

COMPARISON OF EFFECTS OF OLANZAPINE AND RISPERIDONE ON BODY MASS INDEX AND BLOOD SUGAR LEVEL IN SCHIZOPHRENIC PATIENTS

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Abstract : Schizophrenia is one of the most debilitating disorders with devastating effects on its victims and their families. Atypical antipsychotics (AAPs) because of their superior efficacy, reduced side effects, & better compliance, have rapidly become the mainstay of treatment. But, because of paucity of research & literature on the long-term metabolic side effect profile of these AAPs in Indian setup, this prospective study has been carried out to compare the effects of olanzapine & risperidone on body weight, body mass index, & blood sugar level in schizophrenic patients.

Among 60 newly diagnosed DSM-IV patients of schizophrenia enrolled, it was observed that mean body weight & BMI were significantly increased from baseline to 6 & 12 weeks in both olanzapine (n=30) & risperidone groups (n=30) (P<0.001). Also, mean blood sugar was found to be significantly elevated after 6 & 12 weeks of treatment with olanzapine (P<0.001) but not in risperidone group.

Thus, the present study underscores the need for baseline and six weekly monitoring of body weight and blood glucose in routine clinical practice with AAPs.

Key words : *Schizophrenia* *olanzapine* *risperidone*
body mass index blood sugar

INTRODUCTION

Schizophrenia is a disturbance that last for six months or longer, including at least one month of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms.

It is one of the most debilitating psychiatric disorders with devastating effects on both its victims and their families. Furthermore, it extracts enormous economic cost from the society (1).

Till recent times, conventional

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antipsychotic drugs dominated the treatment of schizophrenia. But, later, it was widely recognized that the key pharmacological property of all neuroleptics i.e. their ability to block dopamine D₂ receptors and this action has been proved to be responsible not only for the antipsychotic efficacy but also for most of their undesirable side effects. Therefore, the well established effectiveness of these drugs came to closing stages (1).

Therefore, with the introduction of atypical antipsychotics (AAPs) like olanzapine and risperidone, it became possible to exploit the dual action on serotonin as well as dopamine, which has resulted in greatly increased compliance by minimizing the extrapyramidal side effects (1, 2).

Thus, because of their superior efficacy, reduced side effects, and prospects of better compliance, they have rapidly become the mainstay of treatment and the first line drugs for the treatment of schizophrenia irrespective of its stages (1, 3, 4, 5).

However, it has been gradually noticed that these AAPs are not absolutely free from side effects as once thought. Even after almost a decade of use of AAPs, little research and literature are available illustrating the long-term metabolic side effect profile of these AAPs in Indian population.

Although, many studies have already been done comparing the efficacy and the side effect profile of olanzapine and risperidone in non-Indian population, the unique side effect profile of these drugs is still uncovered in Indian setup, like possible association with increase in weight, body

mass index and blood sugar level (6, 7, 8).

Because of paucity of research and literature illustrating the long-term metabolic side effect profile of these AAPs in Indian setup, this prospective clinical trial has been carried out to compare the effects of olanzapine and risperidone on body weight, body mass index, and blood sugar level in schizophrenic patients.

Aims and objectives

To compare the effects of olanzapine and risperidone on body weight, body mass index and blood sugar level in patients of schizophrenia.

MATERIAL AND METHODS

The present study was approved earlier by the Institutional Ethics Committee of Indira Gandhi Government Medical College, Nagpur. The study was carried out on 60 patients from July 2005 to July 2006. Patients were recruited from Psychiatry OPD, Indira Gandhi Government Medical College, Nagpur.

Inclusion criteria

Newly diagnosed DSM-IV patients of schizophrenia

Patients of either sex between 18–60 years of age.

Exclusion criteria

Patients with history of taking antipsychotics before study.

Patients with history of diabetes mellitus.

Patients taking antidiabetic treatment.

Patients with documented cardiovascular diseases.

At the level of significance $\alpha = 5\%$ and power 90%, the sample size of 30 for each group was calculated using pilot study data of 10 patients in each group. Drugs which were given :

- A. Tablet olanzapine (Oleanz) 5 mg two times a day orally.
- B. Tablet risperidone (Sizodon) 3 mg two times a day orally.

Study design

A prospective, randomized, parallel, open label clinical trial was conducted in psychiatry OPD and department of pharmacology IGGMC, Nagpur. Patients attending psychiatry OPD were screened by the psychiatrist. Those found meeting the inclusion criteria were briefed about the trial. Patient Information Sheets were given to all prospective participants. Written informed consent was obtained from each patient before enrollment in the study by explaining the nature of the study to the patients and their care taker or family members. They were divided randomly into two groups, Group A (n=30) received tablet olanzapine for a period of 12 weeks and Group B (n=30) received tablet risperidone for a period of 12 weeks.

After initial screening, the data regarding age, sex, past medical history, family history, physical examination and clinical examination was recorded in the case report

form. Patient's weight and height was determined at the time of enrollment in the study. Fasting blood sugar was estimated at baseline.

After baseline investigations, patients were given either tablet olanzapine or tablet risperidone according to their enrollment in group A and group B for a period of 12 weeks. All the patients were asked to report in Psychiatry OPD after 6 and 12 weeks for follow up. All the investigations were again repeated at 6 and 12 weeks.

Psychiatric evaluation of the patients was done by the psychiatrist every 15 days. No other psychiatric drug therapy was given to patients during the study period except rescue medications like tablet/injection lorazepam, tablet trihexyphenidyl, tablet clonazepam were available for managing emergency and side effects if any. General clinical safety was monitored by vigilant follow-up of patients for treatment emergent adverse events, if any and recorded in the case report form. Body Mass Index was calculated by formula (9)

$$\text{Body Mass Index} = \frac{\text{Body Weight (in kg)}}{\text{Height}^2 \text{ (in m}^2\text{)}}$$

Fasting blood sugar was quantitatively estimated by GOD/POD (10) method using semi autoanalyser, TRANSASIA, ERBA, CHEM-5-PLUS.

Statistical analysis of data

Mean values of change in body weight, BMI, and BSL (at baseline, 6 weeks, and 12 weeks) were compared between two groups by using **Unpaired 't' test** and in the groups

by **Paired 't' test**. $P < 0.05$ was considered as statistically significant in all analysis.

Abbreviations : No./n – Number, SEM – Standard error of mean, BW – Body weight, BMI – Body Mass Index, BSL – Blood sugar level.

OBSERVATIONS AND RESULTS

Observations and results of the present study are as follows :

Table I shows demographic characteristics of study patients at baseline. Altogether 60 patients, meeting the inclusion criteria were included in the study. Both the groups were comparable without statistically significant difference at baseline.

As shown in Table II, there was no statistically significant difference between

TABLE I: Demographic characteristics of schizophrenic patients.

Groups	Age (years)	Sex	
		Male	Female
Olanzapine (n=30)	25.30±0.823	11	19
Risperidone (n=30)	26.63±0.946	14	16

Values are given as Mean±S.E.M. where appropriate.

TABLE II: Baseline parameters of schizophrenic patients.

Parameters	Olanzapine (n=30)	Risperidone (n=30)
BW (kg)	51.03±1.412	53.47±1.780
BMI (kg/m ²)	19.43±0.533	22.18±0.780*
BSL (mg/dl)	87.30±1.793	86.90±2.039

Values are given as Mean±S.E.M., * $P < 0.05$ versus olanzapine.

olanzapine and risperidone groups in body weight and fasting blood sugar at baseline, except BMI, which was higher in risperidone group ($P < 0.05$).

Table III shows the data for changes in bodyweight, BMI & BSL overtime in olanzapine group. It was observed that mean bodyweight, BMI & blood sugar were significantly increased from baseline to 6 and 12 weeks in olanzapine group ($P < 0.001$).

As shown in Table IV mean bodyweight and BMI were significantly increased from baseline to 6 and 12 weeks in risperidone

TABLE III: Effects of olanzapine on body weight, body mass index & blood sugar after 6 and 12 weeks.

Parameters	Olanzapine (n=30)		
	Baseline	6 week	12 week
BW (kg)	51.03±1.412	52.80±1.440***	55.70±1.410***
BMI (kg/m ²)	19.43±0.533	20.11±0.552***	21.23±0.560***
BSL (mg/dl)	87.30±1.793	94.63±1.830***	104.73±1.850***

Values are given as Mean±S.E.M., *** $P < 0.001$ versus baseline.

TABLE IV: Effects of risperidone on body weight, body mass index & blood sugar after 6 and 12 weeks.

Parameters	Risperidone (n=30)		
	Baseline	6 week	12 week
BW (kg)	53.47±1.780	54.63±1.780***	55.67±1.784***
BMI (kg/m ²)	22.18±0.780	22.66±0.800***	23.08±0.800***
BSL (mg/dl)	86.90±2.039	87.20±1.783	87.93±1.720

Values are given as Mean±S.E.M., *** $P < 0.001$ versus baseline.

group ($P<0.001$) but no statistically significant difference was found in increase in mean blood sugar level after 6 and 12 weeks from baseline in risperidone group.

Table V and Figure 1 shows mean changes in various parameters from baseline to 6 weeks and from baseline to 12 weeks in olanzapine and risperidone group. It was observed that mean changes in body weight, BMI ($P<0.05$ at 6 weeks and $P<0.001$ at 12 weeks) & blood sugar level ($P<0.001$), at 6 week and 12 weeks from baseline were statistically significant in olanzapine group when compared to changes at 6 and 12 weeks in risperidone group.

TABLE V: Changes in various parameters from baseline at 6 weeks in olanzapine and risperidone groups.

Parameters	Change from baseline at 6 weeks	
	Olanzapine (n=30)	Risperidone (n=30)
BW (kg)	1.77±0.157*	1.17±0.240
BMI (kg/m ²)	0.68±0.059*	0.48±0.097
BSL (mg/dl)	7.33±0.569***	0.30±0.699

Values are given as Mean±S.E.M., * $P<0.05$ versus risperidone, *** $P<0.001$ versus risperidone.

TABLE VI: Changes in various parameters from baseline at 12 weeks in olanzapine and risperidone groups.

Parameters	Change from baseline at 12 weeks	
	Olanzapine (n=30)	Risperidone (n=30)
BW (kg)	4.67±0.193***	2.20±0.246
BMI (kg/m ²)	1.80±0.090***	0.90±0.101
BSL (mg/dl)	17.43±1.316***	1.03±0.652

Values are given as Mean±S.E.M., *** $P<0.001$ versus risperidone.

DISCUSSION

Although newer AAPs, like olanzapine and risperidone are the drugs of first choice for schizophrenia because of improvement in negative symptoms and lack of extrapyramidal side effects, (1, 3, 4) by and large, this is not true to the extent that they are absolutely free from side effects. Probably, they may have certain effects on various metabolic parameters which in turn may cause morbidity and affect the drug compliance. Therefore, the present study is highlighting these probable and uncovered issues about AAPs in Indian setup. A total of 60 newly diagnosed patients of schizophrenia based on DSM-IV diagnostic criteria of schizophrenia were included in the study. Both olanzapine and risperidone groups were comparable in age, sex and baseline parameters.

In the present study, olanzapine and risperidone both were associated with significantly elevated body weight and BMI at 6 and 12 weeks.

Allison et al. (11) observed that olanzapine was associated with weight gain of 4.15 kg and risperidone with weight gain of 2.10 kg at 10 weeks from baseline. Conley et al. (12) in a 8 week trial observed mean weight gain of 3.26 kg in olanzapine group and 1.54 kg in risperidone group. Also mean BMI increase was 1.1 kg/m² in olanzapine group and 0.5 kg/m² in risperidone group. Ganguli et al. (8), Garyfallos et al. (2003) (13), Volavka et al. (14), Bobes et al. (15), Breier et al. (16), and Treuer et al. (17) also observed significant weight gain and "Body mass index (BMI) increase after treatment with olanzapine and risperidone. The results

of present study are comparable with these studies.

In the present study, weight gain was estimated at 6 and 12 weeks as there were many reports for this time interval (11, 12, 13, 14). However, estimated weight gain while patients are taking a drug for longer period would be expected to be substantially higher.

The precise mechanism weight gain due to AAPs is not clearly understood at present. However, relative receptor affinity of AAPs for dopamine, serotonergic, and histamine receptors that could lead to increased eating and weight gain has been suggested (6).

Weight gain is believed to be associated with substantial increase in health risks including coronary heart disease, stroke, insulin resistance, diabetes mellitus, as well as possible adverse effects on self esteem and cost (9) and more importantly discontinuation of the treatment, which may predispose them to relapse. Weight gain, therefore, deserves a careful consideration in long term therapy.

Apart from lifestyle modification, selection of right antipsychotic agent for the right patient might minimize the impact of weight gain with antipsychotic medication. However, weight gain should never be a sole criterion for choosing one antipsychotic over another.

In the present study, mean blood sugar was also found to be significantly elevated after 6 weeks and also after 12 weeks of treatment with olanzapine. But, statistically significant increase in mean blood sugar was

not observed in patients who received risperidone.

Sernyak et al. (18) demonstrated significant association between olanzapine and diabetes mellitus, but failed to demonstrate any association between risperidone and diabetes mellitus. Lindenmayer et al. (19) in a prospective trial also observed statistically significant increase in mean blood glucose level after 8 and 12 weeks of treatment with olanzapine. But, no significant change in blood glucose was detected in risperidone group. Fuller et al. (7) and Farewell et al. (6) in their study also revealed that after one year of therapy, olanzapine use was a significant predictor of developing new onset diabetes but not risperidone. The results of the present study are consistent with these studies.

Mean increases in blood glucose in the present study were modest and remained within clinically normal ranges during 12 week of treatment with olanzapine. Also, Fuller et al. (7) and Farewell et al. (6) shown that the average time from the index date to the development of diabetes is more than 15 months.

While the exact mechanism of olanzapine induced hyperglycemia is unknown, it has been hypothesized that AAPs may cause insulin resistance.

Preliminary, emerging data suggest that the weight gain may perhaps be related to hyperglycemia (9). Therefore, increase in weight may explain some of the treatment related changes in glucose metabolism. However, it has been suggested that this may also be direct adverse effects of olanzapine

on glucose tolerance independent of the weight gain, suggesting olanzapine as significant independent risk factor for the development of diabetes (6).

However, whatever the mechanisms, increased awareness of hyperglycemia in patients taking olanzapine for long term is essential, especially those who are at greater risk for glucose intolerance and hyperglycemia.

In any case and irrespective of the fact that underlying mechanism remains to be clarified, the marked difference in the frequency of weight gain and hyperglycemia seen between olanzapine and risperidone is obvious.

Although, significant efforts have been taken to control for potential confounders, these efforts are not full-proof. Factors like patient's weight, social class, dietary habits, daily physical workout, alcoholism, smoking, and medical illnesses may have influenced the results of this analysis. However, presence of these confounding factors, in fact represent the actual psychiatric practicing scenario. Whenever atypical antipsychotics are prescribed in actual clinical setup, most of these factors are present and usually not given 'due consideration by most of the psychiatrists because of their busy schedule. Therefore, if careful attention is paid to all these factors while prescribing atypical antipsychotics, together with lifestyle modification of the patient and monitoring of possible adverse outcomes, then balance will definitely shift in favour of atypical antipsychotics, as the first line drugs for schizophrenia.

Another limitation of the present study is that the duration of twelve weeks might be relatively short which may not have been sufficient enough to allow for more changes in weight and glucose level to emerge. In addition to this, future studies may want to include design elements that will allow a focus on drug dosage as an explanatory factor for the adverse effects.

Therefore, given the concerns regarding endocrine dysregulation with AAPs, the present study underscores the need for baseline and six weekly monitoring of fasting blood glucose in routine clinical practice with AAPs in order to monitor the risk. This study also emphasizes the baseline body weight and regular follow up measurements and point out the possible importance of nutritional counseling of the patients while prescribing AAPs. Therefore, given the current enthusiasms by psychiatrist to prescribe these novel agents, the additional information regarding the relative risk of metabolic side effects of AAPs may help in selecting the appropriate agent for each patient.

Conclusions

Thus at the end of the study we reached to the conclusion that the treatment with both olanzapine and risperidone is clearly associated with significantly elevated weight gain at 6 and 12 weeks and risperidone offers advantage of being associated with significantly lower risk of weight gain compared to olanzapine. The present study also contribute to the growing evidence that olanzapine is associated with increased blood

sugar level at 6 and 12 weeks but not risperidone. So, baseline weight and regular follow-up measurements and also baseline and six weekly estimations of blood sugar

should be done in routine clinical practice while treating schizophrenic patients with olanzapine and risperidone in order to monitor the risk.

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