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COMPARATIVE EFFECTS OF CLOZAPINE AND QUETIAPINE ON METABOLIC PROFILE, SERUM PROLACTIN AND QT_C INTERVAL IN TREATMENT-RESISTANT SCHIZOPHRENIA

Psychiatry

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ABSTRACT

Objective: To compare the effect of clozapine and quetiapine on metabolic parameters, serum Prolactin and QTc in patients with treatment-resistant schizophrenia (TRS).

Method: In this prospective, randomized, open label study, 40 patients (20 each in two groups) with schizophrenia (ICD 10) and fulfilling modified version of Conley and Kelly's criteria of TRS received either clozapine or quetiapine in therapeutic dose for 14 weeks after a 7-day washout period. The final mean (SD) doses were 322.1(52.50) mg/day for clozapine group and 790(30.78) mg/day for quetiapine group. Patient's weight, Body mass index (BMI), fasting blood glucose (FBS), cholesterol, triglyceride, HDL, LDL, VLDL, serum Prolactin and QTc interval on ECG were measured using standard protocol at baseline, 6 weeks, 10 weeks and 14 weeks. Two groups were compared for change in levels from baseline of various variables at 6, 10 and 14 weeks.

Results: Clozapine group had significantly greater (<0.05) rise in weight, BMI, cholesterol, triglyceride, VLDL at 6, 10 and 14 weeks and in LDL at 10 and 14 weeks than quetiapine group. Quetiapine led to significantly higher increase in QTc interval on ECG at 10 and 14 weeks than clozapine. However, no significant difference was present between two groups on change in levels of FBS, HDL and serum Prolactin.

Conclusions: Clozapine was found to be associated with higher metabolic side-effects than quetiapine. However, quetiapine was associated with greater QTc elevation than clozapine. Both the drugs were similar with respect to change in serum Prolactin level.

KEYWORDS

Clozapine, quetiapine, TRS, metabolic profile, serum Prolactin, QTc

Introduction

Clozapine has been mainstay of treatment in treatment resistant schizophrenia (TRS)[1,2]and the drug was approved for TRS by Food and Drug Administration (FDA) in 1989. However, approximately 40%-70% of neuroleptic-resistant schizophrenic patients are either non-responders or intolerant to clozapine.[3] Clozapine is also associated with significant metabolic side effects.[4]Quetiapine, synthesized by combining perlapine and fluperlapine, has structural similarity to clozapine, but with molecular discrepancies explaining the lack of agranulocytosis risk.[5] It has been found to efficacious in treatment of schizophrenia resistant to previous antipsychotics treatment.[6]An Indian study has also found that quetiapine is equally effective to clozapine in terms of improvement in negative symptoms in TRS.[7]Few studies in India have assessed the metabolic side effects associated with clozapine[8]and quetiapine[9] but no studies have been conducted on Indian population comparing metabolic side effects of clozapine and quetiapine in head on head trial in TRS. Also there is scarcity of studies assessing changes in serum Prolactin and QTc with clozapine and quetiapine on Indian population. Hence, current study was carried out to compare the metabolic side effects along with effect on serum Prolactin and QTc of clozapine and quetiapine in patients with TRS.

Materials and Methods

Patients attending the outpatient clinic or those admitted to the inpatient services of the Department of Psychiatry of a tertiary care teaching hospital in North India were considered for the study. It was a comparative, open label, prospective interventional study. For the purpose of the study, modified version of Conley and Kelly's criteria[10] of TRS was used and which is defined as: no clinical response with two different antipsychotics used separately in the dose range of 400–600mg of chlorpromazine per day or equivalents for 6 weeks; no period of good social or occupational functioning at least in last one year, and a minimum Clinical Global Impressions (CGI) Scale rating of 4 (moderately ill); Brief Psychiatric Rating Scale (BPRS) total score > 45, and a score of >4 on 2 out of 4 positive items.

Patients who had received clozapine and/or quetiapine in past; with history of seizure disorder, heart conduction defects, history of agranulocytosis or TLC <3500/mm^3, diabetes mellitus, neurological disorders, head injury, movement disorder, lactating or pregnant women, co morbid substance dependence except nicotine and caffeine, sub normal intelligence and late onset schizophrenia (after 45 years) were excluded from the study.

The trial was registered with Clinical Trial Registry, India.The principles enunciated in the Declaration of Helsinki[11] and Indian Council of Medical Research[12] were followed and study was approved by ethical review committee of the institution.

After enrolment, patients taking oral antipsychotics were given drug free/wash out period of 1 week and patients on long acting depot preparation were given drug free/wash out period of 1 month. The patients were randomly allotted to clozapine group or quetiapine group as per a computer generated random table and it was planned to enroll a minimum of 20 patients in each group. The dosages of the drugs were kept in therapeutic range of 150-450 mg/day for clozapine and 400-800 mg/day for quetiapine.[13] Clozapine was initiated at a dose of 25 mg/day in two divided doses and increased by 25 mg/day whereas quetiapine was initiated at 50 mg/day in two divided doses and increased by 50 mg/day and full efforts were made by the treating clinicians to achieve a minimum therapeutic dose in all the patients within 2 weeks of starting the treatment. After reaching the therapeutic dose, patients took same dose for a period of four weeks. At the end of 4 weeks, if the improvement was not adequate [<50% reduction in Positive And Negative Syndrome Scale (PANSS) score], then the dose of the respective drug was further increased in those patients to the maximum permissible dose and the patients were re-assessed after 4 week and 8-week. Patients were followed for duration of 14 weeks after initiation of treatment.

Any patient having serious adverse drug reaction with any of the two drugs was dropped from the study and managed as per the standard protocol followed in the department. Drugs of the standard pharmaceutical companies approved by institutional drug committee were used. Each patient's socio-demographic and clinical variables were recorded on prescribed Performa designed for the study.

Outcomes

Patient's height was measured at the time of enrolment (baseline), weight and blood pressure was measured[14] by use of standard protocols and techniques at baseline, 6 weeks, 10 weeks and 14 weeks. Body

mass index was computed as body weight (kg) divided by the square of height (m^2). BMI was calculated at baseline, 6 weeks, 10 weeks and 14 weeks. Subjects were advised to undergo laboratory testing in fasting state, but a significant range was present for time since last meal. Since, published data has supported the duration of 8 hour or more since last meal as an appropriate definition of fasting,[15] this was used as cut-off for determining fasting status. Fasting blood glucose, lipid profile and serum prolactin were measured at baseline, 6 weeks, 10 weeks and 14 weeks. ECG was done and QTc measured at baseline, 6 weeks, 10 weeks and 14 weeks. Total leucocyte count (TLC), differential leucocyte count (DLC) and absolute neutrophil count (ANC) were done weekly for patients in clozapine group and at baseline, 6 weeks, 10 weeks and 14 weeks in quetiapine group. To ensure compliance in outpatients, responsibility of giving medication was given to a family member to supervise the intake and seeing that medicine is swallowed in their presence. Caregivers were asked to show the empty strips of medicines to the treating doctor during follow- up visits.

Patient' clinical status was assessed with Brief Psychiatric Rating Scale (BPRS)[16]and Clinical Global Impressions (CGI)[17] at baseline and Positive And Negative Syndrome Scale (PANSS)[18] and Glasgow Antipsychotic Side effect rating Scale (GASS) [19] at 2 weeks, 6 weeks, 10 weeks and 14 weeks.

Statistical method

The statistical analysis included Chi-Square test for categorical variables. Quantitative data was assessed for normality using Kolmogorov-Smirnov test. Quantitative variables were assessed using the T-test. Data was analysed by using SPSS version 17.0 (Version 17.0, IBM) and it was represented in Mean and SD. Where data was skewed, non parametric test (Mann-Whitney Test) was used. Post-hoc power analysis was done using Univariate analysis of variance. Significance level was $p < 0.05$.

Results

A total of 72 patients were screened initially, out of which 19 patients were excluded due to various reasons (not fulfilling inclusion and exclusion criteria, refused to participate in study,etc). Remaining 53 patients were enrolled in the study (24 in clozapine group and 29 in quetiapine group). Subsequently, 13 patients dropped out of the study after first assessment. Out of 13 drop-outs, 1 patient in clozapine group and 5 patients in quetiapine group had dropped out owing to lack of efficacy, 3 patients (1 in clozapine group and 2 in quetiapine group) dropped out due to poor compliance, 2 patients dropped out owing to intolerability of drug (1 in each group) and 2 patients could not be contacted (1 in each group). Finally, 40 patients (20 patients in each group) completed all assessments and were included in final analysis. Patients who dropped out were comparable to patients who completed all assessments on sociodemographic, clinical variables and other parameters i.e. weight, Body mass index, FBS, cholesterol, triglyceride, HDL, LDL, VLDL, serum prolactin and QTc. 20 patients each in clozapine and quetiapine group who completed all assessments did not differ significantly on socio-demographic and clinical variables.

The baseline comparison between the two groups for weight, Body mass index, FBS, cholesterol, triglyceride, HDL, LDL, VLDL, serum prolactin and QTc revealed no statistical significance as shown in table 1.

Table 1. Comparison Between Clozapine And Quetiapine Group at baseline

Variable	Clozapine Group Mean (SD)	Quetiapine Group Mean (SD)	Significance	95% CI	
				Lower	Upper
Weight	62.22(6.62)	62.44(8.16)	0.926	-4.976	4.534
BMI	21.46(1.54)	22.03(1.61)	0.260	-1.582	0.440
FBS	91.95(7.20)	91.65(7.21)	0.896	-4.311	4.911
Cholesterol	185.35(13.66)	182.30(15.80)	0.518	-6.405	12.505
Triglyceride	143.55(13.72)	143.90(14.98)	0.939	-9.547	8.847
HDL	48.20(7.45)	48.40(7.56)	0.933	-5.004	4.604
LDL	158.75(15.54)	159.35(16.43)	0.906	-10.839	9.639
VLDL	33.15(7.02)	33.75(6.54)	0.781	-4.945	3.745
Serum Prolactin	19.40(10.46)	17.80(9.79)	0.620	-4.887	8.087
QTc	411.90(17.31)	412.65(15.05)	0.885	-11.131	9.632

Increase in weight and BMI from baseline in clozapine group was significantly higher than quetiapine at 6, 10 and 14 weeks (table 2).

Table 2. Increase in Weight from baseline among two groups across assessments

Variable	Interval	Clozapine Group Mean (SD)	Quetiapine Group Mean (SD)	Significance P value	95% CI	
					Lower	Upper
Weight	0-6 weeks	1.32(1.42)	0.37(0.28)	0.008	0.284	1.634
	0-10 weeks	2.86(2.37)	0.75(0.35)	0.001	0.991	3.226
	0-14 weeks	3.17(2.68)	1.19(0.59)	0.004	0.714	3.266
BMI	0-6 weeks	0.42(0.50)	0.15(0.89)	0.026	0.035	0.511
	0-10 weeks	1.01(0.95)	0.28(0.14)	0.003	0.288	1.181
	0-14 weeks	1.11(1.01)	0.43(0.24)	0.009	0.188	1.155

There was no statistically significant difference in change in FBS between two groups across different assessments (table 3).

Table 3.Change in FBS from baseline among two groups across assessments

Interval	Clozapine Group Mean (SD)	Quetiapine Group Mean (SD)	Significance P Value	95% CI	
				Lower	Upper
0-6 weeks	3.45(2.58)	3.15(2.06)	0.687	-1.196	1.796
0-10 weeks	6.30(3.89)	4.90(2.95)	0.208	-0.813	3.613
0-14 weeks	9.70(4.68)	7.40(3.05)	0.073	-0.229	4.829

As can be seen from table 4, none of the 40 patients fell into frank diabetes range (>126 mg %) across four assessments, however two patients had impaired glucose tolerance (110-125 mg %) in clozapine group in comparison to one patient in quetiapine group at 10 and 14 weeks.

Table 4. Change in Fasting Blood Sugar across assessments

FBS (mg%)	Baseline		6 Weeks		10 Weeks		14 Weeks	
	Clozapine Group n(%)	Quetiapine Group n(%)	Clozapine Group n(%)	Quetiapine Group n(%)	Clozapine Group n(%)	Quetiapine Group n(%)	Clozapine Group n(%)	Quetiapine Group n(%)
<110	20(100)	20(100)	19(95)	19(95)	18(90)	19(95)	18(90)	19(95)
110-125	0(0)	0(0)	1(5)	1(5)	2(10)	1(5)	2(10)	1(5)
≥126	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
p Value	1.000		1.000		0.548		0.548	

In this study, there was increase in cholesterol, triglyceride, LDL, VLDL levels at 6, 10 and 14 weeks when compared to baseline in both the groups (table 5). Rise in cholesterol, triglyceride and VLDL levels in clozapine group was significantly greater in clozapine group than quetiapine group at 6, 10 and 14 weeks and rise in LDL was significantly higher in clozapine group at 10 and 14 weeks.However there was no significant difference between two groups in reduction in HDL levels across assessments.

Table 5. Change in lipid profile from baseline among two groups across assessments

Variable	Interval	Clozapine Group Mean (SD)	Quetiapine Group Mean (SD)	Significance P value	95% CI	
					Lower	Upper
Cholesterol	0-6 weeks	6.75 (2.67)	4.10(2.47)	0.002	1.003	4.297
	0-10 weeks	11.00 (3.96)	6.60(3.70)	0.001	1.945	6.855
	0-14 weeks	14.50 (5.38)	9.30(4.61)	0.002	1.994	8.406

Triglyceride	0-6 weeks	14.90 (7.25)	5.40(4.02)	<0.001	5.711	13.289
	0-10 weeks	24.20 (10.60)	9.20(5.24)	<0.001	9.584	20.416
	0-14 weeks	32.30 (13.36)	12.55 (6.68)	<0.001	12.805	26.495
HDL	0-6 weeks	-0.95 (1.88)	-0.40 (1.43)	0.304	-0.518	1.618
	0-10 weeks	-1.80 (2.50)	-0.90 (1.92)	0.210	-0.528	2.328
	0-14 weeks	-2.60 (3.91)	-1.55 (2.82)	0.336	-1.133	3.233
LDL	0-6 weeks	8.80 (5.43)	6.10 (4.83)	0.105	-0.592	5.992
	0-10 weeks	14.15 (7.31)	9.45 (6.42)	0.037	0.295	9.105
	0-14 weeks	19.95 (9.94)	13.00 (8.02)	0.020	1.167	12.733
VLDL	0-6 weeks	3.25 (1.21)	2.00 (1.12)	0.002	0.503	1.997
	0-10 weeks	6.72 (2.92)	4.05 (1.99)	0.002	1.044	4.256
	0-14 weeks	9.85 (4.22)	6.20 (2.35)	0.002	1.442	5.858

As it is depicted in table 6, 10 (50%) patients in clozapine groups had borderline high (upto 239 mg %) levels of cholesterol in comparison to 6 patients in quetiapine group at end of study. However, none of the patient had high (≥ 240 mg %) levels of cholesterol.

Table 6.Cholesterol levels among two groups across assessments

Cholesterol (mg%)	Baseline		6 Weeks		10 Weeks		14 Weeks	
	Clozapine Group n(%)	Quetiapine Group n(%)	Clozapine Group n(%)	Quetiapine Group n(%)	Clozapine Group n(%)	Quetiapine Group n(%)	Clozapine Group n(%)	Quetiapine Group n(%)
<200	17(85)	17(85)	15(75)	17(85)	10(50)	15(75)	10(50)	14 (70)
200-239	3(15)	3(15)	5(25)	3(15)	10(50)	5(25)	10(50)	6(30)
≥240	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
p Value	1.000	0.429	0.102	0.197				

There was no statistically significant difference in two groups in change in serum prolactin levels at 6, 10 and 14 weeks from baseline (table 7)In present study, 6 patients in each group had prolactin levels higher than normal levels (0-20 ng/dl for male and 0-25ng/dl for female20) at baseline. At 14 weeks, none of the patients in both the groups had prolactin levels higher than the normal limit.

Table 7. Change in Serum Prolactin from baseline among two groups across assessments

Interval	Clozapine Group Mean (SD)	Quetiapine Group Mean (SD)	Significance P Value	95% CI	
				Lower	Upper
0-6 Weeks	3.15(3.13)	3.25(3.64)	0.926	-2.274	2.074
0-10 weeks	5.05(5.94)	4.50(4.99)	0.753	-2.962	4.062
0-14 weeks	7.35(7.55)	6.20(6.05)	0.598	-3.229	5.529

Table 8 showed that there was decrease in QTc interval in clozapine group at 6, 10 and 14 weeks when compared to baseline and increase in quetiapine group at 6, 10 and 14 weeks when compared to baseline and there was statistically significant difference between two groups across different assessments.

Table 8. Change in QTcfrom baseline among two groups across assessments

Interval	Clozapine Group Mean (SD)	Quetiapine Group Mean (SD)	Significance P Value	95% CI	
				Lower	Upper
0-6 Weeks	-0.80(3.32)	2.50(1.79)	0.001	1.593	5.024
0-10 weeks	-0.95(4.65)	4.10(2.07)	<0.001	2.711	7.390
0-14 weeks	-1.10(6.58)	6.25(2.81)	<0.001	4.058	10.642

Discussion

The present study is the first study in Indian population to compare the effect of quetiapine and clozapine on metabolic profile, serum prolactin and QTc interval in patients with Treatment Resistant Schizophrenia (TRS). It is a comparative, randomized, open label, prospective study. In this study all components of lipid profile (cholesterol, triglyceride, HDL, VLDL, LDL) were measured which has not been done in earlier studies.

Weight gain and associated metabolic problems are regarded as the major issues associated with new antipsychotic drugs.[21] Direct appetite stimulation by effect of drugs on brain areas involved in feeding control, and endocrine effects of the antipsychotics drugs are the mechanism proposed for development of metabolic changes with atypical antipsychotics. Experimental and clinical research has shown that the blockade of adrenergic, muscarinic, serotonergic (5HT1B, 2A, 2C), dopaminergic (D1–5), and histaminergic (H1) receptors increases appetite.[22,23]

In present study, clozapine led to significantly greater weight gain and increase in BMI than quetiapine. Mean (±SD) increase at 14 weeks in clozapine and quetiapine group was 3.17 (±2.68) Kg and 1.19 (±0.59) Kg respectively. This finding is consistent with findings of two metaanalysis which reported that both clozapine and quetiapine are associated with weight gain and clozapine causes greater weight gain than quetiapine.[21,24] Mean (±SD) increase in CATIE 3 trials in clozapine and quetiapine group was 3.98 (±10.96)Kg and 0.31 (±8.61) Kg respectively.[25]

Clozapine led to greater increase in FBS than quetiapine, however difference between two groups was not statistically significant. Mean (±SD) increase in FBS at 14 weeks from baseline was 9.70 (±4.68) mg/dl in clozapine group and 7.40 (±3.05) mg/dl in quetiapine group. At the end of 14 weeks, 2 patients (10%) in clozapine group and 1 patient (5%) in quetiapine group had impaired glucose tolerance none of the patients had levels in diabetic range. Mean (±SD) increase in CATIE 3 trials in clozapine and quetiapine group was 9.0 (±34.0) mg/dl and 9.9 (±51.4) mg/dl respectively.[25] These findings are similar to those in a metaanalysis of studies which reported that olanzapine and clozapine produced greatest increase in blood glucose levels followed by quetiapine and risperidone and explained that 'change in glucose levels' may be somewhat 'weaker' than the other metabolic outcomes because glucose changes will be more affected in the long term.[24]

Clozapine led to significantly greater elevation in cholesterol than quetiapine group and more number of patients in clozapine group had elevated levels than quetiapine group. In CATIE 2 trials also, clozapine led to mean (±SD) change of 7.3 (±4.6) mg/dl from baseline and quetiapine lead to mean (±SD) change of -13.0 (±6.8) mg/dl from baseline, however difference was not statistically significant.[26] A metaanalysis has reported that clozapine show more elevation in cholesterol levels than quetiapine.[24]

Increase in triglyceride levels was significantly greater in clozapine group (32.30 mg/dl) than quetiapine group (12.55 mg/dl) in our study is in concordance to CATIE 3 trial which reported of 13.9 mg/dl and 55.5 mg/dl in quetiapine and clozapine group respectively.[25] Relatively higher changes could be due to long duration of the study. In CATIE 1 trial, increase in triglyceride levels at 3 months in quetiapine group was 11.9 mg/dl.[27]

However, no statistical difference was present for change in HDL levels from baseline to different assessments between two groups. Mean reduction in quetiapine and clozapine group was 1.55 mg/dl and

2.60 mg/dl respectively at 14 weeks. Mean reduction of 1 mg/dl in HDL levels was found in quetiapine group in CATIE 1 trial.[27]

Clozapine led to significantly greater increase in LDL and VLDL levels than quetiapine group. In another trials also, clozapine and quetiapine have been found to increase levels of LDL and VLDL, however there is no head to head trials of these two drugs. [28,29]

The present study also measured the levels of prolactin as prolactin increase is generally associated with several side effects such as amenorrhoea, galactorrhoea, sexual dysfunction, and osteoporosis; a possible association with breast cancer has also been discussed, but the link is not proven.[21]Both drugs reduced levels of serum prolactin, however no significant difference was present between two groups and at the endpoint, levels of serum prolactin of all patients reached within the normal limit. Patients in our study were taking other antipsychotics before recruitment, which might have led to raised prolactin levels at baseline. Although washout period of 1 week was given before baseline assessment, it might not be sufficient for prolactin levels to reach normal levels as studies have reported that it may take upto 3 weeks to return to normal levels.[30]This could be a cause for subsequent reduction with clozapine and quetiapine during study period. These findings are consistent with CATIE 2 and CATIE 3 trials [Mean (±SD) change in clozapine and quetiapine was 9.8 (±15.0) ng/ml and 1.3 (±25.7) ng/ml respectively] where both clozapine and quetiapine led to decrease in serum prolactin levels.[26,25] A recent metaanalysis has also reported that quetiapine did not cause significantly increase in prolactin concentrations compared with placebo, however clozapine was not included in this analysis.[21]

In present study, QTc was consistently increased from baseline to all assessments in quetiapine group whereas no such significant change was seen in clozapine group and difference between two groups was significant. In present study, mean (±SD) change in QTc at 14 weeks from baseline was 6.25 (±2.81) msec and -1.10 (±6.58) msec in quetiapine and clozapine group respectively which is consistent with CATIE trials.[25,31]

To conclude, clozapine was associated with greater metabolic side-effects than quetiapine and its use should be preferably discouraged in patients with deranged metabolic profile. Also physical examination and laboratory investigations for metabolic parameters should be done at baseline and at regular intervals. Quetiapine led to greater increase in QTc than clozapine, hence regular ECG monitoring is needed at baseline and subsequent dose escalations. Both drugs did not lead to any significant increase in serum prolactin levels. However, post-hoc analysis showed that study had inadequate power to detect difference between two groups for FBS, HDL and serum prolactin and it might have led to lack of significant difference between two groups on these variables. Also, this study was conducted at a single site and had smaller sample size which limits its generalizability. So, further multi-centric studies with greater sample size and longer duration of study should be carried out.

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