The Effects of Topiramate on Weight Gain in Patients with Schizophrenia: A Double-Blind Randomized Placebo-Controlled Clinical Trial

Hamidreza Jamilian[1], Mehran Shayganfard[2]

[1]*Associate Professor, Department of Psychiatry, Arak University of Medical Sciences, Arak, Iran*
[2]*Assistant Professor, Department of Psychiatry, Arak University of Medical Sciences, Arak, Iran*

Conflict of Interest: None declared

This article has been peer reviewed.

Article Submitted on: 11th November 2017

Article Accepted on: 18th March 2018

Funding Sources: None Declared

Correspondence to: Dr Hamidreza Jamilian

Address: Department of Psychiatry, Arak University of Medical Sciences, Arak, Iran

Email: mjamilian@yahho.com

Cite this article: Jamilian H, Shayganfard M. The effects of topiramate on weight gain in patients with schizophrenia: a double-blind randomized placebo-controlled clinical trial. J Pioneer Med Sci. 2018; 8(2):55-59

ABSTRACT

BACKGROUND: Weight gain among patients with schizophrenia is challenging. To evaluate the effects of topiramate on treatment of schizophrenia and weight gain management.

METHODS: For this double-blind randomized placebo-controlled clinical trial; 59 patients at Arak University Hospital were recruited. In the control group (n=29) atypical antipsychotic agent equivalent to 20 mg of olanzapine was given while the intervention group (n=30) was treated with atypical antipsychotic equivalent to 20 mg of olanzapine and topiramate at dose of up to 200 mg for 12 weeks. The Positive And Negative Syndrome Scale (PANSS) and Body Mass Index (BMI) of patients were measured at baseline and during the study.

RESULTS: 59 patients, 31 males (52.5%) and 28 females (47.5%) with mean age of 29.9±7.67 years (ranged 16.7-47.3 years) were randomized. In the two groups, total PANSS significantly decreased after 12-week therapy (P=0.001). BMI in the control group decreased by only 0.25% from baseline to week 12 and was not significant (p=0.69). In topiramate group, the reduction of BMI from baseline to week 12 was 8.3% and was statistically significant (26.67±3.51 to 24.47±3.55, P=0.001). The difference between the treatment and control groups regarding BMI in weeks 8 and 12 and PANSS in weeks 4, 8 and 12 was significant (P<0.05).

CONCLUSION: Our results indicated that topiramate at a dose of 200 mg/day is a safe agent and induces weight loss and significantly decreases PANSS score in patients with schizophrenia.

Keywords: Schizophrenia; Topiramate; Antipsychotic; Weight Gain, Positive and Negative Syndrome Scale

INTRODUCTION

Weight gain in schizophrenia is a common problem. It is well established that the prevalence of obesity in schizophrenic patients is three times more than the normal population [1]. Several factors are associated with weight gain in these patients, but atypical antipsychotic agents are one of the most important factor among other possible factors [2,3]. Topiramate, a sulfonate substituted derivative of monosaccharide D-fructose is an anticonvulsant agent and has been used in treatment of migraine, neuropathic pain and bipolar affective disorder [4-6], and as a side effect it has been associated with weight loss [7]. Through a non- benzodiazepine mechanism, topiramate potentiates inhibitory GABAergic transmission [8,9]. Some studies have indicated that topiramate inhibits antipsychotic-induced weight gain [10,11]. Moreover, another study revealed that topiramate 200 mg/day is effective as an adjuvant agent in treatment of schizophrenic patients with excess weight gain [11]. Van *et al.* found that topiramate, as an adjunctive agent, in treatment of anxiety disorder inhibits Selective Serotonin Reuptake Inhibitor (SSRI)-related weight gain [12]. In line with these findings, a comprehensive meta-analysis on general population showed topiramate can reduce patient weight by about 6.5% during six months [13]. A randomized clinical trial has pointed out less marked cognitive effects of topiramate 200 mg/day when given as an add-on agent in patients with schizophrenia [14]. Although, these

studies have shown topiramate to be an effective agent on antipsychotic-induced weight gain in schizophrenic patients without remarkable side effect, most of these studies are limited due to the lack of control groups. Moreover, in Iranian patients, studies examining the use of topiramate are uncommon. Therefore, to address these concerns we conducted this randomized, placebo-controlled, double-blinded clinical trial to evaluate the effect of topiramate on weight gain management in Iranian patients with schizophrenia on antipsychotic treatment.

METHODS

For this randomized, double-blind, placebo-controlled clinical study, 59 patients (inpatient and outpatient) referred to the Arak university Hospital were recruited (IRCT 201303287373N3). All patients met the DSM-4 diagnostic criteria for schizophrenia. The criteria for enrollment were (1) age between 16 and 50 years; (2) candidate for maintenance therapy with an atypical antipsychotic; and (3) overweight, defined by a BMI >25 kg/m^2. Exclusion criteria were (1) substance abuse during the past six months (2) suicidality, (3) nephrolithiasis, (4) seizures, and (5) previous treatment with topiramate. The enrolled participants were counseled and written, informed consent was obtained from patients or patient's guardian, as per the institution's protocol. Moreover, the study protocol was approved by ethics committee of Arak university of medical sciences (Code:91-141-15). The comparison of BMI between and within groups was the primary outcome, and evaluation of PANSS was the secondary outcome.

Randomization: Patients were randomized in two groups to receive placebo (control group) (n=29) or topiramate (treatment group) (n=30). The random allocation sequence was computer-generated and enclosed in sequentially numbered opaque sealed envelopes. This was a parallel randomization and only treatment group received topiramate. All patients in two groups were treated with one kind of atypical antipsychotic agent equivalent to 20 mg of olanzapine. In treatment group topiramate (tablet 100 mg, Arya co.) was started at dose of 25 mg /BD (50 mg/daily) for 4 days, then 25 mg was added every 4 days and increased to 200 mg during the study (12 weeks). The atypical antipsychotic agents in topiramate group were as follows: 17 patients received olanzapine, 11 patients risperi-done, 1 patient quetiapine and 1 patient received clozapine. In control group all patients received placebo and any one of the antipsychotics as follows: 14 patients olanzapine, 11 patients risperidone, 3 patients quetiapine, and 2 patients were given clozapine.

The PANSS was used to quantify changes in schizophrenic negative and positive symptoms in patients in the two groups at baseline and at weeks 2, 4, 8, and 12. Moreover, the BMI of patients was measured at baseline and at weeks 4, 8 and 12 after the treatment.

Statistical Analyses: Data were analyzed using Statistical Package for Social Studies (SPSS) version 21. Categorical data are presented as numbers (%), and continuous data as mean ± SD. We used the Student's t test to compare continuous variables and chi-2 test to compare categorical variable. The repeated measures ANOVA was used to compare subjects in each group from baseline to 12 weeks. A p value of < 0.05 was considered significant.

RESULTS

Of the 59 patients, 31 were male (52.5%); and 30 out of the total 59 patients were randomized to the treatment group. Mean±SD age of the patients was 29.88±7.67 (ranged 16.7-47.30) years in both groups. Both groups were balanced regarding gender and age (P=0.79, P=0.26 respectively) (Table 1). In the control group, BMI did not show remarkable change and only 0.25% reduction was observed from baseline to week 12 (27.96±3.85 to 27.81±3.91, p=0.69) (Table 1). On the other hand, the topiramate treatment group had significant decrease 8.3% in BMI from baseline to week 12 (26.67±3.51 to 24.47±3.55, P=0.001) (Table 1). The difference between the treatment and control groups regarding BMI at weeks 8 and 12 was significant (P=0.001) (Table 1). In both topiramate treatment and control groups, the subtotal positive, negative, and general score domains of PANSS significantly decreased from baseline to week 12(P=0.001) (Table 2). Moreover total PANSS scores in topiramate and control groups significantly decreased from baseline to week 12 (in control from 98.79±4.22 to 52.89±3.69, P=0.001) (in topiramate from 99.46±10.04 to 44.66±4.91, P=0.001, (ANOVA repeated measurement) (Table 3). Subtotal positive and general score showed significant difference between topiramate and control groups at weeks 4, 8 and 12. However, the subtotal negative score

Table 1: Comparison of sex, age and BMI from baseline to week 12 in two groups

	Control	Treatment	P (Independent t test)
Male	16(51.6%)	15(48.4%)	0.79
Age, years	31.02±8.26	28.78±7.01	0.26
BMI week 0	27.20±1.62	26.62±1.31	0.13
BMI week 4	27.18±1.63	26.45±1.42	0.11
BMI week 8	27.15±1.63	25.50±1.30	0.001
BMI week 12	27.13±1.60	24.26±1.08	0.001

Table 2: Positive and negative syndrome scale, subtotal scores (P,N,G) from baseline to week 12 in two groups

	Control	Treatment	P (Independent t test)
subTotal P score week 0	27.58±3.92	28.86±3.80	0.20
subTotal P score week 2	24.75±3.35	23.90±3.82	0.36
subTotal P score week 4	21.31±3.28	17.66±3.73	0.001
subTotal P score week 8	17.20±3.58	13.96±3.07	0.001
subTotal P score week 12	14.37±269.	10.13±2.43	0.001
P(repeated measurement)	0.001	0.001	
subTotal N score week 0	23.20±3.62	22.10±3.47	0.23
subTotal N score week 2	21.72±3.16	21.36±3.32	0.67
subTotal N score week 4	15.13±2.48	16.50±3.40	0.08
subTotal N score week 8	13.13±2.94	14.23±3.27	0.18
subTotal N score week 12	11.48±2.82	12.33±3.27	0.29
P(repeated measurement)	0.001	0.001	P
subTotal G score week 0	48.00±3.86	48.50±10.63	0.81
subTotal G score week 2	37.24±4.12	36.33±4.83	0.44
subTotal G score week 4	32.96±4.60	30.06±4.38	0.01
subTotal G score week 8	29.55±2.91	25.73±3.92	0.001
subTotal G score week 12	27.03±3.80	22.20±3.91	0.001
P(repeated measurement)	0.001	0.001	

Table 3: Positive and negative syndrome scale from baseline to week 12 in two groups

	Control	Treatment	P (Independent t test)
Total score week 0	98.79±4.22	99.46±10.04	0.74
Total score week 2	83.72±4.29	81.60±4.41	0.06
Total score week 4	69.41±5.48	64.23±4.75	0.001
Total score week 8	59.89±3.61	53.93±4.51	0.001
Total score week 12	52.89±3.69	44.66±4.91	0.001
P(repeated measurement)	0.001	0.001	

Table 4: Adverse effects in topiramate treatment and control groups

	Treatment	Control
Paresthesia	14	3
nausea	2	3
anorexia	7	2
Dizziness	4	1
drowsiness	9	4
Headache	1	1
Psychomotor retardation	3	1

did not show significant difference between topiramate and control during the study period (Table 2). The difference between two groups in total PANSS score was not significant at baseline but was significant at weeks 4, 8 and 12 (Table 3).

Safety of the therapy: The intolerable side effects did not occur at any dose, even in the placebo group, and no patients were withdrawn from the study. However, some patients did complain of transient and mild side effects (Table 4).

DISCUSSION

In this current randomized placebo-controlled trial that enrolled patients with schizophrenia on standard antipsychotic therapy, we found significant weight loss in patients who were given topiramate than patients who were given placebo. Similarly, we found significant reduction in PANSS scores with topiramate as compared to placebo. Topiramate therapy was also associated with lower scores for PANSS individual domains.

Previous reports found that one of the adverse effect of antipsychotic agents is high incidence of weight gain, which may be as high as up to 50% [9-14,16]. Of the conventional antipsychotics, thioridazine and chlorpromazine cause more weight gain [17]. On the other hand, weight gain associated with clozapine, olanzapine, and risperidone is not much different than the conventional antipsychotics [18-20].

Several studies have shown effect of topiramate on weight loss in schizophrenic patients who take atypical antipsychotic agents such as clozapine, olanzapine and risperidone [5-11, 22, 24-25]. While we used one dose with dose escalation, a Korean study found that daily dose of 200 mg topiramate was associated with significantly higher weight loss than 100 mg daily dose [10]. Some studies have reported that topiramate not only prevent olanzapine-induced weight gain and adverse metabolic effects but also improves clinical manifestations of schizophrenia [21,22]. Studies have also found that topiramate use is associated with reduced PANSS scores in patients with schizophrenia although these findings were not seen in all trials [22,23,26].

Topiramate was well-tolerated in our study, adverse effects were mild, and no patient withdrew from the study. We did not see serious adverse effects such as nephrolithiasis, acute angle glaucoma, or metabolic acidosis which were reported in some studies [27-29]. Of note, all adverse effects in both groups were transient and resolved over time during the study period.

The main strength of our study is its randomized placebo-controlled study design. However, relatively small sample size may have resulted in our inability to see some outcomes. Furthermore, because duration of the study was short, we were unable to determine if the effect of topiramate on weight gain was sustained over a longer period.

CONCLUSION

In summary, we show that topiramate can be used as a preventive therapy for weight gain in patients with schizophrenia. Further clinical trials with longer duration of follow-up are needed to validate our findings and examine if topiramate is safe and effective over extended periods.

ACKNOWLEDGEMENTS

We would like to thank nursing, administrative and secretarial staff of the hospital's psychiatry department and clinic for their contribution to maintenance of our patient record, without which this project would not have been impossible.

REFERENCES

1. Coodin S. Body mass index in persons with schizophrenia. *Can J Psychiatry*. 2001;46(6):549–555.
2. Brown S, Birtwistle J, Roe L, *et al*. The unhealthy lifestyle of people with schizophrenia. *Psychol Med*. 1999;29(3):697–701.
3. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156(11):1686–1696.
4. Biton V, Montouris GD, Ritter F, *et al*. A randomized, placebo-controlled study of topiramate in primary generalized tonic–clonic seizures. *Neurology*. 1999;52:1330–1337.
5. Chengappa KNR, Levine J, Rathore D, *et al*. Long-term effects of topiramate on bipolar mood instability, weight change and glycemic control: a case-series. *Eur Psychiatry*. 2001;16(3):186–190.
6. Gordon A, Price LH. Mood stabilization and weight loss with topiramate. *Am J Psychiatry*. 1999;156(6):968–969.
7. Ben-Menachem E, Axelsen M, Johanson EH, Stagge A, Smith U. Predictors of weight loss in adults with topiramate-treated epilepsy. *Obes Res*. 2003;11(4):556–562.
8. Arnone D .Review of the use of topiramate for treatment of psychiatric disorders. *Ann Gen Psychiatry*. 2005;4(1):5.
9. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia*. 2000;41(Suppl 1):S3–S9.
10. Ko YH, Joe SH, Jung IK, Kim SH. Topiramate as an adjuvant treatment with atypical antipsychotics in schizophrenic patients experiencing weight gain. *Clin*

Neuropharmacol. 2005:28(4):169–175.
11. Lee C, Wu KH, Habil H, Dyachkova Y, Lee P. Treatment with olanzapine, risperidone or typical antipsychotic drugs in Asian patients with schizophrenia. *Aust N Z J Psychiatry*. 2006;40(5):437–445.
12. Van AM, Mancini C, Pipe B. Topiramate treatment for SSRI-induced weight gain in anxiety disorders. *J Clin Psychiatry*. 2002;63(11):981–984.
13. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med*. 2005;142(7):532-546.
14. Aldenkamp AP, Baker G, Mulder OG. A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures. *Epilepsia*. 2000;41:1167–1178.
15. Mousavi SG, Golchin SH , Afshar H. Add-On Topiramate In Treatment of Schizophrenia. *Journal of Isfahan Medical School*. 2007;25;85(in Persian).
16. Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. *Acta Psychiatr Scand*. 1999;100(1):3–16.
17. Dufresne RL, Valentino D, Kass DJ. Thioridazine improves affective symptoms in schizophrenic patients. *Psychopharmacol Bull*. 1993;29(2):249–255.
18. Nemeroff CB. Dosing the antipsychotic medication olanzapine. *J Clin Psychiatry*. 1997;58(Suppl 10):45–9.
19. Umbricht DSG, Pollack S, Kane JM. Clozapine and weight gain. *J Clin Psychiatry*. 1994;55(Suppl B):157–60.
20. Ganguli R. Weight gain associated with antipsychotic drugs. *J Clin Psychiatry*. 1999;60(Suppl 21):20–4.
21. Narula PK, Rehan HS, Unni K.E.S, Gupta N. Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: A double-blind, placebo-controlled trial. *Schizophr Res*. 2010;118(1-3):218–223.
22. Hahn MK, Remington G, Bois D, Cohn T. Topiramate Augmentation in Clozapine-Treated Patients With Schizophrenia. *J Clin Psychopharmacol*. 2010;30(6):706-710.
23. Lévy E, Agbokou C, Ferreri F, Chouinard G, Margolese HC. Topiramate induce weight loss in schizophrenia; A retrospective case series study. *Can J Clin Pharmacol*. 2007;14(2):234-239.
24. Talaei A, Faridhoseini F, Kazemi H. Effect of topiramate on drug associated weight gain of patients with schizophrenia and bipolar I disorders: a dose ranging study. *Turkish Journal of Psychiatry*. 2015; 27(2).
25. Shapiro M, Reid A, Olsen B, Taasan M, McNamara J. Topiramate, zonisamide and weight loss in children and adolescents prescribed psychiatric medications: A medical record review. *Int J Psychiatry Med*. 2016;51(1):56–68.
26. Behdani F, Hebrani P, Rezaei Ardani A, Rafee E. Effect of Topiramate Augmentation in Chronic Schizophrenia: A Placebo-Controlled Trial. *Arch Iran Med*. 2011;14(4):270-275.
27. Banta JT, Hoffman K, Budenz DL. Presumed topiramate-induced bilateral acute angle-closure glaucoma. *Am J Ophthalmol*. 2001;132(1):112–114.
28. Kuo RL, Moran ME, Kim DH, *et al*. Topiramate-induced nephrolithiasis. *J Endourol*. 2002;16:229–231.
29. Ko CH, Kong CK. Topiramate-induced metabolic acidosis: report of two cases. *Dev Med Child Neurol*. 2001;43:701–704.