Efficacy and safety of antipsychotic medications in psychiatric illness

ORIGINAL ARTICLE

AN EVALUATION OF EFFICACY AND SAFETY OF ANTIPSYCHOTIC MEDICATIONS IN PATIENTS SUFFERING FROM PSYCHIATRIC ILLNESS

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ABSTRACT:

BACKGROUND: An antipsychotic agent are tranquilizing psychiatric medications primarily used for the treatment of psychosis, however the use of atypical antipsychotics has been associated with adverse drug reactions like weight gain, diabetes and abnormal lipid profile levels. Present study evaluates the efficacy and safety of haloperidol, risperidone and olanzapine in patients suffering from psychiatric illness. MATERIALS AND METHODS: The study was carried out at tertiary care teaching hospital, department of psychiatry after obtaining written informed consent from the patients. They were randomized into three groups - Group I (n=31) (haloperidol 10 mg/day, orally), Group II (n=34) (risperidone 4-6 mg/day, orally) and Group III (n=38) (olanzapine 10 mg/day, orally). Patients presenting complaints, height, weight, BMI and blood pressure were recorded at baseline, 3rd and 6th months. Data was analysed using a suitable statistical tests. RESULTS: It was observed that clinical improvement was seen in all 3 groups. Maximum improvement was seen at 2nd follow up which was 45.16%, 50% and 44.74% in group I, group II and group III respectively. Comparative analysis at the end of 3rd and 6th month showed that there was statistically significant difference (p<0.05) observed in weight and BMI. At the end of 6 months, weight and BMI levels were increased higher in olanzapine treated group which was 10.61% and 11.16% respectively. Patients treated with haloperidol showed minimum changes in weight and BMI. CONCLUSION: Haloperidol, risperidone and olanzapine having a similar efficacy in controlling clinical symptoms, however improvement rate is higher with olanzapine treatment. Typical antipsychotic agents are associated with less disturbances in weight and BMI levels in comparison with atypical antipsychotic agents.

Keywords: Psychiatric illnesses, olanzapine, risperidone, haloperidol

INTRODUCTION

Psychiatric illness is a psychological pattern, potentially reflected in behavior, that is generally associated with distress or disability and which is not considered part of normal development.1 Worldwide about 450 million people are estimated to be suffering from neuropsychiatric illness with 10 % prevalence in adult population.2 In India the prevalence of psychiatric illness are reported to be 58 to 73 per 1000 population as per different studies. Although several non pharmacological treatment options are available e.g. cognitive behavioral therapy, psychoanalysis, systemic therapy or family therapy, counseling (professional) and co-counseling (between peers), psychoeducation programs, electroconvulsive therapy (ECT) and psychosurgery but pharmacological treatments are the most effective evidence based treatment in psychiatric illness. Antianxiety, antidepressants, mood stabilizers and antipsychotic medications are used for the treatment of various psychiatric illness. Despite the different conventional medications there may be considerable overlap in the disorders for which they are actually indicated, and there may also be off-label use of these medications.3 An antipsychotic agents are tranquilizing psychiatric medications primarily used for the treatment of psychosis, particularly in schizophrenia and bipolar disorder. In the past 15 years, several other atypical antipsychotic medications have been approved to overcome extrapyramidal side effects associated with the use of typical antipsychotics at clinically effective doses. Despite these benefits, the use of atypical antipsychotics has also been associated with adverse drug reactions like weight gain, diabetes and abnormal lipid profile. Weight gain and abdominal obesity are important risk factors for insulin resistance and dyslipidemia. It was hypothesized that weight gain was an important cause of antipsychotic related metabolic

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disorder until it was discovered that some atypical antipsychotic agents like olanzapine and clozapine can increase insulin resistance and triglyceride levels without associated weight gain, while some atypical antipsychotic agents may have more direct adverse effects on glucose metabolism independently of any effects on body weight.  
Efficacy of these antipsychotic medications is still a debatable area. Various studies on efficacy of antipsychotics have been done showing no significant differences in the effects produced by them. Civil Hospital, Ahmedabad (CHA) is a tertiary care teaching hospital with 1800 beds with daily turnover of around 2000 outdoor patients.

MATERIALS AND METHODS
The current study was carried out at Civil Hospital, Ahmedabad, a tertiary care teaching hospital attached to B. J. Medical College over a period of 18 months with effect from October 2010 to April 2012 after obtaining an approval of Institutional Ethics Committee, permission from Medical Superintendent and Head of the Department of Psychiatry. An observational, continuous, prospective, single centre study was carried out in patients prescribed with antipsychotic medications enrolled at Department of Psychiatry, Civil Hospital, Ahmedabad. Patients ageing ≥ 18 years, with either gender reporting to the psychiatry outpatient department or admitted in psychiatric ward of Civil Hospital, Ahmedabad and who are diagnosed as having psychotic disorder as well as prescribed antipsychotic drugs (either haloperidol, risperidone, or olanzapine) with patients/guardians who are willing to give informed consent were included in the study. Pregnant or lactating female patients, taking other drugs for some chronic diseases and patient/guardians who are not willing to give informed consent were excluded from study.

A total of 116 patients were enrolled and divided randomly in three groups as: a) Group I, haloperidol (10mg/day) (n=36) b) Group II, risperidone (4-6 mg/day) (n=40) c) Group III, olanzapine (10 mg/day) (n=38) treated group.

Symptomatic evaluation
Out of total 103 patients included in the study, it was observed that sleeplessness (46.60%), selftalking (42.72%) and hallucinations(41.74%) were the most common symptoms followed by suspiciousness (28.16%), irrelavent talking (24.27%) and fearfulness (14.56%) (Figure 1).

Clinical improvement was assessed as a time of decrease in presenting complaints. It was revealed from the study that there was improvement in the presenting complaints in all patients of 3 groups. Maximum improvement was seen at 2nd follow up which was 45.16%, 50% and 44.74% in group I, group II and group III respectively. The comparative analysis showed that at 1st and 2nd follow up improvement was higher in group III while at 3rd, 4th and 5th follow up higher improvement was seen in group I while 100% improvement was seen till all patients reached 6th follow up (Figure 2).

Weight, BMI and Blood Pressure
It was observed that weight, BMI, Systolic and diastolic blood pressure were comparable and there was no statistical significant difference observed in above mentioned parameters between all three groups at baseline level. It was observed from present study that in group I, there were statistically significant changes observed at 3 months and 6 month in body weight (p<0.05) and BMI(p<0.05) as compared to baseline (Table 1) while no statistical significant change observed in systolic and diastolic blood pressure. In risperidone (4-6 mg/day) treated group.

\[
\text{BMI} = \frac{\text{Weight}}{(\text{Height})^2}
\]

Blood pressure was measured as per guidelines of American Heart Association Council on High Blood Pressure Research and recorded in millimeter of mercury. The data collected was compiled, entered in Microsoft Excel spreadsheet 2007 and analyzed. p value less than 0.05 were considered to be statistically significant.

RESULTS
The aim of the study was to evaluate the efficacy and safety of antipsychotic medications in patients diagnosed as suffering from psychiatric disorders. A total of 116 patients were enrolled during study period, out of these, 103 patients were followed up every month for 6 months while 13 patients were lost to follow up and hence, analysis was carried out for 103 patients. Patients were categorized into three groups: a) Group I, haloperidol (10mg/day) (n=31) b) Group II, risperidone (4-6 mg/day) (n=34) c) Group III, olanzapine (10 mg/day) (n=38) treated group.

\[
\text{BMI} = \frac{\text{Weight}}{(\text{Height})^2}
\]
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Table 1: Analysis of metabolic parameters in patients treated with antipsychotic medications (n=103)

<table>
<thead>
<tr>
<th>Metabolic parameters</th>
<th>Haloperidol (10 mg/day)</th>
<th>Risperidone (4-6 mg/day)</th>
<th>Olanzapine (10 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 Months</td>
<td>6 Months</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.1 ± 1.65</td>
<td>57.9 ± 1.61</td>
<td>58.9 ± 1.53</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.1 ± 0.36</td>
<td>22.4 ± 0.36</td>
<td>22.8 ± 0.32</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>122.4 ± 0.59</td>
<td>121.4 ± 0.39</td>
<td>121.5 ± 0.34</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>81.4 ± 0.48</td>
<td>80.6 ± 0.26</td>
<td>80.6 ± 0.24</td>
</tr>
</tbody>
</table>

Values are expressed in mean ± SEM; * = p<0.05 as compared to baseline, ^ = p<0.05 as compared to 3rd follow-up (Students un paired ‘t’ test)

Table 2: Comparative changes in metabolic parameters at the end of 3rd and 6th months (n = 103)

<table>
<thead>
<tr>
<th>Metabolic parameters</th>
<th>At the end of 3 month</th>
<th>Group I (Haloperidol 10 mg/day) (n = 31)</th>
<th>Group II (Risperidone 4-6 mg/day) (n = 34)</th>
<th>Group III (Olanzapine 10 mg/day) (n = 38)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>57.9 ± 1.69</td>
<td>54.6 ± 1.77</td>
<td>60.5 ± 1.59</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.4 ± 0.36</td>
<td>21.4 ± 0.39</td>
<td>23.7 ± 0.34</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>121.4 ± 0.41</td>
<td>120.8 ± 0.22</td>
<td>121.5 ± 0.41</td>
<td>P &gt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80.6 ± 0.27</td>
<td>80.5 ± 0.69</td>
<td>81.3 ± 0.32</td>
<td>p &gt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

At the end of 6 month

| Weight (kg)          | 58.9 ± 1.68 | 56 ± 1.78 | 63.6 ± 1.58 | p < 0.05 |
| BMI (kg/m²)          | 22.8 ± 0.36 | 21.9 ± 0.38 | 24.9 ± 0.34 | p < 0.001 |
| Systolic BP (mmHg)   | 121.5 ± 0.38 | 120.6 ± 0.21 | 121.7 ± 0.45 | p > 0.05 |
| Diastolic BP (mmHg)  | 80.6 ± 0.27 | 80.9 ± 0.34 | 81.9 ± 0.34 | p > 0.05 |

Values are expressed in mean ± SEM; One way ANOVA; p < 0.05 significance

Figure 1: Symptomatic evaluation of complaints (n=103)
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Figure 2: Comparison of improvement in clinical symptoms in patients treated with antipsychotic medication (n = 103)

Figure 3: Comparative changes in weight and BMI at the end of 3 months (n = 103)

Figure 4: Comparative changes in weight and BMI at the end of 6 months (n = 103)

statistically significant change ($p<0.05$) was observed in weight and BMI as compared to baseline and $3^{rd}$ follow up at the end of 6 months. (Table 1) In group III (olanzapine 10mg/day), statistically significant change ($p<0.001$) in all the parameters was observed the end of 6 months as
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compared to baseline and 3rd follow up except blood pressure (Table 1). Comparative analysis of the metabolic parameters at the end of 3 months showed that there was a statistically significant difference (p<0.05) observed in weight and BMI (ANOVA) (table 2). It was observed that statistically significant difference observed in weight (p<0.05) and BMI (p<0.001) at the end of 6 months (ANOVA) (table 2) It was observed that at the end of 3 months, weight and BMI levels were increased higher in olanzapine (10 mg/day) treated group which was 5.21% and 5.8% respectively (Figure 3). It was observed that at the end of 6 months, weight and BMI levels were increased higher in olanzapine (10 mg/day) treated group which was 10.61% and 11.16% respectively. Patients treated with haloperidol showed minimum changes in metabolic parameters (Figure 4).

DISCUSSION

Symptomatic evaluation

It was observed from present study that sleeplessness, selftalking and hallucinations were the most common symptoms. Schizophrenia presents with many symptoms because several forms of the disorder exist, including the paranoid type (characterized by extreme suspicions), disorganized type (with predominant disorganized speech and behavior) and catatonic type (with movement abnormalities).15 According to the Diagnostic and Statistical Manual of the American Psychiatric Association, core features of schizophrenia common to most forms of the illness include hallucinations, disorganized thoughts and behavior, delusions and negative symptoms like a lack of emotional expressiveness, verbalization, voluntary, purposeful movements. These variability of symptoms may be related to different underlying pathogenecity as positive symptoms are associated with mesolimbic dopamine hyperactivity while negative symptoms with decreased dopamine activity in the prefrontal cortex. Present study showed that improvement in clinical symptoms were noted from 2nd month of starting the treatment with all the antipsychotic medications which was quite similar to other studies suggesting improvement from 2-3 month of starting of therapy.16 A double blind randomized 6 weeks trial between risperidone and haloperidol in schizophrenic patients by Vijaysagar KJ et al.,(2005), suggested that both haloperidol and risperidone in schizophrenia patients were equally efficacious in treating the symptoms of schizophrenia. Similar result also reported with some studies.17 Other studies comparing the efficacy of haloperidol, risperdone and olanzapine revealed that all three treatment having similar efficacy in treating symptoms of psychiatric illnesses

Weight, BMI and Blood pressure

On evaluation of metabolic parameters treatment with haloperidol (10 mg/day) resulted into statistically significant (p<0.05) increase in weight and body mass index (BMI) after 6 months of treatment. It was observed that at the end of 6 months mean increase in weight and BMI were 1.8kg (3.15%) and 0.7 kg/m² (3.17%) respectively. Parez IR et al., 2007, concluded that patients on haloperidol treatment (n=43) showed increased in weight gain. We also observed that patients receiving risperidone (4-6 mg /day) treatment showed statistically significant (p<0.05) changes in blood glucose levels (FBS, PP2BS, HbaA1C) and lipid profile (cholesterol, triglyceride, LDL, HDL) at the end of 6 months of treatment. JW Newcomer et al.(2009) showed that there was a significant (p<0.05) increase in weight (3.6 kg) after 24 week treatment with risperidone (5 mg/day), which is synonymous with present study. Thus haloperidol and risperidone associated with less chances of significant increase in visceral obesity which is an important factor for development of insulin resistance and metabolic syndrome.18 It was observed from the present study that there was statistically significant weight gain (p<0.05, 6.1kg) and increased in BMI (p<0.05, 2.5 kg/m²) observed in olanzapine treated patients. Nemeroff et al. (1997) concluded that patients receiving olanzapine (10 -12 mg/day) showed mean increase of 12 kg after 1 year of treatment, which was statistically significant (p<0.05).20

Comparative analysis of all groups in the present study showed that there was statistically significant changes in weight and BMI levels at the end of 3 months treatment, which was similar to study carried out by Gautam S et al., (2011), reported significant (p<0.05) changes in blood glucose levels and lipid profile at end end of 3 months.20 Other studies which compared haloperidol, risperidone and olanzapine treatment groups in same doses (as present study) also concluded that there were significant changes observed weight and BMI levels at the end of 6 months treatment and which was maximum in patients treated with olanzapine.21

Possible mechanisms for changes in metabolic parameters

There may be multiple factors responsible for more changes in metabolic parameters in treatment with atypical antipsychotics (risperidone and olanzapine) as compared to typical antipsychotic medication e.g. haloperidol. Decrease in noradrenaline and adrenaline turnover and plasma concentrations during olanzapine treatment may also be relevant to understanding drug effects on glucose metabolism that could occur independent of changes in adiposity. As decrease noradrenaline concentration
leads to lesser stimulation of β3 receptors in brown adipose tissue, which eventually leads to decrease fat burning and more fatty tissue accumulation and development of metabolic syndrome.25 Olanzapine-induced body weight gain may be associated with functional changes in the muscarinic neurotransmission in the dorsal vagal complex and hypoglossal nucleus as olanzapine, but not haloperidol, treatment induces a significant decrease in the binding density of M2 receptors in dorsolateral vagal complex of rats.23 The mechanism for weight gain and eventually metabolic disturbances with atypical antipsychotics has been correlated to blockade of 5-HT2C receptors, which is supported by the evidence that mutant mice in which 5-HT2C “knockout” been produced are becoming obese. Drugs which block 5-HT2C receptors make the body unable to shut off appetite, and are associated with increased weight gain.24 Olanzapine having more 5-HT2C receptors blocking property than risperidone. Recently H1 receptor blockade is another reason for the weight gain, which can be produced by clozapine and olanzapine.25 The mechanisms by which H1-histamine antagonism might induce weight gain are currently unknown, although prior studies have demonstrated that H1-histamine receptor antagonism increases feeding in rodents and depletion of neuronal histamine increases feeding.26 Another receptor association been found out for these metabolic changes and these are associated with β3-adrenergic receptors. Blockade of β3 receptors in brown adipose tissue, which eventually leads to decrease fat burning and more fatty tissue accumulation. Leptin is an adipocyte derived hormone which acts on leptin receptors present in the hypothalamus of the brain, where it inhibits appetite by counteracting the effects of neuropeptide Y (a potent feeding stimulant secreted by cells in the gut and in the hypothalamus) and promoting the synthesis of melanocyte stimulating hormone (an appetite suppressant). Number of studies also have reported that adipocyt and plama leptin concentration are associated with metabolic changes. Ghrelin is an orexigenic peptide whose concentration increases with the treatment with atypical antipsychotic agents.27 Ghrelin increases the release of neuropeptides like neuropeptide Y, agouti related peptide, orexin A and B, endorphins which eventually stimulates the appetite centres in lateral hypothalamus. Sporn AL et al., 2005, suggested that olanzapine induced metabolic changes are associated with failure of mitochondrial function and fat oxidation results in ectopic fat storage, insulin resistance and type II diabetes mellitus.28 Recent preclinical study also favors the findings suggesting that olanzapine and clozapine are associated with an increase in fat intake which increases a level of free fatty acids and eventually metabolic syndrome which is less with haloperidol. Genetic factors also play an essential role in development of metabolic dysregulations with olanzapine. Muller DJ et al. (2005) revealed that polymorphism of SNAP-25 and Mnl I and tai I gene is associated with antipsychotic induced weight gain.29 Ellingrod VL et.al.,(2002), reported a positive association between 759 C polymorphism of the 5HT2C receptor gene and olanzapine induced weight gain.30

CONCLUSION
Hence we conclude that haloperidol, risperidone and olanzapine having a similar efficacy in controlling clinical symptoms, however improvement rate is higher with olanzapine treatment. Typical antipsychotic agents are associated with less disturbances in weight and BMI levels comparison with atypical antipsychotic agents while neither group of medication having significant effect of blood pressure. Atypical antipsychotic agents produce significant disturbances in weight and BMI levels. Olanzapine treatment is associated with high risk of abnormal metabolic changes. Prescribers should be aware about detailed pharmacological information of antipsychotic medications. Prescribing of atypical antipsychotics should be considered after assessment - history including personal and family, general and laboratory parameter measurement. Atypical antipsychotics should be avoided in high risk patients like, obesity, insulin resistance, hypertension, hyperlipidemia. Thus prescription of antipsychotic agents must be based on patient’s metabolic parameters and they should be measured during the course of treatment.

REFERENCES


