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Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: A double-blind, placebo-controlled trial

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ABSTRACT

Background: Olanzapine associated weight gain (WG) is a major concern in patients with schizophrenia. The purpose of this study was to assess the efficacy of topiramate to prevent olanzapine induced WG in these cases. We also studied various metabolic parameters.
Methods: In this 12-week, double-blind, parallel group study, seventy-two drug-naïve, first-episode schizophrenia patients were randomized to receive olanzapine + placebo (olanzapine group) or olanzapine + topiramate (100 mg/day) (topiramate group). Weight, body mass index, fasting glucose, insulin, insulin resistance (IR), leptin, lipids and blood pressure were assessed at baseline and at 12 weeks. The patients were clinically evaluated using Positive and Negative Syndrome Scale (PANSS) and were monitored for adverse effects.
Results: Topiramate resulted in a weight loss of 1.27 ± 2.28 kg ($p<0.01$), decrease in leptin ($p<0.001$), glucose, cholesterol, triglyceride levels and systolic and diastolic blood pressure. In the olanzapine group, there was a significant WG, hyperglycemia, hyperinsulinemia, increased IR, hyperleptinemia, hypercholesterolemia and hypertriglyceridemia ($p<0.001$).There was a greater clinical improvement (PANSS scores) ($p<0.001$) in the topiramate group. The adverse effects were well tolerated.
Conclusions: Topiramate could prevent olanzapine induced weight gain and adverse metabolic effects. It also results in a greater clinical improvement when used with olanzapine in schizophrenia.

1. Introduction

Management of schizophrenia involves a combination of pharmacological and behavioral therapies. Pharmacological treatment is an essential component of clinical management through the different stages of illness. Among the second generation antipsychotics, olanzapine is an effective medication for reduction in psychopathology and disease symptoms, a long duration of successful treatment, and low rates of hospitalizations for an exacerbation of schizophrenia (Jayaram et al., 2006; Lee et al., 2006; Leucht et al., 2009; Lieberman et al., 2005). Although olanzapine is a first line agent for schizophrenia, its use is limited by adverse effects like weight gain (WG) and other metabolic abnormalities including hyperglycemia, hyperlipidemia, hyperinsulinemia and metabolic syndrome (Atmaca et al., 2003; Graham et al., 2005; Hosojima et al., 2006; Lindenmayer et al., 2003; Melkersson et al., 2000). There is a need to explore agents which can prevent these treatment associated metabolic changes in patients with schizophrenia.

Topiramate, a newer anticonvulsant has been associated with weight loss as a side effect (Ben-Menachem et al., 2003;

Abbreviations: WG, Weight gain; BMI, Body mass index; FBG, Fasting blood glucose; TC, Total cholesterol; IR, Insulin resistance.

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Smith et al., 2000). Several case reports have shown topiramate to control antipsychotic-induced weight gain without aggravation of their psychotic symptoms (Lin et al., 2005). A higher dose of topiramate (200 mg/day) was found to be effective as an adjuvant treatment in patients with schizophrenia experiencing excess weight gain (Ko et al., 2005). A recent study by Afshar et al. (2009) concluded that topiramate could control antipsychotic-induced weight gain and schizophrenic symptoms. Similar findings were reported by Kim et al. (2006) in their 12-week open-label study. However, their study was limited by a small sample size and lack of placebo control and evaluation of biochemical parameters. These studies suggest the need for further rigorous, double-blind, placebo-controlled trials to elucidate the beneficial effects of topiramate on patients' psychopathology, clinical symptoms and biochemical/metabolic parameters.

Our comprehensive study was aimed at assessing the potential of topiramate to prevent olanzapine induced WG and biochemical/metabolic abnormalities to improve the patient compliance and decrease the disease morbidity. This prophylactic role of topiramate was evaluated in drug-naïve, first-episode schizophrenia patients, thus avoiding the confounding effects of prior antipsychotic therapy. We have also monitored patients for clinical improvement and adverse effects.

2. Materials and methods

2.1. Subjects

Patients were male and female, 18–65 years of age (both inclusive) attending the psychiatry clinic at a tertiary care hospital in New Delhi, India. The first-episode, drug-naïve patients met the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD -10) Diagnostic Criteria for Research for schizophrenia (ICD-10 DCR WHO, 1994). The patients were excluded if they had a history of any other neuropsychiatric illness; they were on Selective Serotonin Reuptake Inhibitors (SSRIs), mood stabilizers or any other drug which could potentially influence the weight; positive substance abuse diagnosis in last 3 months; or a significant medical disorder. Pregnant and lactating women and women of childbearing age not using adequate contraception were excluded. The sample consisted of stable inpatients and outpatients.

The study was approved by The Institutional Review Board. It was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). A written informed consent was taken from all the patients and they were free to withdraw their consent to participate at any time during the study.

2.2. Study design

This was a parallel, double-blind, placebo-controlled 12-week prospective study where patients were randomly assigned to either olanzapine + placebo (olanzapine group) or olanzapine + topiramate (topiramate group) treatment. The dose of olanzapine ranged from 5 to 20 mg/day in both the groups and could be increased or decreased (within range) based on the discretion of the physician. Topiramate was initially started at a dose of 50 mg/day and after 1 week of therapy, increased to 100 mg/day and maintained on the same dose throughout the study period. The patients were followed up for 12 weeks.

2.3. Clinical and biochemical assessments

The patients recruited for the study underwent a complete physical examination including vitals, weight (kg), and Body Mass Index (BMI) — weight (kg)/height (m^2) at baseline. The patients were evaluated clinically using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Laboratory investigations included fasting blood glucose (FBG) (mg%), fasting serum lipids (mg%) (Total Cholesterol (TC), Triglycerides, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Very Low Density Lipoprotein (VLDL) cholesterol). Serum insulin (μIU/ml) and serum leptin (ng/ml) were also estimated. Insulin resistance (IR) was assessed using the homeostasis model assessment (HOMA-IR) originally described by Matthews et al. (1985). The blood samples were obtained between 8 AM and 10 AM after overnight fasting. The first estimates were done in the treatment-free state (baseline) and the last dose was administered 10–14 h before the blood samples were withdrawn at the end of the study period (12 weeks).

2.4. Statistical analysis

Statistical analysis was done using SPSS software for windows. Independent student's *t* test was used to compare parameters between the two groups and paired student's *t* test was used to compare the values at baseline and at 12 weeks in each study group. The significance level was set at $p<0.05$, 2-tailed. Results are presented as mean ± S.D. Fisher's exact test was used to compare the adverse effects. A Pearson's correlation analysis was done to study the association between the mean change in weight and change in biochemical parameters in each group.

3. Results

Ninety-eight patients were screened for the study. Twenty-six patients were excluded due to various reasons: twelve patients had a current substance abuse diagnosis; five patients had a significant medical disorder; seven women of childbearing age were not using adequate contraceptive measures and two women were pregnant. Seventy-two patients were randomly assigned to the two groups. However, 34 patients (10 inpatients, and 24 outpatients) in the olanzapine group and 33 patients (8 inpatients, and 25 outpatients) in the topiramate group were included in the analysis. In the olanzapine group, one patient was lost to follow up and one was non compliant with treatment. In the topiramate group, two patients were lost to follow up and one patient withdrew from the study due to personal reasons. The baseline characteristics were similar in both the groups (Table 1). The biochemical parameters including FBG, TC, triglycerides, LDL, HDL, VLDL, insulin, leptin, and IR ($p=0.186$–0.834) were comparable at baseline. There was no significant difference in the mean modal dose of olanzapine in