In clozapine, risperidone and olanzapine treated groups statistically significant changes were found in FBS, RBS and HbA1c at the end of 6<sup>th</sup> months as compared to baseline ( $p < 0.05$ ). (Table-I)

Almost half of the patients were treated with

risperidone (53%) followed by olanzapine (19.5%), quetiapine (13.9%) and clozapine (13.6%).

Overall 23.6% of the patients developed diabetes mellitus and among them patients who were treated with risperidone, 42.5% of the patients developed diabetes mellitus. There was statistically significant association between atypical antipsychotics and diabetes mellitus ( $p < 0.05$ ). (Table-II)

Overall 21.3% of the patients developed hyperglycemia and among them patients who were treated with risperidone, 38.9% of the patients developed hyperglycemia. There was statistically significant association between

atypical antipsychotics and hyperglycemia ( $p < 0.05$ ). (Table-III)

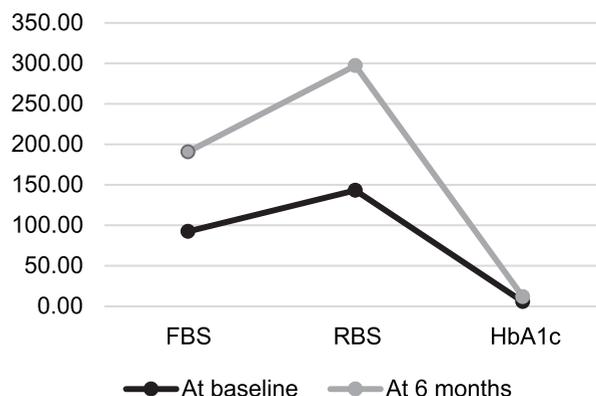


Figure-1. Mean change in FBS, RBS AND HbA1c Levels

Parameters		Quetiapine	Clozapine	Risperidone	Olanzapine
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
FBS (mg/dl)	Baseline	94.62 ± 8.59	91.09 ± 7.42	92.88 ± 9.50	91.05 ± 8.66
	6 months	91.74 ± 17.38	103.24 ± 12.00	97.54 ± 15.95	101.44 ± 15.38
	P-value	0.28	0.001	0.001	0.001
RBS (mg/dl)	Baseline	146.00 ± 13.22	145.17 ± 13.68	142.14 ± 15.96	142.77 ± 13.81
	6 months	147.30 ± 19.64	163.65 ± 26.37	150.30 ± 26.75	162.68 ± 34.60
	P-value	0.61	0.001	0.001	0.001
HbA1c (%)	Baseline	5.81 ± 0.36	5.96 ± 0.32	5.82 ± 0.40	5.81 ± 0.33
	6 months	5.91 ± 0.54	6.40 ± 0.79	5.98 ± 0.74	6.24 ± 0.78
	P-value	0.03	0.001	0.001	0.001

Table-I. Analysis of parameters in patients treated with different antipsychotics

Atypical Antipsychotics	Diabetes Mellitus		Total	P-Value
	Yes	No		
Quetiapine	6(7.5%)	41(15.9%)	47(13.9%)	0.001
Clozapine	17(21.3%)	29(11.2%)	46(13.6%)	
Risperidone	34(42.5%)	145(56.2%)	179(53%)	
Olanzapine	23 (28.8%)	43(16.7%)	66(19.5%)	

Table-II. Association between atypical antipsychotic drugs and diabetes mellitus

Atypical antipsychotics	Hyperglycemia		Total	P-value
	Yes	No		
Quetiapine	5(6.9%)	42(15.8%)	47(13.9%)	0.003
Clozapine	16(22.2%)	30(11.3%)	46(13.6%)	
Risperidone	28(38.9%)	151(56.8%)	179(53%)	
Olanzapine	23(31.9%)	43(16.2%)	66(19.5%)	

Table-III. Association between atypical antipsychotic drugs and hyperglycemia

## DISCUSSION

The risk of developing diabetes mellitus increases for schizophrenia and bipolar disorder. The reasons are multifactorial, combining specific biological pathways, genetic susceptibility, ecological factors, and antipsychotics.<sup>13</sup> In the current study we have evaluated the effect of antipsychotics on RBS, FBS and HbA1c levels of the patients with schizophrenia and bipolar disorder.

Patients seeking antipsychotic medication were diagnosed with elevated levels of blood glucose which increased over time. This finding is consistent with earlier studies that found that non-diabetic schizophrenic patients had adverse effects on glucose control after initiation of antipsychotic treatment, which can vary in severity independent of adiposity and potentially increase long-term cardiovascular risk.<sup>14</sup> In the present study results showed statistically significant increase in FBS, RBS and HbA1c level after six months of treatment with antipsychotics ( $p < 0.05$ ). This finding support the fact that treatment naive bipolar and schizophrenia patients are at 2 to 3 times more risk of developing type 2 diabetes in adults as compared to healthy population.<sup>15</sup> Another similar study showed that schizophrenia patients who were treated with various antipsychotics showed a continuous increase in fasting and post load plasma glucose levels on follow up. The mean FBS at baseline was 88.50 mg/dl which significantly increase as 102.93 mg/dl at the end of 14<sup>th</sup> week ( $p < 0.05$ ), whereas mean post load plasma glucose was 130.17 mg/dl at baseline which significantly increase as 153.02 mg/dl at the end of 14<sup>th</sup> week ( $p < 0.05$ ).<sup>16</sup>

Quetiapine is an antipsychotic medication of second generation which is associated with the incidence of diabetes mellitus and hyperglycemia.<sup>17,18</sup> Most of the hyperglycemia occurred within 3 months after initiation of treatment. It has also been noted that the risks of diabetes caused by the use of quetiapine varied insignificantly from that induced by conventional antipsychotics.<sup>19-21</sup> In the present study, the patients treated with quetiapine showed

decrease in FBS and RBS at the end of 6<sup>th</sup> month as compared to baseline, whereas HbA1c level increase at the end of 6<sup>th</sup> month. About 7.5% of the patients treated with quetiapine developed diabetes and 6.9% developed hyperglycemia at the end of 6 months. In a retrospective study, it has been found that 267 non-diabetic psychiatric patients who were treated with quetiapine 2.2% developed new-onset diabetes after 1.6 years.<sup>22</sup>

Clozapine is an antipsychotic serotonin-dopamine antagonist (SDA) but in terms of binding to serotonin and dopamine receptors, efficacy and likelihood of side effects it varies from other SDA antipsychotics.<sup>23</sup> Various studies have shown that there was a significantly higher incidence of metabolic syndrome among subjects taking clozapine than among subjects taking other antipsychotics.<sup>24</sup> The impaired blood glucose level is an important parameter for the metabolic syndrome which leads to type II diabetes mellitus development.<sup>25</sup> A study reported that over 1/3 of the participants were diagnosed with diabetes who were treated with clozapine after 5 years of follow-up therapy.<sup>26</sup> The occurrence of clozapine-induced diabetes is generally thought to occur as part of a slowly evolving metabolic syndrome. Therefore, testing of fasting blood glucose is prescribed at baseline, after one-month treatment and then every 4 to 6 months during clozapine therapy.<sup>27</sup> Several case reports identified an occurrence of hyperglycemia shortly after beginning clozapine with managed diabetes subjects.<sup>28</sup> In the present study, 21.3% developed diabetes and 22.2% developed hyperglycemia after six months of treatment with clozapine. In a meta-analysis of 47 studies it has been found that associations of hyperglycemia and diabetes with clozapine were identified most commonly followed by olanzapine.<sup>29</sup>

Olanzapine and risperidone shared the similar *in vitro* characteristics but they distinguish by virtue of their spectrum of receptor binding affinities, chemical structure, pharmacokinetics, neuropharmacology and *in vivo* neuroimaging profile.<sup>30</sup> Few studies recommend that patients treated with olanzapine showed better response as compared to risperidone.<sup>31</sup> In the present

study, the mean FBS level at baseline was 92.88 which significantly increase to 97.54 at the end of six months in patients treated with risperidone whereas in olanzapine group the mean FBS level was 91.05 at baseline which significantly increase to 101.44 at the end of six months. About 42.5% of the patients developed diabetes and 38.9% developed hyperglycemia in risperidone group whereas in olanzapine group 28.8% developed diabetes and 31.9% developed hyperglycemia at the end of six months. In a previous study it has been observed that mean FBS in risperidone versus olanzapine were 93.4 and 100.7 mg/mL at baseline, whereas at the end of 12<sup>th</sup> month the mean FBS in risperidone increased and in olanzapine decreased (108.9 vs 91.7), however there was insignificant changes was observed in FBS levels between the risperidone and olanzapine groups.<sup>30</sup> Olanzapine is now commonly used as a first-line treatment for schizophrenia, providing efficacy that is equal to or better than other antipsychotic drugs, and has less extrapyramidal symptom, which is then a stigmatizing and sometimes incapacitating side effect for the patient.<sup>16,32</sup> However, due to increasing evidence of hyperglycemic symptoms, as is also clear from our research, a prescription option now needs to be based.

Nonetheless, as is also apparent from our research, due to growing evidence of hyperglycemic consequences, a prescription option also needs to be focused on an evaluation of the potency of each medication as well as its potential to cause metabolic side effect. In fact, schizophrenia and bipolar disorder is a chronic disease requiring ongoing antipsychotic treatment, and an antipsychotic drug with less diabetes-related risk can be maintained to avoid psychotic regression and long-term degradation with least effect on glucose dysregulation.<sup>32</sup>

## CONCLUSION

Non-diabetic treatment naïve schizophrenia and bipolar disorders patients have higher chances developing side-effects on the glucose regulations after initiation of antipsychotic therapy. Overall, the early identification and diagnosis of antipsychotic-induced diabetes mellitus and

hyperglycemia requires proper evaluation, reporting, and physician and patient awareness.

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3	Rajesh Kumar	Supervision of study.	
4	M. Hassan Sheikh	Data collection and literature review.	
5	Tarachand Devrajani	Data collection and data review.	