ORIGINAL ARTICLE

Metabolic effects of adding Topiramate on Aripiprazole in bipolar patients aged between 6-18 years, a randomized, double-blind, placebo-controlled trial

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Background: second-generation antipsychotics (SGAs) are associated with metabolic side effects in child and adolescents. The aim of this study is to evaluate the metabolic effects of adding topiramate on aripiprazole in patients with bipolar disorder (BD) aged between 6 and 18 years. **Materials and Methods:** A 12-week, double-blind, placebo-controlled, randomized trial was conducted in the child psychiatric units of university hospitals. Forty patients aged between 6 and 18 years with new diagnosis of BD participated in the study. Eleven patients were excluded. Subjects received aripiprazole plus topiramate (Group 1, $n = 15$) or aripiprazole (Group 2, $n = 14$) for a 3-month period. Young mania rating scale (YMRS) was used for measuring the manic symptoms severity. Primary outcome measures included weight, height, body mass index (BMI), waist circumference, abdominal circumference, and blood pressure. Secondary outcome measures included fasting blood glucose, hemoglobin A1C, fasting insulin, and fasting lipid profile. Changes in metabolic profile during the study were obtained by using repeated measures of variance. **Results:** During a 3-month follow-up, YMRS measures decreased significantly in both groups with a significant difference between groups ($P < 0.05$). The mean of weight, BMI, and high-density lipoprotein levels in group 2 were significantly increased ($P < 0.05$), and the mean of low-density lipoprotein level in group 1 was decreased ($P < 0.05$). No significant differences were observed in anthropometric parameters and metabolic indices between groups ($P > 0.05$). **Conclusion:** Adding topiramate on aripiprazole is effectivefor controlling bipolar disorder as well as metabolic adverse effects of SGAs in juvenile patients.

Key words: Bipolar disorders, manias, metabolic syndrome, topamax

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INTRODUCTION

Juvenile bipolar disorder is a life-long psychiatric illness associated with significant morbidity and increased mortality due to both medical comorbidities such as metabolic syndrome (Mets) and high suicide rate.[1,2] The presence of Mets seems to be related not only to the general medical status but also to the psychiatric status of people with bipolar disorder (BD).[3-5] It has been reported that patients with comorbid BD and Mets undergo more hospitalizations and show poorer insight and global functioning and lower treatment adherence.[6] Hence, effective pharmacological treatment is an important component of treatment.[7] Pharmacological treatments may reduce long-term morbidity in juvenile BD.[8] The use of second-generation antipsychotics or second-generation antipsychotics (SGAs) has been developed because of their effectiveness and much lower rates of extrapyramidal side effects compared with old-generation drugs.[9] However, in many cases, SGAs have unwanted side effects, especially Mets.[10] It has been shown that SGA-related Mets is even more dramatic in children and adolescents than in adults and these patients already suffer from low self-esteem

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and the stigma of being different from their peers.[11] Nonpharmacological and pharmacological strategies have been approved for counteract Mets in adult population, but studies in child and adolescents are currently limited to metformin due to safety concerns and efficacy issues of other medications in this population.[12,13] The objective of this study was to assess the metabolic effects of adding topiramate on aripiprazole in bipolar patients aged between 6 and 18 years, in a randomized, double-blind, placebo-controlled trial.

MATERIALS AND METHODS

Participants

Regarding to previous similar studies and difference between two means formula (α = 5%, d = 2.5 and power = 80%), 40 new bipolar patients aged between 6 and 18 years who were visited or were admitted in child psychiatric units of hospitals affiliated with Isfahan University of Medical Sciences were participated in the study.

Inclusion criteria

Inclusion criteria were lack of chronic physical illness or comorbid psychiatric disorder, negative history of receiving antipsychotic drugs or mood stabilizers or any other drugs that could change appetite during recent 3 months before the study, lack of history of allergic reaction to topiramate, lack of history of renal insufficiency or renal stone, and age between 6 and 18 years.

Exclusion criteria

Exclusion criteria were patient's or family's unwillingness to continue participation in study, the need for electroconvulsive therapy (ECT) treatment during the study, and any unexpected new physical illness that could potentially change medical care of the patient. The written consent was signed by parents/guardians and the assent was given by adolescents.

Design

This study was designed as a double-blind, placebo-controlled trial and conducted from July 2020 to July 2021 during 3 phases (0, 1, 3 months). Our study was approved in the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.235), and the study protocol was registered in the Iranian Registry of Clinical Trials (IRCT20200606047668N1). All the researchers of this study were believed in Helsinki Ethical principles. Study treatments were randomly assigned using an online computerized randomization system. Eligible participants received double-blind topiramate (Darou Pakhsh, IRAN) and aripiprazole (Dr. Abidi, IRAN) as Group 1 or aripiprazole as Group 2 in 1:1 ratios. Starting dose of aripiprazole in both groups was 5 mg/day orally and increased weekly to a maximum dose of 10–30 mg/day. Subjects in group 1 were given topiramate starting at 12.5 mg orally/day, which was titrated up by 12.5 mg/week as tolerated without side effects (nausea, vomiting and memory disturbances) up to a target dose of 150 mg/day. Patients were evaluated over a 12-week period to monitor psychiatric symptoms and metabolic profile and side effects and were instructed not to change their baseline diet or activity level during the study. Diagnosis of BD and rule-out of other comorbid psychiatric disorders were made by a child and adolescent psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria and by a semi-structured diagnostic interview, using kiddie schedule for affective disorders and schizophrenia that provides reliable and valid youth psychiatric diagnoses in Iranian population.[14,15] Symptom severity improvement was assessed using young mania rating scale (YMRS) that has adequate psychometric properties in the Iranian population.[16] The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 h.

Clinical measures and safety monitoring were conducted during all visits. Laboratory tests for metabolic profile including fasting blood sugar(FBS), triglyceride(TG),chol esterol(Chol), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and hemoglobin A1C (HbA1C) were conducted at weeks 0, 4, and 12. Girls above the age 9 took a urine pregnancy test before initiating the research. Primary outcome measures included weight, height, body mass index (BMI), waist circumference, abdominal circumference, and blood pressure. Secondary outcome measures included lipid profile, FBS, HbA1C, fasting insulin, and fasting lipid profile.

Statistical analysis

After data gathering, measures analyzed with Statistical Package for the Social Sciences (SPSS Inc., Chicago, USA) version 14 were shown as n (%) and mean ± standard deviation (SD). Significance determined as $P < 0.05$. Regarding normal distribution of measurements, based on Kolmogorov–Smirnov test, Chi-square test and independent *t*-test were used when appropriate. For quantitative outcome measures, we used repeated-measures analyzes of covariance after adjustment of confounding variables such as age, gender, history of previous hospitalization or substance use disorder, and the dose of aripiprazole.

RESULTS

Participants consisted of 40 new bipolar patients between age 6 and 18 with equal numbers in topiramate and placebo groups. Eleven of participants were excluded from study (5 in topiramate group and 6 in placebo group). Six

patients were excluded due to incomplete use of drug or unwillingness to stay in study. Two participants excluded due to exacerbation of symptoms and need for ECT and other appropriate treatments and three patients were excluded due to drug side effects. In this study, one of the participants in control group suffered from restlessness and irritability after drug administration. One of participants in treatment group expressed dystonia. Elevated liver enzymes were observed in another patient in the same group during the study. All of them were referred for further evaluation and appropriate intervention [Figure 1].

Finally, 75% of participants in Group 1 and 70% in Group 2 completed the study. The mean age of participants that completed the trial was 12.93. Among these, 44.8% were girls. The statistical analysis did not show any significant difference in baseline characteristics such as age, gender, previous hospitalization history, educational status of the patients and parents, and history of metabolic disorders in family members between groups [Table 1].

Groups 1 and 2 were not significantly different regarding the dose of aripiprazole at the baseline in time 0 (0 vs. 0 mg), after 4 weeks in time1 (12.33 ± 4.58 mg vs. 10.89 ± 3.61 mg) and at the end point of study at time 2, respectively (15.33 ± 8.12 mg vs. 13.57 ± 3.49 mg) ($P > 0.05$). Mean topiramate dose in Group 1 in time1 was 52.50 ± 27.63 mg, and at the time 2 was 55.00 ± 27.06 mg ($P > 0.05$).

The severity of bipolar symptoms decreased significantly over a 3-month period of time in both groups while using YMRS ($P < 0.001$). In addition, the mean ± SD of YMRS was lower in Group 1 compared to Group 2 but this difference was only statistically significant at the time 2 (7.53 ± 4.15 vs. 12.67 ± 7.15) ($P < 0.028$) [Table 2].

In pairwise comparison of all anthropometric parameters during time 0, time 1, and time 2, there was no significant difference between groups ($P > 0.05$). But in Group 2, the mean ± SD of weight in time 2 (61.49 ± 17.84) was higher in comparison with time 0 (59.06 ± 18.40) with statistically significant difference ($P = 0.012$). BMI comparison in Group 2 has a similar pattern and statistically significant ($P = 0.016$) different levels in time 2 (24.41 ± 4.08) compared with time 0 (23.92 ± 4.08) [Table 3].

Finally, within-group comparison of metabolic parameters concluded that the mean of LDL in Group 1 decreased significantly during the 3-month follow-up ($P = 0.015$). In contrast, mean of HDL in Group 2 significantly increased during the same period of time ($P = 0.024$). Comparison of other metabolic parameters revealed no significant

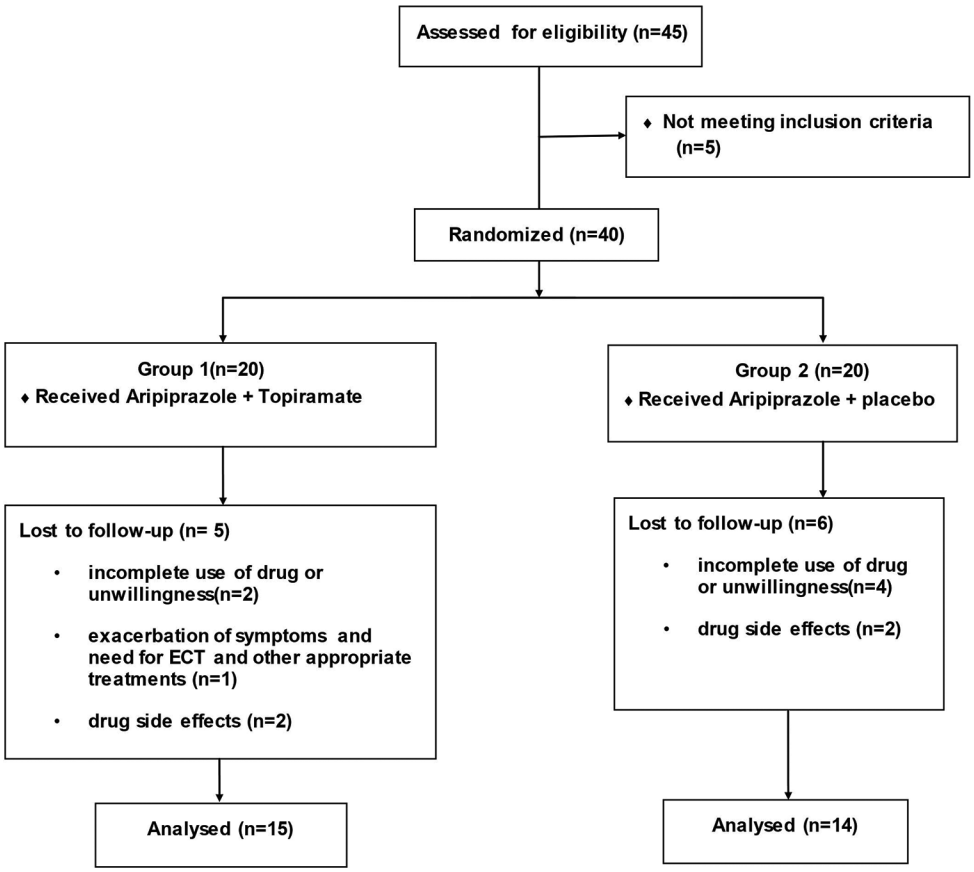

Figure 1: consort diagram

Table 1: Baseline demographic and clinical characteristics of patients

Characteristics	Group 1 (*n*=15), *n* (%)	Group 2 (*n*=14), *n* (%)	*P*
Age (years)	13.13±1.64	12.71±3.07	0.64
Gender			
Boy	9 (60.0)	7 (50.0)	0.71
Girl	6 (40.0)	7 (50.0)	
Previous hospitalization history	1 (6.7)	0	0.99
History of substance use	1 (6.7)	0	0.99
Education status			
Illiterate	0	2 (14.3)	
Primary	4 (26.7)	6 (42.9)	0.06
high school	11 (73.3)	6 (42.9)	
Father's level of education			
Illiterate	0	1 (7.1)	0.74
Primary	3 (20.0)	2 (14.3)	
Diploma	9 (60.0)	8 (57.1)	
University	3 (20.0)	3 (21.4)	
Mother's level of education			
Illiterate	0	1 (7.1)	0.10
Primary	5 (33.3)	1 (7.1)	
Diploma	4 (26.7)	10 (71.5)	
University	6 (40.0)	2 (14.3)	
History of family disease			
DM	2 (13.3)	6 (42.9)	0.10
HTN	4 (26.7)	6 (42.9)	0.45
IHD	4 (26.7)	6 (42.9)	0.45
Obesity	9 (60.0)	4 (28.6)	0.13
Hyperlipidemia	4 (26.7)	4 (28.6)	0.90

Aripiprazole plus topiramate (Group 1); Aripiprazole (Group 2). DM=Diabetes mellitus; HTN=Hypertension; IHD=Ischemic heart disease

Table 2: Comparison of Young Mania Rating Scale within and between groups

YMRS	Group 1 (*n*=15)	Group 2 (*n*=14)	*P*[a]
T0	29.93±6.27	33.36±8.50	0.22
T1	12.87±6.25	14.50±5.79	0.47
T2	7.53±4.15	12.67±7.15	0.02
P[b]	<0.001	<0.001	

[a]Comparison of the mean of the variable between the two groups using independent *t*-test; [b]Comparison of mean variable changes over time (over 3 months) in each of the two groups using Repeated measure ANOVA; Aripiprazole plus Topiramate (Group 1); Aripiprazole (Group 2). YMRS=Young Mania Rating Scale; T0=Before intervention; T1=After 4 weeks from the start of intervention; T2=At the end of 3 months

difference within and between groups during time 0-time 2 interval ($P > 0.05$) [Table 4].

DISCUSSION

This study showed that a 3-month treatment with aripiprazole (with and without topiramate) would result in improvement of manic symptoms' severity. Moreover, addition of topiramate to this treatment amplifies the aforementioned positive therapeutic effects. In addition, this study revealed that a 3-month treatment with aripiprazole in placebo group was significantly associated with weight gain and subsequent BMI changes. Although adding topiramate would not result in weight loss and decrease in BMI, counteracts with some SGA-induced metabolic adverse effects such as weight gain and morbid obesity. Other findings included significant decrease in LDL levels in Group 1 and statistically significant increase of HDL levels in Group 2; however, these changes were within normal range and would have no clinical significance. Data on metabolic effects of topiramate in BD of young child and adolescents are limited and previous studies have shown different results.[17-19] In 2007, Tramontina S *et al*. who used a different methodology showed that topiramate has antimanic effects in adolescents and is effective in decreasing weight when given over 12 weeks.[20] They examined patients who presented with over 5% increase in their weight when compared with baseline, but in our study, the preventive effects of Topiramate were considered. Similar study by Li *et al*. in 2008 on effects of topiramate on weight and metabolism in children with epilepsy demonstrated that BMIs of children with epilepsy decreased significantly during a 12-week treatment period with topiramate, but the decrease had no correlation to the dosage of topiramate, suggesting that topiramate-induced weight loss is independent of its dosage.[21] Similar to our study, they found no significant differences on plasma FBS and insulin indices before and after the treatment and the author concluded that the change of glucose metabolism could not be a key factor to cause decrease of weight in topiramate treatment. Shapiro M, *et al*. who came up with similar findings[22] found that topiramate and zonisamide may be utilized for weight loss in a pediatric psychopharmacological treatment regimen but their participants population included epileptic patients and the study design was medical record review. Javad Mahmoudi-Gharae *et al.* in 2012 compared the effects of topiramate versus valproate sodium as an add-on therapy to a combination of lithium and risperidone (Li + Ris) on body weight and serum lipid profile in children and adolescents with BD.[23] They found that when topiramate and valproate sodium are used for 6 weeks as adjunctive treatment to a combination of Li + Ris, they act alike on lipid milieu of children and adolescents with BD. Other finding of this study was that Both Li + Ris/Valproate and Li + Ris/Topiramate therapies can lead to an increase in BMI z-score. This increase was statistically significant with Li + Ris/Valproate therapy, which suggests that topiramate could attenuate the ongoing weight gain from lithium and risperidone. However, according to the discussion in the end of their study, it should be emphasized that metabolic changes could have been potentially obscured by administration of the combination regimen used in this trial. In addition, past treatment exposures, including prior "double hit" by lithium and risperidone, may have influenced the result of

Table 3: Comparison of anthropometric parameters within and between groups

Anthropometric parameters	Group 1 (*n*=15)	Group 2 (*n*=14)	*P*[a]
Height (cm)			
T0	159.73±8.28	155.28±16.44	0.36
T1	160.00±8.49	156.53±16.62	0.48
T2	161.73±9.14	157.43±16.89	0.39
P[b]	0.33	0.89	
Weight (kg)			
T0	65.31±16.49	59.06±18.40	0.34
T1	64.28±15.51	60.18±17.67	0.51
T2	63.63±15.20	61.49±17.84	0.73
P[b]	0.86	0.01	
BMI (kg/m^2)			
T0	25.41±5.33	23.92±4.08	0.40
T1	24.95±4.99	24.10±3.82	0.61
T2	24.09±4.11	24.41±4.08	0.83
P[b]	0.59	0.01	
WC (cm)			
T0	89.20±11.79	83.57±11.84	0.21
T1	86.33±11.21	83.93±12.23	0.58
T2	85.47±12.46	84.93±12.34	0.90
P[b]	0.25	0.92	
HiC (cm)			
T0	97.93±13.18	93.39±13.54	0.36
T1	97.07±11.58	95.18±14.82	0.70
T2	95.05±12.31	96.86±13.82	0.71
P[b]	0.94	0.84	

[a]Comparison of the mean of the variable between the two groups using independent *t*-test; [b]Comparison of mean variable changes over time (over 3 months) in each of the two groups using Repeated measure ANOVA; Aripiprazole plus Topiramate (Group 1); Aripiprazole (Group 2). BMI=Body mass index; HiC=Hip circumference; WC=Waist circumference; T0=Before intervention; T1=After 4 weeks from the start of intervention; T2=At the end of 3 months

this study, which precludes precise conclusions about direct metabolic changes with valproate sodium and topiramate. Fox CK, *et al*. assessed the safety and efficacy of short-term meal replacement therapy followed by topiramate for BMI reduction in adolescents with severe obesity.[24] In summary, their trial during 24 weeks with topiramate at a dose of 75 mg/day demonstrated limited efficacy for BMI reduction in adolescents with severe obesity compared to placebo.

Animal studies have shown that topiramate could increase the insulin sensitivity and decrease the blood concentration of insulin, both of which will cause a loss of appetite and an increase of lipid metabolism.[25] Wilkes' group found that topiramate could reduce insulin resistance.[26]

CONCLUSION

In summary, this trial demonstrates the efficacy of topiramate as adjuvant treatment for controlling BD as well as metabolic adverse effects of SGAs in juvenile patients.

Table 4: Comparison of metabolic parameters within and between groups

Variables	Group 1 (*n*=15)	Group 2 (*n*=14)	*P*[a]
SBP (mmHg)			
T0	111.80±11.39	106.86±9.31	0.21
T1	114.07±11.67	109.36±14.37	0.34
T2	114.40±11.60	109.93±7.99	0.24
P[b]	0.93	0.34	
DBP (mmHg)			
T0	67.47±8.11	66.00±10.08	0.66
T1	66.07±8.65	70.50±9.69	0.20
T2	67.00±6.71	71.71±7.05	0.07
P[b]	0.19	0.42	
TG (mg/dL)			
T0	116.87±41.46	100.36±29.97	0.40
T1	118.60±53.18	103.57±64.08	0.49
T2	122.80±53.23	100.85±78.97	0.39
P[b]	0.57	0.18	
TC (mg/dL)			
T0	155.00±28.53	151.93±37.55	0.80
T1	153.00±27.96	161.00±40.34	0.53
T2	150.40±27.41	158.38±40.18	0.54
P[b]	0.85	0.52	
LDL (mg/dL)			
T0	90.40±21.58	79.96±34.10	0.33
T1	86.93±25.99	90.93±33.07	0.71
T2	83.48±35.28	89.77±34.83	0.64
P[b]	0.01	0.68	
HDL (mg/dL)			
T0	42.37±4.53	46.86±11.44	0.21
T1	42.47±8.97	54.57±19.71	0.05
T2	45.00±9.80	48.23±12.15	0.44
P[b]	0.33	0.02	
FBS (mg/dL)			
T0	92.00±8.16	89.50±8.75	0.06
T1	90.67±8.28	89.43±6.85	0.66
T2	94.13±15.00	90.85±6.41	0.47
P[b]	0.56	0.57	
HbA1C (%)			
T0	5.26±0.31	5.02±0.47	0.11
T1	5.13±0.28	5.26±0.51	0.39
T2	5.17±0.44	5.27±0.41	0.55
P[b]	0.29	0.61	
Fasting insulin level (IU/L)			
T0	16.19±12.05	10.52±7.18	0.13
T1	16.66±13.30	11.62±6.01	0.20
T2	18.16±13.11	12.90±7.53	0.21
P[2]	0.43	0.70	

[a]Comparison of the mean of the variable between the two groups using independent *t*-test; [b]Comparison of mean variable changes over time (over 3 months) in each of the two groups using Repeated measure ANOVA; Aripiprazole plus Topiramate (Group 1); Aripiprazole (Group 2). BP=Blood pressure; SBP=Systolic BP; DBP=Diastolic BP; TG=Triglycerides; TC=Triglycerides; LDL=Low-density lipoprotein cholesterol; HDL=High-density lipoprotein cholesterol; FBS=Fasting blood sugar; HbA1C=Hemoglobin A1c; T0=Before intervention; T1=After 4 weeks from the start of intervention; T2=At the end of 3 months

Although metabolic and anthropometric parameters remained in normal clinical range during this study, they

may be due to lower metabolic adverse effect of aripiprazole compared with other SGAs, small sample size, or short duration of study. The limitation of this study included large amount of participant dropouts in both case and control groups and subsequent small sample size to observe more clinically significant effects. Given this limitation, further investigations with longer follow-up can provide more accurate results.

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Conflicts of interest
There are no conflicts of interest.

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