

Effect of Topiramate on Drug Associated Weight Gain of Patients with Schizophrenia and Bipolar I Disorders: A Dose Ranging Randomized Trial



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SUMMARY

Introduction: The aim of this study was to explore the probable prophylactic effects and evaluate different doses of topiramate on body weight in patients treated with olanzapine.

Materials and Methods: This was a 12 week, double-blind, placebo-controlled clinical trial (Iranian Clinical Trial Registration Code: 201402085280N15) to assess the preventative effects and estimate the optimal dosage of topiramate in drug-induced weight gain. Sixty eight patients aged 18 to 60 that were hospitalized and treated with olanzapine between 2009-2011 due to the onset of an acute episode of schizophrenia or a manic episode of bipolar I disorder were selected in Mashhad, the second largest city in the northeast of Iran. Patients were randomly assigned to 4 groups, including 1- placebo; 2- 50 mg/day; 3- 100 mg/day; and 4- 200 mg/day topiramate. Two psychiatrists assigned participants to an intervention group and followed up the treatment process. Raters weighed patients at baseline and also at weeks 1, 2, 4, 6, 8, and 12, respectively. Waist and wrist circumferences were measured at baseline and weeks 4, 8, and 12. Body weight, BMI, wrist, and waist circumference changes were outcome measures of the study. Collected data were analyzed by ANOVA, post hoc Tukey test, Krukskal-Walis, mann-whitney U, and Cohen's *d* with SPSS version 14. A p-value of less than 0.05 was considered significant.

Results: All outcome measures were significantly less than the placebo group compared to the topiramate groups at the end of the fourth week and continued to twelfth week. Nevertheless, there was no statistically significant difference in the measures of any of the topiramate groups with each other at any interval.

Conclusion: All doses of 50, 100, and 200mg were shown effective in preventing olanzapine-related obesity in schizophrenic and/or bipolar patients.

Keywords: olanzapine, topiramate, weight gain, bipolar I disorder, schizophrenia

INTRODUCTION

Topiramate, a new anticonvulsant drug, is a sulfamate-substituted monosaccharide with α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist properties, γ -amino-butyric acid (GABA) potentiating action, and Na⁺ and L-type Ca⁺⁺ channel neuronal inhibitory activities. It is also suggested to be an inhibitor of specific carbonic anhydrase isoenzymes (Deutsch et al. 2004, Arnone

2005). Previous reports revealed certain mood-stabilizing properties, which were not corroborated by the most recent studies (Ketter 2005, Post and Altshuler 2009). Although, the studies suggest that topiramate can be used to treat schizophrenia, its role as an adjunct therapy and alleviating schizophrenic symptoms still remains controversial (Afshar et al. 2009, Hosak and Libiger 2002, Drapalski et al. 2001, Johanssen 2008, Dursun and Deakin 2001, Behdani et al. 2011).

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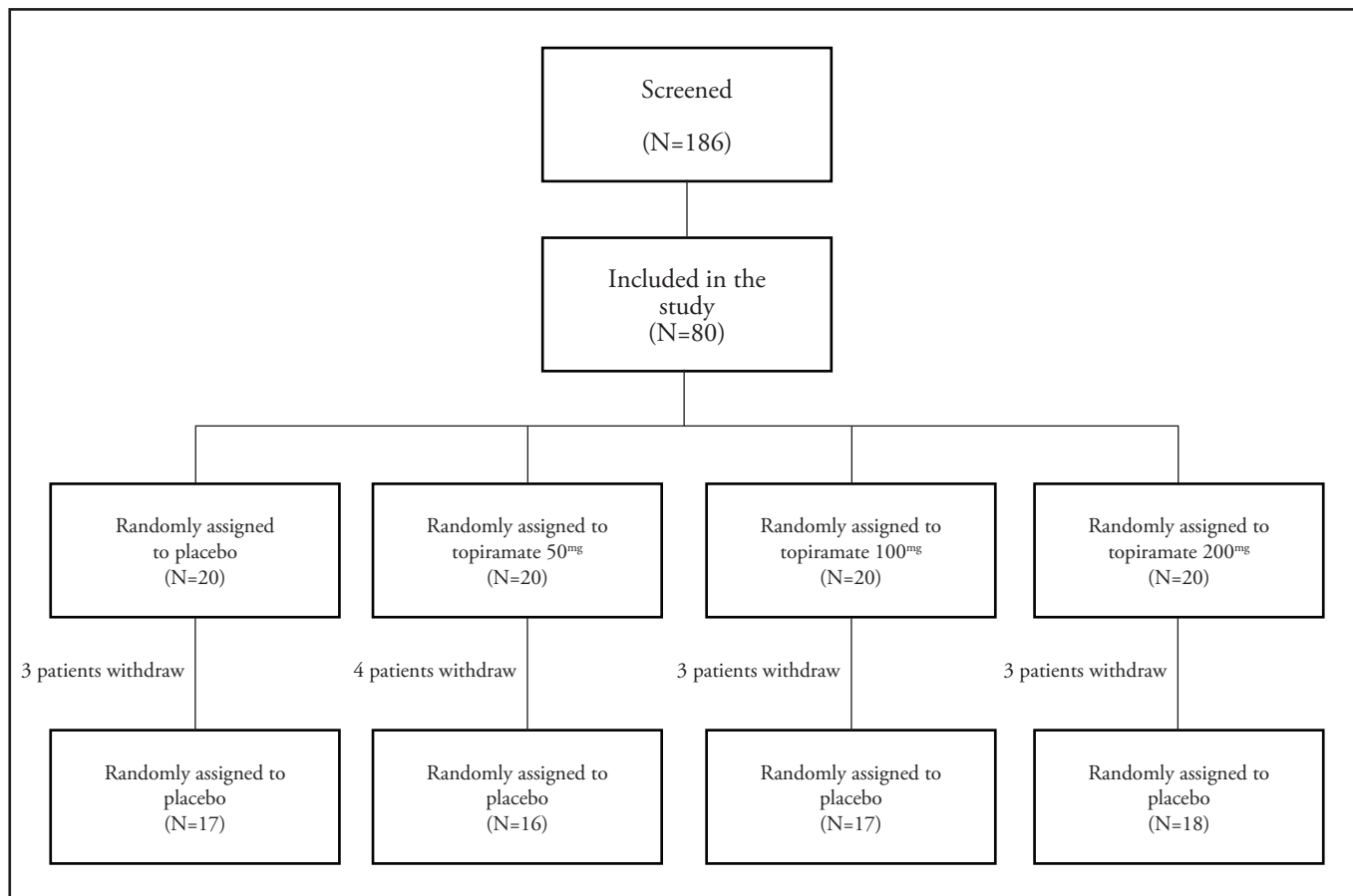


Figure 1. Disposition of study subjects

Drug-induced excessive body weight gain is a common side effect in the treatment of psychiatric patients (Baptista et al. 2001). According to a vast number of evidences, drug-induced weight gain is often associated with many psychotropic agents especially mood-stabilizers and second generation antipsychotics (Chengappa et al. 2001, Lin et al. 2005). A meta-analysis about antipsychotic-induced weight gain suggested that olanzapine, a second generation antipsychotic, is one drug with a high association to body weight gain, especially in dosages typically administered in patients with schizophrenia or bipolar mood disorder (Allison et al. 1999). The excessive weight gain is associated with a reduction in patient's compliance, increasing risk of hypertension, hyperlipidemia, diabetes mellitus, obstructive sleep apnea, and cardiovascular diseases. In addition, it may potentially lead to decreasing in life expectancy (Ko et al. 2005, Himmerich et al. 2004, Konradsson et al. 2007).

This after-effect can be reversed by topiramate, which is based on a series of open-label studies and case reports (Ko et al. 2005) along with a few well-designed, controlled studies (Arnone 2005, Konradsson et al. 2007). It is suggested that topiramate's GABA augmenting activity, along with its carbonic anhydrase inhibition, glutamate pathway inhibition

and Na⁺ and Ca⁺⁺ channel modulation may affect appetite-satiety sensation (Bray et al. 2003, Antel and Hebebrand 2012). Although there are reports that indicate topiramate ability to reverse the weight gain associated after usage of second generation antipsychotics, there are lots of ambiguities about prophylactic effects of the drug or the optimal dosage. In this study, we aimed to explore the potential prophylactic effects of topiramate on body weight in patients treated with olanzapine and determine an optimal dose for this drug.

MATERIALS and METHODS

This study was a 12 week, double-blind, placebo-controlled clinical trial (Iranian Clinical Trial Registration Code: 201402085280N15) for topiramate as an adjunctive medication to evaluate its potential effects in preventing weight gain and determine an optimal dosage for therapy. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences. Patients aged 18 to 60 that were hospitalized and treated with olanzapine due to the onset of an acute episode of schizophrenia or bipolar I disorder were selected for the study. They were all recruited from a referral psychiatric hospital in Mashhad, the second largest

city in the northeast of Iran between March 2009 and July 2011. All the patients met the full criteria for schizophrenia or manic-phase Bipolar I Disorder, based on the Diagnostic and Statistical Manual of Mental Disorder Forth edition-Text Revised (DSM-IV-TR).

In order to ascertain the diagnoses, two board-certified psychiatrists were assigned to conduct interviews with patients and their families, by which baseline information including vital signs, demographic data, family, and medication history as well as drug-related adverse effects were collected. They also screened participants regarding exclusion/inclusion criteria. Participants were excluded if they were determined to have hypertension, hyperlipidemia, diabetes mellitus, seizure, renal failure, nephrolithiasis, and/or neurological deficits. Patients with a history of any substance-use over the past 6 months (except for nicotine), intolerance to topiramate, recent use (less than 6 months) of lithium carbonate, sodium valproate/valproic acid, tricyclic antidepressants, clozapine, olanzapine, and topiramate were also excluded. Written informed consent (according to declaration of Helsinki) was obtained from the participants, their first degree relatives, or legal guardians.

Patients were randomly assigned to 4 groups by the lead researcher including; 1- placebo; 2- 50 mg/day; 3- 100 mg/day; and 4- 200 mg/day topiramate by main researcher of the study using computerized random number table (Figure 1). Both patients and raters were blinded to treatment regimen; however, care providers were aware of it. Olanzapine was administered to all participants and started with 5 mg/day on day 0 and was raised to the optimum 15-20 mg/day based on patient tolerability within 2 weeks. Topiramate or a placebo was prescribed from the day 0 as well. Topiramate was started at a dose of 25 mg/day. In the 50, 100, and 200 mg/day topiramate groups, the daily dose was increased by 25 mg every 3 days based on tolerability until reaching the target dosage. A research pharmacist prepared identical tablets of placebo, 50-, 100-, or 200-mg dosages of the medications. As topiramate and olanzapine had been titrating in the beginning of the study, patients were clinically assessed and the adverse effects of the medication were monitored. Two psychiatrists managed patients throughout the period of the study (12 weeks), and decided whether the patients needed a change in medication regimen (so should excluded from the study) or to continue in the study protocol. As it was mentioned previously, they were not blind to the treatment status of patients and did not perform any rating scales. Patients were followed for an additional 4 weeks on their stable antipsychotic medications. Raters weighed patients at baseline and also at weeks 1, 2, 4, 6, 8 and 12, respectively. Waist and wrist circumferences were measured at baseline and weeks 4, 8 and 12, respectively. Weight changed could also be translated to body mass index (BMI) alterations. Raters were not

aware of the patients' group. All data were analyzed based on intention-to-treat analysis.

Body weight, wrist, and waist circumference were assessed as outcome measures. Net amounts of weight, wrist, and waste circumference did not change significantly in comparison with the first day of the study and throughout the 12 weeks of the survey. Therefore, we decided to report and analyze our data via comparative changes in weight, wrist, and waste circumference in contrast with day Zero.

After the end of the study, collected data were analyzed by Analysis of Variance (ANOVA) following by post hoc Tukey test for data with normal distribution and Krukskal-Walis and mann-whitney U for data with non-normal distribution, using SPSS version 14. A p-value of less than 0.05 was considered statistically significant. Statistically significant results were analyzed for the effect size, using Cohen's *d* (Relative Size of Effects which was calculated by mean of experimental group minus mean of control group divided by standard deviation or $ES=(E-C)/sd$).

RESULT

In this study, 80 eligible patients were randomly assigned to four groups (either three different doses of topiramate or placebo, each contained 20 participants). They were subsequently assessed regarding the preventive role of topiramate in weight gain, using changes in weight, BMI, wrist, and waist circumference indices. Sixty eight patients completed the study. Twelve patients dropped before the end of the study (3 patients from the placebo and 100 mg topiramate, 4 patients in the 50 mg topiramate group, and 2 patients in 200 mg group). Nine patients were excluded due to the lack of therapeutic efficacy by olanzapine, while three patients were excluded due to loss of follow up or consent withdrawn. Demographic homogeneity of the group registered is shown in table 1. Groups were not significantly different in terms of age, sex, and olanzapine dosage. Similar findings were determined for the baseline values including weight, BMI, wrist, and waist circumference between the four groups ($P > 0.05$).

Normal distribution of the results on weight, body mass index, waist circumference, and wrist circumference were assessed using the Kolmogorov-Smirnov Z test. Most of the variables are normally distributed except weight change in the first week and wrist circumference change in the fourth week in the group receiving 200 mg of topiramate, and waist circumference change in the eighth and twelfth weeks in the group receiving placebo.

Table 2 provides a comparison in cases with normal distribution using ANOVA and non-normal distribution applying Kruskal-Wallis. Results did not reveal any significant changes in weight and body mass index by the end of the second week.

Table 1. Demographic variables of the participants according to intervention and placebo groups

		group				P
		Placebo	50mg	100mg	200mg	
Age (year)		34.47±11.19	36.59±12.61	30.75±11.46	37.06±13.51	0.45*
Sex	Male	9	16	12	12	0.06**
	Female	8	1	5	5	
Weight at baseline (kg)		62.6±11.0	62.5±10.9	68.6±17.4	62.7±14.0	0.48***
BMI at baseline (kg/m ²)		22.8±3.7	22.2±3.6	23.6±4.7	22.8±3.8	0.80***
Wrist circumference at baseline (cm)		16.7±1.4	17.1±1.2	17.1±1.8	16.5±1.3	0.52***
Waist circumference at baseline (cm)		86.1±9.7	81.8±12.6	86.1±13.6	77.3±13.9	0.14***
Olanzapine dosage (mg)		17.4±2.4	17.9±2.4	18.1±2.4	17.4±2.4	0.73

mg: Milligram, Kg: Kilogram, m: Meter, cm: Centimeter

P<0.05 considers as significant

*t-test

** χ^2

*** ANOVA

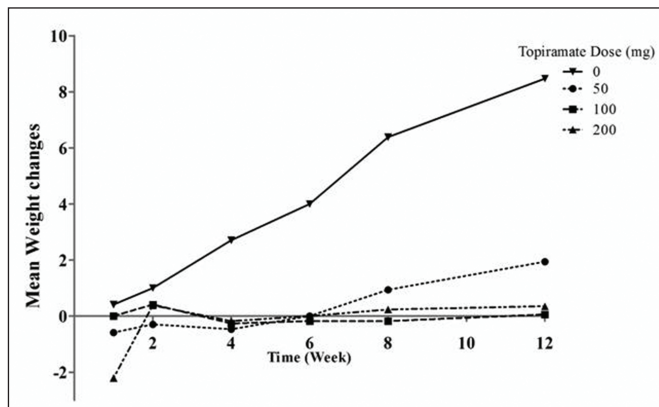
Table 2. Comparison of the changes in weight, BMI, wrist and waist circumference in intervention and placebo groups throughout 12 weeks of the study

Variable		group				P	Cohen's d Effect size		
		Placebo	50	100	200		50	100	200
Weight changes (kg)	By the end of first week	0.412±1.502	-0.590±1.698	0.000±1.510	-2.206±9.847	0.43*			
	By the end of second week	1.000±1.541	-0.294±1.961	0.411±0.411	0.382±1.710	0.32**			
	By the end of forth week	2.706±1.992	-0.471±2.239	-0.264±3.345	-0.177±2.404	0.00**			
	By the end of sixth week	4.000±2.291	0.000±2.475	-0.177±3.610	0.000±2.894	0.00**			
	By the end of eighth week	6.382±2.826	0.941±2.703	-0.177±3.712	0.235±3.270	0.00**			
	By the end of twelfth week	8.471±3.573	1.941±3.307	0.059±3.561	0.353±3.823	0.00**	0.688 large	0.762 large	0.739 large
BMI changes (kg/m ²)	By the end of first week	0.172±0.520	-0.231±0.502	-0.126±1.098	0.081±0.581	0.38**			
	By the end of second week	0.39±0.52	-0.12±0.72	-0.04±1.43	0.19±0.65	0.36**			
	By the end of forth week	0.99±0.70	-0.17±0.83	-0.22±1.64	-0.30±1.26	0.01**			
	By the end of sixth week	1.50±0.81	-.02±0.89	-0.14±1.79	0.08±1.97	0.00**			
	By the end of eighth week	2.40±1.04	0.31±0.94	-0.17±1.78	0.10±1.08	0.00**			
	By the end of twelfth week	3.13±1.34	0.67±1.13	0.10±1.79	0.17±1.29	0.00**	0.705 large	0.714 large	0.749 large
Wrist changes (cm)	By the end of forth week	0.3±0.4	0.0±0.5	-0.2±0.5	-0.1±0.3	0.047*			
	By the end of eighth week	0.5±0.3	-0.2±0.9	0.0±0.8	0.1±0.6	0.04**			
	By the end of twelfth week	0.7±0.4	0.2±0.6	0.1±0.8	0.1±0.7	0.02**	0.410 moderate	0.472 moderate	0.495 moderate
Waist changes (cm)	By the end of forth week	2.1±1.5	-0.4±2.3	-0.4±3.2	0.5±1.6	0.01**			
	By the end of eighth week	2.3±7.4	1.8±2.9	0.2±3.5	1.0±2.6	0.00*			
	By the end of twelfth week	3.7±7.9	2.6±3.2	0.5±3.5	0.9±3.3	0.00*	-	-	0.220 small

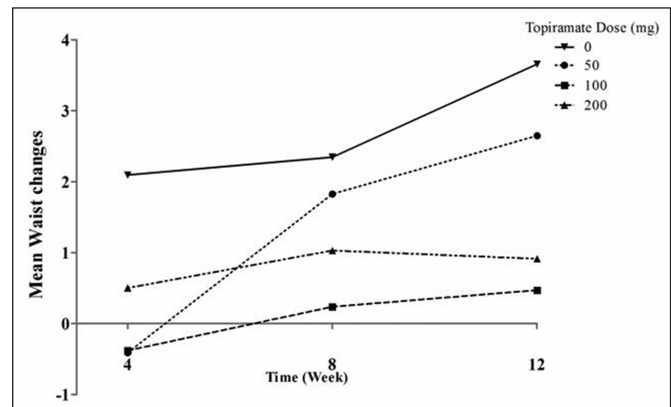
mg: Milligram, Kg: Kilogram, m: Meter, cm: Centimeter

*Kruskal-Wallis

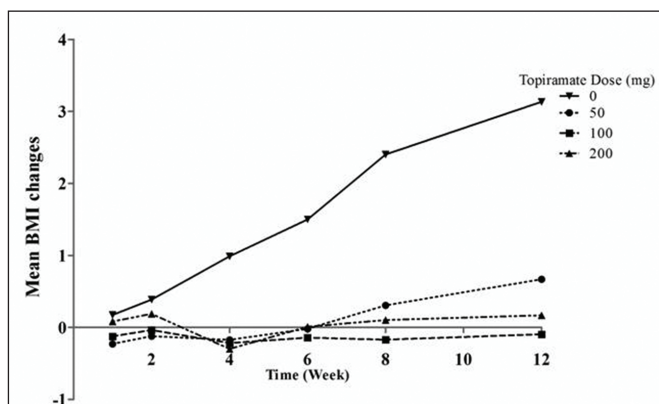
** ANOVA



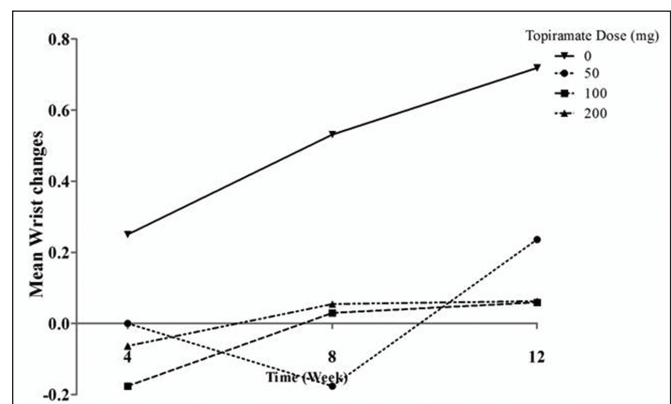
Line chart 1. Comparison of the weight changes between intervention and placebo groups in contrast to day zero throughout 12 weeks of the study



Line chart 3. Comparison of the wrist circumference changes between intervention and placebo groups in contrast to day zero throughout 12 weeks of the study



Line chart 2. Comparison of the BMI changes between intervention and placebo groups in contrast to day zero throughout 12 weeks of the study



Line chart 4. Comparison of the waist circumference changes between intervention and placebo groups in contrast to day zero throughout 12 weeks of the study

Yet, significant changes in all outcome measures started at the end of the fourth week are shown in table 2. Tukey's post hoc analysis (for data with normal distribution) as well as Mann-Whitney test (for data without normal distribution) was used for pair wise comparison of the study groups. Results have been shown in line charts 1-4.

Line chart 1 depicts changes in the average weight of all four groups compared to day zero. Table 2 highlights considerable difference in the average weight changes at weeks 4, 6, 8 and 12 between intervention groups with placebo group, which can also be noted in the chart. Minimum weight changes in comparison to day zero were detected in the group receiving 100 mg topiramate in all weeks of study except week 4. In this case, the group receiving 50 mg topiramate had the minimum increase in weight. Nevertheless, there was no statistically significant difference in any of the topiramate groups at any interval.

Line chart 2 compares BMI changes in contrast to day zero in all four groups. Table 2 reveals a significant disparity among the four groups in BMI changes at weeks 4, 6, 8 and 12,

respectively. As observed, minimum BMI changes were noted in those receiving 100 mg topiramate in all weeks except week 4 in which the group receiving 200 mg topiramate had the minimum increase in BMI. Nevertheless, statistically significant changes were still absent in all groups receiving topiramate.

As shown in table 2, there was a significant difference among the four groups in terms the average of wrist circumference changes at weeks 4, 8 and 12, respectively. Line chart 3 shows wrist circumference changes compared to day zero in all four groups. It is also noteworthy that this index varied significantly in the 50 mg topiramate group at week 8, 100 mg topiramate group at week 12, and in those on 200 mg topiramate in the weeks 4 and 12, compared to the placebo group. However, the index was not statistically different in all topiramate-receiving groups at any interval.

Line chart 4 and table 2 show data on changes in waist circumference in comparison to baseline (day zero). The index was significantly different between the four groups at weeks 4, 8 and 12, respectively. There were also significant differences

between all the three topiramate groups in contrast with the placebo group in all different weeks of the study with the only an exception being subjects that received 200 mg of topiramate, which were not significantly different from patients on placebo at week 4. Minimum changes in waist circumference were also noted in the 100 mg topiramate group throughout all weeks. However, the index was not statistically different in all topiramate-receiving groups with each other at any interval.

DISCUSSION

The prevalence of weight gain and obesity among patients with severe psychiatric disorders is on the rise, just like the general population (Birt 2003). Compared to the general population (after controlling for age and sex), BMI was higher in patients with schizophrenia and bipolar disorder. In addition to the effect of severe psychiatric disorders on unhealthy diet and lifestyle (e.g. lack of exercise), consuming atypical antipsychotic drugs was also effective in causing the problem (Lin et al. 2005, Himmerich et al. 2004, Birt 2003). Patients' weigh gain can lead to non-compliance and many medical problems (Ko et al. 2005). Therefore, treatment of overweight in patients with schizophrenia and bipolar disorder has been effective in reducing morbidity, increasing longevity, and improving the disease outcome (Lin et al. 2005, Himmerich et al. 2004).

We studied 68 patients taking olanzapine and examined the preventive role of topiramate in weight gain. To the best of our knowledge, this was the first study with the aim of determining the most efficient prophylactic dosage of topiramate to prevent weight gain in patients receiving olanzapine. Comparing demographic characteristics affecting weight, including age and sex, with variables associated with weight, such as wrist and waist circumferences, prior to starting topiramate drug treatment, there was no significant differences among the four groups. Therefore, it would be a safe assumption to attribute subsequent changes to topiramate effects. However, preponderance of female participants in the placebo, though non-significant ($P=0.06$), may be considered as a probable confounding factor when compared with the intervention group.

Our findings with regard to the efficacy of topiramate in weight reduction are comparable to others. Ko et al (2005) assessed the efficacy of different dosages of topiramate in treating overweight patients under maintenance treatment with olanzapine and other second-generation antipsychotics. In this study, the highest rate of weight loss was observed in the patients under treatment with 200 mg of topiramate (Ko et al. 2005). In the study by Nickel et al. in 2005 on female patients on olanzapine treatment, 250 mg of topiramate per day as adjuvant was compared with placebo. The results of

the trial after 10 weeks were significant (4.4 kg weight loss in topiramate group compared to 1.2 kg in placebo group). In this study, the highest response rate was observed in the group with highest weigh gain during the first two months of treatment with olanzapine (Nickel and Nickel 2005). The same effect for adjuvant topiramate was also reported for patients treated with mood stabilizers such as lithium and sodium valporate (Fiedorowicz et al. 2012).

As shown in the results, the beginning of drug effects was observed starting the fourth week, with no significant weight change over the first two weeks. Thus, it can be stated that the preventive effect of topiramate in patients' weigh gain will most likely begin starting the second week of treatment. However, Rucker et al. in their meta-analysis reported that the effect will be sustained even following 24 weeks, never reaching a plateau as opposed to other weight reducing drugs such as sibutramine and orlistat (Rucker et al. 2007). The therapy was shown superior to placebo in BMI, waist, and wrist circumference reduction all throughout the follow-up weeks (week 4, 6, 8 and 12). This significant difference in the end of 12th week was further analyzed in terms of effect size. Although the calculated effect size was medium and small for wrist and waist, it was seen that the effect of topiramate on weight and BMI was practically significant (Cohen's $d > 0.6$) (table 2). This indicates a large effect size as well as the sustainability of the drug effect for main outcome measures as corroborated by other studies (Nickel and Nickel 2005, Fiedorowicz et al. 2012). The effect might have continued if our trial had been further extended. It will be of great importance to determine the chronicity of the majority of severe psychiatric conditions and their constant need for continuous long term treatment with anti-psychotic medications.

Comparing different doses of topiramate in the present study showed that prescribing topiramate with different doses per day had the greater effect than placebo on weight and associated parameters. Doses of below 100 mg were not shown less efficacious in weight reduction by the end of the twelfth week. However, a trend can be seen in the charts in the way that patients who received 50 mg of topiramate may not sustain a stable weight or they may even gain some weight despite medication. There was no considerable difference between 100 and 200 mg topiramate ($p=0.993$ 303 ± 0.9 vs. 3.5 ± 0.5). Therefore, based upon our twelve-week follow up, it can be inferred that increasing the dosage to 100 mg or above does not necessarily lead to achieving optimum results, while further rise of the dose may raise the risk of complications such as cognitive adverse effects, nephrolithiasis, and glaucoma (Banta et al. 2001, Kuo et al. 2002). Major adverse effects had not been reported in past studies. However, other unwanted side effects such as parasthesia and change in taste are likely to result in poor compliance and even discontinuation

of Topiramate by patients, which may lead to recurrence and flare-up of the underlying disorders (Kramer et al. 2011).

Our study did not evaluate the adverse effects of the topiramate by a standard assessment tool. However, patients were clinically examined according to probable side effects. No patient was excluded from the study because of side effects, which is suggestive of the safety of the drug in the patient population. Ko et al reported a dose of 200mg for maximum weight reduction, which differed from the present study (Ko et al. 2005). They only included patients diagnosed with schizophrenia, whereas our population had a mixed population with bipolar patients as well. Racial difference and its effect on drug metabolism should also be considered. These prompt further investigation in separate groups of patients with a single diagnosis as well as pharmacogenetic studies delineating the role of race and its impact on pharmacokinetics and pharmacodynamics of the drug.

The mechanism of action remains largely unknown, with an assumption highlighting the inhibitory effects on glutamatergic neurons (Ketter et al. 1999). Inhibiting AMPA receptors in animal experiments was shown to cause water and food intake reduction and thus, weight loss (Zheng et al. 2002). It was also suggested that repeated stimulation of AMPA and kainite receptors, owing to its neurotoxicity, contribute to the pathogenesis of schizophrenia (Afshar et al. 2009). Topiramate was also claimed to enhance lipoprotein lipase in adipose tissue in animal experimentation (Richard et al. 2000). The drug also inhibits carbonic anhydrase, which may lead to a reduction in appetite, yet there will be no change in energy expenditure (Fiedorowicz et al. 2012).

Limitations

This study succeeded in investigating the effects of Topiramate at different doses on four distinct groups, with the primary objective of determining the optimum dose for prophylaxis. However, there were certain limitations such as few participants, ethnicity, and race disparity. Patients were also not divided based on their diagnosis. In addition, they were not matched according to their diet after discharging from hospital. Topiramate side effects were not objectively investigated by a valid assessment tool and patients were only under clinical examination in this respect. Therefore, it can limit generalizability of our study and clinicians need to make a rational decision whether they can use the drug based on the side effect profile of the medication.

Conclusion

Doses of 50, 100, and 200mg were all shown to be effective in preventing Olanzapin-related obesity in Schizophrenic and/or Bipolar patients without any significant difference among doses in a twelve-week period of follow up. However, longer

duration of following the patients may reveal the difference among various doses of the drug. It seems that clinicians should weigh risk and benefits of topiramate and find an optimum dosage that has the fewest side effects and clinical favorable outcomes.

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