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The effect of zonisamide on antipsychotic-associated weight gain in patients with schizophrenia: A randomized, double-blind, placebo-controlled clinical trial ☆

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ABSTRACT

Background: Many patients with schizophrenia suffer from metabolic symptoms and weight gain in which predispose them to obesity, diabetes, and cardiovascular problems.
This trial examines the efficacy and safety of zonisamide on weight and body mass index in patients with schizophrenia being administered with atypical antipsychotics.
Method: In this 10-week, double blind randomized placebo controlled clinical trial, forty one patients with schizophrenia diagnosed according to DSM-IV-TR criteria who were taking a stable dose of atypical antipsychotic are allocated into one of the two groups of zonisamide or placebo group. Weight, body mass index, waist circumference, and adverse effects were assessed.
Results: The two groups were not statistically different regarding baseline characteristics on age, gender, education, diagnosis, weight, body mass index, daily cigarette smoking, and the duration of illness. After 10 weeks, the patients in the placebo group had significantly gained weight, while the patients in the zonisamide group lost weight (mean = 1.9, SD = 2.2 versus mean = −1.1 kg, SD = 1.4). The changes of body mass index in the two groups were significantly different. Body mass index decreased in the zonisamide group (mean = −0.3, SD = 0.4) while it increased in the placebo group (mean = 2.2, SD = 6.9). There was a significance difference between the two groups regarding waist circumference at the end of trial ($P < 0.0001$), too. The waist increased in the placebo group while it decreased in the zonisamide group (mean = 1.1, SD = 1.7 versus mean = −0.7, SD = 1.2, respectively), as well.
The frequencies of adverse effects were not significantly different between the two groups and zonisamide was tolerated well.
Conclusion: Zonisamide as an adjuvant treatment is tolerated well and markedly affect on the weight loss of patients with schizophrenia being treated with atypical antipsychotics.

1. Introduction

Metabolic syndrome is a common problem in patients with schizophrenia (Papanastasiou, 2012). Its rate in these patients is about two times more than that of general population leading to increased mortality rates (Papanastasiou, 2012). 42.6% of men and 48.5% of women with schizophrenia suffer from the metabolic syndrome (Cohn et al., 2004). A study from Asia reported the rate of 46.7% (Said et al., 2012). Metabolic syndrome including increased body mass index is associated with receiving atypical antipsychotics in patients with schizophrenia (Bell et al., 2009). Comorbidity of diabetes and schizophrenia further reduces the cognitive function of these patients (Takayanagi et al., 2012).

Different medications are examined to attenuate antipsychotic-related weight gain. Metformin promoted weight loss (Wang et al., 2012; Wu et al., 2012) and there are promising reports about topiramate (Ko et al., 2005; Narula et al., 2010). However, the reports about metformin and sibutramine are mixed (Baptista et al., 2008). Nevertheless, some medications such as atomoxetine (Ball et al., 2011), mirtazapine (Cho et al., 2011), fluoxetine (Poyurovsky et al., 2002; Bustillo et al., 2003), famotidine (Poyurovsky et al., 2004), and the cannabinoid-1 receptor antagonist rimonabant (Kelly et al., 2011) are not effective to decrease weight in patients with schizophrenia. Metformin reduces hepatic glucose production and decreases intestinal glucose absorption (Matson and Fallon, 2012). In addition, metformin may decrease food intake (Zhou et al., 2001). Sibutramine also decreases food intake (Araujo and Martel, 2012).

Zonisamide is an antiepileptic medication. It is a benzisoxazole derivative. Zonisamide inhibits Na(+) channels and reduces T-type Ca(2+) currents. The half-life of zonisamide is about 60 h (Brodie

☆ Then, this trial was registered at http://www.irct.ir. The registration number of this trial was Irct registration number: IRCT201103283930N5.

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et al., 2012). Therefore, it can be administered once daily. Zonisamide is generally tolerated well. The most common adverse effects of zonisamide are somnolence, dizziness, anorexia, and weight loss (Brodie et al., 2012). Zonisamide causes weight loss in overweight female patients with epilepsy (Kim, 2003). A sixteen-week randomized, double-blind, placebo-controlled trial showed that zonisamide (up to 600 mg/day) significantly decreased weight in obese adults (Gadde et al., 2003). Therefore, it was recommended for treating obesity.

A case report reported that zonisamide decreased weight and waist circumference in 3 patients with schizophrenia treatment by zonisamide plus antipsychotics (Yang et al., 2010). A 22-week, open-label study showed that weight gain in patient with schizophrenia who received zonisamide plus olanzapine was less than that of the patients who received olanzapine alone (Hoffmann et al., 2012). Another study on patients with bipolar disorder or schizophrenia being treated with olanzapine showed that patients who are treated with zonisamide less than that of the placebo group experienced weight gain. However, the patients in the zonisamide group experienced a higher rate of adverse effects (McElroy et al., 2012). In contrast, another clinical trial on patients with bipolar disorder failed to show the effect of zonisamide on weight and body mass index (Dauphinais et al., 2011).

To the best of the authors' knowledge, few double-blind, placebo-controlled trials have been conducted to investigate the efficacy of zonisamide for antipsychotic related weight gain in patients with schizophrenia. In addition, there is a controversy about the effect of zonisamide on weight in patients with bipolar disorder. This is a 10-week randomized, double-blind, placebo-controlled clinical trial that examined the efficacy of zonisamide to decrease antipsychotic-induced weight gain in patients with schizophrenia. Considering the results of published reports (Yang et al., 2010; McElroy et al., 2012), it is expected that zonisamide is effective on antipsychotic associated weight gain.

2. Method

2.1. Trial design

This study was a single-center, 10-week, randomized, double blind, parallel-group clinical trial. This trial was conducted in the psychiatry clinics at Ebn-e-Sine and Hafez Hospitals affiliated with Shiraz University of Medical Sciences. This trial was conducted in 2011 to 2012.

2.2. Participants

Participants of this trial were outpatients ($n = 29$) and inpatients ($n = 12$) with the age range between 16 and 65 years old. Patients and their caregiver were interviewed face to face using the structured clinical interview in accordance with criteria set out in the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition—Text revised (DSM-IV-TR). They met DSM-IV-TR diagnostic criteria for schizophrenia (APA, 2000). The inpatients were administered zonisamide about 2 to 5 days before their discharge from hospital.

Those patients with a marked medical or neurological problem such as thyroid function problem, psychotic disorders other than schizophrenia, pregnancy, lactating women, the lack of enough contraception in women who were in reproductive age, taking medication leading to marked weight gain or loss, any special nutritional regime or intensive exercise program to decrease weight, positive history of renal stone, and a current diagnosis of substance use disorder were excluded.

The patients had to have a relatively stable improvement with the total score of PANSS ≤ 60 (Wang et al., 2012).

This trial was approved by the Ethics Committee of Shiraz University of Medical Sciences and it was conducted according to the Declaration of Helsinki and subsequent revisions. Providing written informed consent by the patients or caregivers was necessary for their participation in this trial.

2.3. Randomization, allocation concealment, and blinding

Forty one patients with schizophrenia were randomized into one of the two groups. There were 21 patients in the zonisamide group and 20 other patients were in the placebo group. Randomization was according to a computerized random number generator. The pharmacist who gave medication to the patients used this list of random numbers. The patients, his/her caregiver, and the clinician who rated the patients and the physician who referred the patients were blind to the group allocation.

2.4. Intervention

The patients in the zonisamide group received antipsychotics plus zonisamide (150 mg/day in a single dose). The patients in the placebo group received antipsychotics plus placebo. The duration of this trial was 10 weeks. Zonisamide was started at a dose of 50 mg/day and it was titrated up to 150 mg/day during two weeks (Yang et al., 2010). Both zonisamide and placebo were in the form of identical capsules. The doses of con-current medication were not markedly changed during the trial. Moreover, the patients were taking the con-current medications for at least 3 weeks before entering this trial. However, medications such as benzodiazepines or biperiden could be administered or their doses could be changed whenever it was applicable and necessary. Only two patients dropped from this trial. Both of them dropped after one month from the onset of intervention.

Patients were visited at baseline, week 4, week 8, and week 10 after randomization. A phone number was provided and the patients could call whenever they had any question or experiencing any adverse effect. In addition, they could refer to psychiatric emergency department if they had any concern about possible adverse effects. Moreover, they were visited during the first month according to their previously scheduled routine visits.

2.5. Outcome

The primary outcome measure was the score of body mass index and weight. Body mass index was calculated as weight (kilograms) divided by height (meters squared). In addition, the height of patient was assessed. All the assessments occurred in the morning hours.

Waist was also measured. For measuring waist, the top of patient's hip bone and bottom of patient's ribs were found. Patients were requested to breathe normally. Then, the tape measure was placed between these landmarks and wrapped it around waist.

Secondary outcome measure was The positive and negative syndrome scale (PANSS) for schizophrenia. PANSS was used to evaluate schizophrenia symptoms (Kay et al., 1987). It was completed through an interview by the trained resident of psychiatry. PANSS includes 30 items with the subscales of positive symptoms, negative symptoms, and general psychopathology. There are 7 items for positive symptom subscale. negative symptom subscale contains 7 items and the remaining 16 items belong to general psychopathology subscale.

Adverse effects were systematically assessed through clinical examination and self-report using a checklist.

2.6. Statistical analysis

The Statistical Package for Social Sciences, version 11.5 (SPSS 11.5) for windows was used for statistical analysis of data. Categorical variables were defined as frequencies and percents. Categorical variables were compared between the two groups using chi-squared tests or Fisher's exact tests, whenever it was applicable.