Original Article

Topiramate versus Valproate Sodium as Adjunctive Therapies to a Combination of Lithium and Risperidone for Adolescents with Bipolar I Disorder: Effects on Weight and Serum Lipid Profiles

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Objective: To compare 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 bipolar disorder.
Methods: In a single-blind randomized clinical trial, thirty children and adolescents with bipolar disorder type I in the manic or mixed phase ,treated with the combination of Li+Ris at therapeutic doses for at least 4 weeks who had the indication of add-on therapy due to a recurrent episode; a partial response or non response in the current episode or relapse were included. Participants were randomly assigned to receive either topiramate or sodium valproate as the third drug add-on therapy for a total of 6 weeks. Weight, height and serum lipid profiles were determined at baseline and at the end of week 6.
Results: Differences in the mean levels of lipid profiles at baseline and after week 6 evaluation were not significant in both treatment groups.
BMI z-score increased in both treatment groups, being significant only in the Li+Ris/Valproate group, increasing from (mean ±SD) 0.38 ±0.55 to 0.72 ±1.23 ($p<0.05$). Between group changes in BMI z-score was not significant.Among the BMI percentile categories, participants in the normal weight subgroup showed a significant increase in BMI z-score during the 6 week trial, compared to overweight/obese subgroup, in both Li+Ris/Valproate and Li+Ris/Topiramate treatment groups. Elevated mean serum level of triglyceride and a high proportion of participants with elevated total cholesterol (≥ 170 mg/dl), triglyceride (≥ 110 mg/dl), and BMI percentile 85-<95 at baseline (before randomization) and at the end of 6 week study were noted.
Conclusion: When topiramate and valproate sodium are used for six weeks as adjunctive treatment to a combination of Li+Ris, they act alike on lipid milieu of children and adolescents with bipolar disorder.
Both Li+Ris/Valproate and Li+Ris/Topiramate therapies can lead to an increase in BMI z-score. This increase is statistically significant with Li+Ris/Valproate therapy. This suggests that topiramate could attenuate the ongoing weight gain from lithium and risperidone .
In this study, the majority of participants who gained weight were those with BMI less than 85th percentile. This suggests that normal weight patients may have greater weight gain potential than overweight/obese patients.High proportion of metabolic abnormalities among the patients at baseline, which remained elevated throughout the trial, warrants cardiometabolic monitoring in this population.

Keywords: *Body weight, Lipids, Lithium, Risperidone, Topiramate, Valproate sodium*

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Bipolar disorder (BD) in children and adolescents is a chronic psychiatric condition (1) requiring long term pharmacotherapy with conventional mood stabilizers including lithium and antiepileptic drugs (AEDs) and/or antipsychotics (2). Adults with BD are known to have a higher prevalence of medical co-morbidities including obesity, metabolic and cardiovascular illnesses (3-7) related to the disorder itself or to its treatment (5, 8). Less is known about metabolic and cardiovascular co-morbidities in children and adolescents with BD; however, greater prevalence of obesity/overweight (8,9), cardiovascular and metabolic risk factors is also reported in this group (8). Atherosclerotic cardiovascular disease is a well known consequence of abnormal lipid profiles both in adult and adolescent populations (10, 11).Additionally, children and adolescents may be more vulnerable and have an accelerated development of such adverse

effects when compared with adults (12- 14). Furthermore, obesity in adolescents is a reason for non-adherence to treatment (15) and is associated with increased psychiatric burden (9) .

Current treatment guidelines suggest that valproate sodium is effective both as monotherapy in acute treatment of children and adolescents with manic or mixed episodes without psychosis and as augmentation therapy for those with a partial response to monotherapy, or with psychotic symptoms (2). However, the recommendations were mainly based on uncontrolled trials. According to the results of a recent double-blind, randomized, placebo-controlled trial, divalproex extended-release (ER) is not effective as monotherapy in children and adolescents with BD type I (BD1), either in the mixed or in the manic phase (16). Wagner et al. concluded that no evidence supports divalproex ER utilization in this age group and it is not likely that the formulation of divalproex affect efficacy (16). In terms of drug safety, a 6-month open-label extension of the above study, reported similar side effect profile of divalproex ER in youth as in adult population; weight gain, nausea and increased appetite being the most common side effects of this medicine (17).

Topiramate may provide some benefits in treating children and adolescents with BD1; controlled studies are needed to better define its role either as monotherapy or a combination regimen (18, 19). DelBello et al. conducted a randomized, double-blind, placebo-controlled trial of topiramate monotherapy in youth BD1. The results of the study were inconclusive due to early discontinuation of topiramate, since lack of topiramate efficacy was observed in a mania trial in adults (18). Regarding studies conducted on adults with BD1, topiramate monotherapy did not show significant difference in efficacy as compared to placebo (20). In addition, Chengappa et al. demonstrated that the efficacy of adjunctive topiramate and adjunctive placebo in lithium or valproate sodium treated BD1 subjects were not different (21).

Antipsychotics (5, 9, 12-14, 22-25), and mood stabilizers used in the management of BD are linked with adverse metabolic effects (5, 8, 14). When multiple classes of psychotropic medications are co prescribed, the metabolic and cardiovascular related side effects become more frequent (23). A recent meta-analysis concluded that children exposed to combination of antipsychotics and mood stabilizers were more prone to gain weight than when mood stabilizers were given alone (14) .

Given findings from a r ecent meta-analysis of mood stabilizers in children and adolescents' BD, data is sparse for body composition effects and is lacking for fasting lipid effects (14).

Correspondingly, current data on the influence of AEDs on lipid profile are mainly obtained from studies conducted in pediatric and adult patients with epilepsy (26-29); or in adult population with BD (30). Furthermore, the results of the studies are contradictory (31-33).

Regarding antipsychotics, findings on the effects of atypical antipsychotic on lipid profile in children and adolescents is not conclusive yet (34).Dyslipidemia is a common finding in hospitalized adolescents exposed to atypical antipsychotics (25) .

To reduce complications inflicting on this already prone population, psychiatrists should pay attention to choosing proper medications. A number of studies have found an advantage with topiramate in terms of body weight, including pediatric BD population (15, 35, 36) .

Given the fact that bipolar symptoms may not always be controlled by one class of agents (14), finding a combination of mood stabilizers with therapeutic gains and lower risk of adverse metabolic effects seems essential. To our knowledge, a co mparative study between tolerability of topiramate and valproate sodium in treatment of BD in youth has not been conducted yet.We present the results of a p rospective, single-blind, randomized trial of topiramate versus valproate sodium added to lithium and risperidone therapy (Li+Ris) on BMI and lipid profile in adolescents with BD. In this study, we also evaluated the prevalence of abnormal lipid profiles and BMI according to a widely accepted criteria defining elevated levels specific for adolescents (13). The present study is a part of a larger trial (37); the primary objective of the global trial was to compare the effectiveness of adjunctive topiramate versus valproate sodium added to a combined treatment of Li+Ris in children and adolescents with BD. Secondary objectives were to compare their effects on serum lipid profile and body weight.

Materials and Method

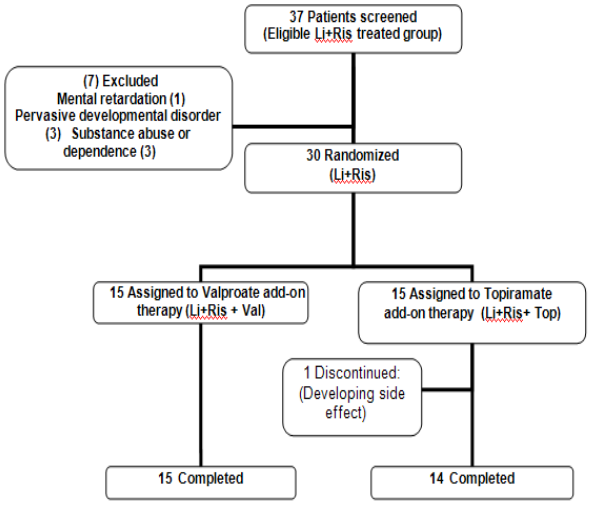
Patient population

The study was conducted in the department of child and adolescent psychiatry, at Roozbeh hospital affiliated to Tehran University of Medical Sciences. Diagnosis of BD and comorbidities were made by a child and adolescent psychiatrist according to DSM-IV-TR criteria, and by a s emi-structured diagnostic interview , using Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime version (K-SADS-PL).

Symptom severity improvement was assessed using Young Mania Rating Scale (YMRS), and Clinical Global Impression (CGI) scale.

Inpatient adolescents aged between 11-18 years with the diagnosis of current BD1 disorder in the manic or mixed phase ,eligible for adding adjunctive therapy ,who were treated with Li+Ris at therapeutic doses for at least 4 weeks were selected .

In the context of the center the study was accomplished in, children and adolescents with BD are regularly initiated on two agents (Li+Ris) together. Therefore, those patients who received the above combination for



Abbreviations: Li: Lithium, Ris: Risperidone, Top: Topiramate, Val: Valproare sodium

Figure 1. Flowchart for the Process of the Study

at least 4 weeks and met the criteria for adjunctive therapy entered the study. Indications for receiving adjunctive therapy included experiencing a recurrent episode, a partial response or no response in the current episode, or relapse evaluated by one child and adolescent psychiatrist.

The definition of response, relapse, recurrence, remission and recovery in our study is as follows :

Response: no symptoms or significant reduction (50%) in bipolar symptoms; relapse: a DSM manic or mixed episode occurring during the period of remission; recurrence: the emergence of symptoms during the period of recovery; remission: a period of > 2 months with no bipolar symptoms; recovery: the absence of significant symptoms of mania or mixed episode for >2 months.

The exclusion criteria included (i) Comorbidity of mental retardation, pervasive developmental disorder, seizure disorder, anorexia nervosa according to clinical assessment; (ii) a severe mental illness requiring ECT or other treatment modalities during trial; (iii) any contraindication to the study drugs; (iv) current substance abuse or dependence within 3 months; (v) pregnancy; (vi) clinically significant medical illness; (vii) body weight under 30 kg; (viii) positive personal or family history of nephrolithiasis.

The study was performed in accordance with the Declaration of Helsinki, and was approved by Ethic Committee of Tehran University of Medical Sciences. A Written informed consent was obtained from the participants and their parents prior to initiation of valproate sodium or topiramate.

Study design

Participants' flow chart is shown in Figure 1.

YMRS was applied to assess illness severity before and after initiation of topiramate or valproate sodium .

Topiramate was initiated at a dose of 25 mg/day; dosage was increased by 25 mg every 3 days to a maximum dose of 200 mg/day or increased as tolerated. Valproate sodium was initiated at a dose of 10 mg/kg in divided doses with increases of 5 mg/kg every 3 days to a maximum daily dose of 20 -30 mg/kg or as tolerated. Dosing schedules were designed based on experience of the investigators. Lithium and risperidone were kept stable at therapeutic serum level and dose respectively.

Concomitant treatments with haloperidol injections (as needed for severe agitation) and biperiden (in the event of facing EPS symptoms) were allowed. Participants were not allowed to have any other concomitant treatments, including medications for their co-morbid illnesses .

Mean lithium dose as well as its serum level and doses of risperidone, biperiden and haloperidol were recorded at the commencement, during each week and at the end of the study.

Valproate sodium trough plasma level was measured once after titration was completed. Side effects of the study drugs were systematically recorded every two weeks using a checklist .

Weight, height and serum lipid profiles were determined at baseline (a day before adding the adjunctive medications to Li+Ris) ,and at the end of week 6 of adjunctive therapy. Body weight of the patients, in light clothing without shoes, was measured using a digital scale; height was measured using a wall mounted stadiometer. Blood samples for total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL) were taken between 8 to 9 a.m. after a 12- hour overnight fast. All morning medications were held until after the blood draw. Controlled fasting status and treatment adherence were determined and confirmed by the nursing staff for inpatients and by parents' reports for outpatients. TC, HDL and TG were measured using enzymatic assays, and LDL was calculated from the Friedewald equation (38). The Quetelet Index BMI was calculated as weight (kg) divided by height (m2).

Statistical analysis

Lipid values and BMI were assessed to confirm that results were normally distributed and appropriate for parametric analysis. Mean scores comparison before-after interventions in each group and between groups' changes were performed using two tailed, paired sample t-test and unpaired t-tests respectively. Repeated measure ANOVA was used to compare weekly changes of drug doses and lithium level during treatment. Also, unpaired t-tests were used to compare parametric demographic characteristics and baseline level of lipid and BMI scores. Non parametric variables were compared using Chi-square, Mann-Whitney and Wilcoxon signed rank tests. Significant levels were considered 0.05.

Table. 1 Demographic and illness characteristics of participants and their comparison between two groups

variables		Total subjects (N=29)	Subjects receiving Li+Ris/Val (N=15)	Subjects receiving Li+Ris/Top (N=14)	P value[a]
Age (mean±SD)		15.72±1.30	15.93±1.53	15.50±1.01	0.382
Gender (N / %)	male	11 / 37.9	5 / 33.3	6 / 42.9	
	female	18 / 62.1	10 / 66.7	8 / 57.1	0.710
Clinical characteristics					
illness duration (month)		20.07±17.93	16.42±11.48	24.00±22.84	0.282
number of Previous episodes		1.96±0.86	1.73±0.70	2.21±0.97	0.137
number of Hospitalization		1.53±0.94	1.07±0.61	2.08±0.99	0.004
Illness severity					
YMRS score	Base line	25.17±10.17	24.80±11.91	25.57±8.33	0.843
	End point	11.72±10.58	12.00±13.40	11.42±6.91	0.888
Drugs[b]					
Lithium	Mean dose (mg)	1377.58±279.53	1276.66±314.45	1485.71±193.57	0.04
	Maximum dose (mg)	1800	1800	1800	…
	Mean serum level (mEq/L)	0.97±0.14	0.99±0.18	0.94±0.09	0.447
Risperidone	Mean dose	3.04±1.36	3.00±1.59	3.07±1.18	0.892
	Maximum dose	6	6	6	…
Valproate sodium	Mean dose	927.27±134.83	927.27±134.83	…	…
	Maximum dose	1200	1200	…	…
Topiramate	Mean dose	177.08±31.00	…	177.08±31.00	…
	Maximum dose	250	…	250	…

[a] Between group mean score comparison using independent sample T test except for gender which chi square test was used
[b] lithium and rispridone data are reported based on baseline assessment but Valproate and Topiramate data are reporded according to the final recording
… Data was not applicable
Abbreviations: YMRS= Young Mania Rating Scale, Li: Lithium, Val: Valproate sodium, Ris: Risperidone, Top: Topiramate

Table.2 Subtypes of bipolar disorders and comorbidies among participants according to K-SADS-PL interview

Diagnosis and comorbidities N(%)	Total Subjects (n=29)	Subjects receiving Li+Ris/Val (n=15)	Subjects receiving Li+Ris/Top (n=14)
BID manic episode without PF	5(17.2)	3(20)	2(14.3)
BID manic episode with PF	2(6.9)	1(6.7)	1(7.14)
BID mixed episode without PF	19(65.5)	10(66.6)	9(64.28)
BID mixed episode with PF	2(6.9)	0	2(14.3)
ADHD	12(41.4)	5(33.3)	7(50)
OCD	5(17.2)	2(13.3)	3(21.4)
Specific phobia	3(10.3)	0	3(21.4)
ODD	2(6.9)	0	2(14.3)
CD	5(17.2)	2(13.3)	3(21.4)
Enuresis	1(3.4)	1(6.7)	0
Tic disorder	3(10.3)	1(6.7)	2(14.3)
PTSD	3(10.3)	1(6.7)	2(14.3)
GAD	1(3.4)	1(6.7)	0

Abbreviations: Li: Lithium, Val: Valproate sodium, Ris: Risperidone, Top: Topiramate, BID: Bipolar I Disorder, PF: Psychotic feature, ADHD: Attention deficit/Hyper activity Disorder, OCD: Obsessive compulsive Disorder, ODD: Oppositional Defiant Disorder, CD: Conduct Disorder, PTSD: Post Traumatic Stress Disorder, GAD: Generalized Anxiety Disorder

Results

Thirty adolescents complied with the study criteria; twenty nine subjects completed the study.

One participant in the topiramate/ Li+Ris group was withdrawn due to a d ecrease in hearing acuity and developing paresthesia of the face initiated one week after starting the study; therefore, topiramate was discontinued. Patient's symptoms resolved completely after topiramate discontinuation. No significant difference was observed at baseline among participants in terms of mean age and sex distribution, duration of illness, number of previous episodes, illness severity, risperidone dose (Table1), weight, BMI z-score, and lipid profiles. S ignificant differences were observed between the two groups in lithium dose and in the number of hospitalizations at baseline.

Subtypes of BD and co-morbidities are shown in table 2.

Using repeated measure ANOVA, no statistically significant difference was observed between the two treatment groups in mean weekly dose of lithium, risperidone, and lithium serum levels during the study.

Twenty five patients were inpatients during the entire trial. Two participants in the Li+Ris/Valproate sodium group (one at week 4 and one at week 5) ,and three in Li+Ris/Topiramate group (two at week 4 and one at week 5) were discharged from the hospital and were subsequently followed as outpatients . Mean final serum level of lithium (+SD) in topiramate and valproate sodium groups were 1± 0.16 mEq/L and 0.91± 0.20 mEq/L, respectively.

Mean therapeutic valproate sodium serum level was 64.1± 22 µg/mL.

Before-after changes in each group

After completion of the trial, differences in the mean levels of TC, TG, LDL and HDL at baseline and after week 6 did not reach significance in neither group. However, patients in Li+Ris/Valproate sodium group demonstrated decrease, and those in Li+Ris/Topiramate group showed increase in mean TC levels. Additionally, both groups showed increases in mean serum levels of TG, HDL and decreases in mean LDL levels. BMI z-score increased in both groups; however, this increase reached significance only in Li+Ris/Valproate sodium group. Significant increases in weight and BMI z-scores were found when all patients were considered as a whole.

Between group differences of outcome measures

No significant differences in lipid and BMI changes between topiramate and valproate sodium groups were found.

Analysis of endpoint changes according to BMI percentile categories

When analyzing across BMI percentile subgroups, in the normal weight category, a significant increase in absolute weight change was noted among all patients as a whole and also in Li+Ris/Topiramate and Li+Ris/Valproate sodium treated subjects at the end of the trial. A statistically significant difference was also found between normal weight and overweight/obese categories in the percent weight change and BMI z-score in Li+Ris/Valproate sodium group. Subjects in the normal weight category achieved 10.05±8.99% increase while overweight/obese group achieved only 1.25± 9.09% increase in weight.

Furthermore, BMI z-score change from baseline was significant in the normal weight category in both Li+Ris/Valproate sodium and Li+Ris/Topiramate groups.

Development of abnormalities in categorical shifts

At baseline, a high proportion of participants had elevated TG (≥ 110 mg/dl) and TC (≥170 mg/dl) levels which remained high through the end of the study. Interestingly, all patients in the valproate sodium group had high TG levels at week 6. P roportion of participants with LDL ≥ 130 mg/dl decreased in both treatment groups at the end of the study; no patients in topiramate and only 6.7% in valproate sodium groups had high LDL at the time. Percentage of subjects with BMI percentile <85th increased in both treatment groups (Table 5).

Discussion

This study found no significant differences between topiramate and valproate s odium on lipid milieu, when added to Li+Ris, in adolescents with BD after 6 weeks. Data from our other study (37)demonstrated that patients in both arms experienced significant reductions in symptoms with no significant difference in between.

It should be emphasized that in the present study metabolic changes could have been potentially obscured by administration of the combination regimen used in this trial. Additionally, past treatment exposures, including prior "double hit" by lithium and risperidone may have influenced the result of this study, which precludes precise conclusions about direct metabolic changes with valproate sodium and topiramate.

To the authors' knowledge, effects of valproate sodium and topiramate on lipid profile either as monotherapy or in combination with antipsychotics and lithium in children and adolescents with BD have not yet been reported. However, there is some information on metabolic effects of topiramate and valproate sodium when used as monotherapy in children and adolescents with epilepsy, although not conclusive. As a point of reference for our findings, we have mentioned and discussed various studies. In children with epilepsy, valproate sodium monotherapy has been associated with variable effects on serum lipids (26, 27, 31, 39). Eiris et al. reported low levels of TC and LDL in epileptic children receiving valproate sodium monotherapy after a mean duration of 4.1years (26).

and 5.8 years (39). On the other hand, some trials conducted on children with epilepsy have found no changes (27,31, 33, 40) or significant increase (41) in LDL levels after valproate sodium monotherapy. In terms of TG and HDL levels, there are reports on increased, decreased and unchanged levels of these lipid factors in children with epilepsy on valproate sodium monotherapy (31, 33, 40).

When considering topiramate effects on s erum lipids, one study showed that monotherapy with topiramate in epileptic children was associated with a slight decrease in TC, TG and HDL after 12 months of treatment (28).

Combination of Li+Ris with either valprorate sodium or topiramate, resulted in BMI z-score increase in both groups; however, this increase was only significant in the valproate sodium group. Many psychotropic drugs are allied with weight gain (42); however, as mentioned earlier, data is sparse for mood stabilizers in pediatric population with BD for this side effect. Significant weight gain in adolescents treated with risperidone has been reported after a mean duration of 4.9 months (43). Fraguas et al. evaluated the effects of 6 month therapy with risperidone on metabolic factors

Table 3: The comparison of Base line[a] and outcome measurements between two groups after 6 weeks of treatment

variables	Total subjects Mean ± SD score (N=29)			Subjects receiving Li+Ris/Val Mean ± SD score (N=15)			Subjects receiving Li+Ris/Top Mean ± SD score (N=14)			P value[c]
	Base line	End point	P value[b]	Base line	End point	P value[b]	Base line	End point	P value[b]	
TC	171.51±30.97	168.77±25.17	0.683	170.70±37.50	163.27±27.13	0.488	172.40±23.30	174.66±22.08	0.788	0.477
LDL	96.30±28.79	89.64±24.51	0.285	96.60±35.40	86.17±25.10	0.313	97.10±20.90	93.36±24.50	0.670	0.647
HDL	46.14±7.19	48.95±10.99	0.224	44.80±8.20	46.05±7.40	0.379	47.50±5.90	52.06±13.40	0.336	0.483
TG	145.33±29.22	150.86±27.22	0.302	151.40±32.60	155.23±20.30	0.645	138.80±24.60	146.18±33.4	0.304	0.741
TG/HDL ratio	3.23±0.92	3.22±0.81	0.960	3.49±1.11	3.41±0.50	0.692	2.95±0.59	3.02±1.03	0.806	0.660
Weight	59.08±13.67	61.42±13.78	0.034	60.80±16.27	63.89±16.70	0.065	57.25±10.50	58.78±9.71	0.080	0.466
Weight change (absolute)	…	2.34±5.65	…	…	3.09±5.98	…	…	1.53±5.36	…	0.466
Weight change (%)	…	4.66±9.16	…	…	5.95±9.82	…	…	3.28±8.54	…	0.444
BMI Z-score	0.39±1.26	0.67±1.04	0.003	0.38±1.55	0.72±1.23	0.018	0.40±0.91	0.61±0.84	0.089	0.479
BMI percentile	64.65±31.63	69.13±28.55	0.220	65.86±35.68	68.13±32.27	0.714	63.35±27.94	70.21±25.14	0.095	0.531

[a] Two groups show no significant differences at baseline variables scores using independent sample T test considering $p<0.05$

[b] The comparison of baseline to end point change scores in each treatment group separately using paired T test.

[c] The comparison of change scores after 6 weeks treatment between two groups using independent sample T test

… Data is not applicable. Abbreviations: TC= total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, BMI: body mass index, Li: Lithium, Val: Valproate sodium, Ris: Risperidone, Top: Topiramate

Table4: Endpoint changes comparison in normal and overweight/obese participants in each separate treatment group and between treatment groups

variables	Total subjects Mean ± SD score (N=29)		P Value[e]	Subjects receiving Li+Ris/Val Mean ± SD score (N=15)		P Value[e]	Subjects receiving Li+Ris/Top Mean ± SD score (N=14)		P Value[e]	Change scores between treatment groups[d]	
	Normal weight[a] N=17	Over weight[b]/obese[c] N=12		Normal weight N= 8	Over weight/obese N=7		Normal weight N=9	Over weight/obese N=5		Normal weight P value	Over weight/obese p-value
Weight change (Absolute)	3.67±3.83**	0.45±7.29	0.265	4.77±4.51*	1.17±7.19	0.269	2.69±3.05*	-0.55±8.15	0.495	0.131	0.624
Weight change (%)	7.49±7.62	0.65±9.97	0.060	10.05±8.99	1.25±9.09	0.049	5.21±5.73	-0.19±12.17	0.205	0.102	0.570
BMI Z-score change	0.46±0.45**	0.015±0.29	0.008	0.61±0.47*	0.02±0.26	0.015	0.33±0.42**	0.006±0.37	0.142	0.083	0.745
TG/HDL ratio change	-0.14±1.03	0.19±0.60	0.471	-0.20±1.02	0.06±0.33	0.563	-0.09±1.11	0.36±0.86	0.841	0.885	0.935

a BMI ≤85th percentile for sex and age

b BMI >85th – 95th percentile for sex and age

c BMI ≥ 95 th percentile for sex and age

d Two groups comparison using Mann-whitney test

e The comparison of change scores between normal weight and overweight/obese participants in each treatment group separately using Mann-whitney test

*The comparison of baseline to end point change scores in normal and overweight participant separate groups using wilcoxon signed rank test with significant level < 0.05

**The comparison of baseline to end point change scores in normal and overweight participant separate groups using wilcoxon signed rank test with significant level < 0.01

Abbreviations: HDL: high-density lipoprotein, TG: triglyceride, BMI: body mass index, Li: Lithium, Val: Valproate sodium, Ris: Risperidone, Top: Topiramate

Table.5 Development of body weight and lipid abnormalities

Variables	Subjects receiving Li+Ris/Top N (%)		Subjects receiving Li+Ris/Val N (%)	
	Baseline	End-point	Baseline	End-point
TC≥ 170 mg/dl	9 (64.3)	9(64.3)	9(60)	9(60)
LDL≥ 130 mg/dl	1(7.1)	0(0)	2(13.3)	1(6.7)
HDL < 40 mg/dl	1(7.1)	1(7.1)	5(33.3)	3(20)
TG≥110 mg/dl	13(92.9)	13(92.9)	13(86.7)	15(100)
BMI < 85th	9(64.3)	11(78.6)	8(53.3)	9(60)
BMI ≥ 85th - <95th percentile[a]	5(35.7)	2(14.3)	5(33.3)	4(26.7)
BMI ≥ 95th percentile [a]	0(0)	1(7.1)	2(13.3)	2(13.3)

A sex and age- adjusted BMI expressed in percentile (population mean: 50th percentile) obtained from calculators (http://www.stokes.chop.edu/web/zscore/ (The childrens hospital of Philadelphia).
Abbreviations: TC= total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, BMI: body mass index, Li: Lithium, Val: Valproate sodium, Ris: Risperidone, Top: Topiramate

in children and adolescents with no or little prior exposure to antipsychotics. Risperidone was associated with significant increase in weight and BMI z-score (22). Weight gain is also a common side effect of lithium (1). Nevertheless, in our study, risperidone dose and lithium serum levels were similar in the two groups; topiramate therapy was not associated with a significant change in BMI z-score; while, valproate sodium add-on therapy significantly increased this score. Chengappa et al. suggested that topiramate was effective and resulted in weight loss when used as a 5-week add-on therapy for adult patients with BD who were resistant to their current mood stabilizers which included lithium or risperidone (36). To explain why no weight loss was observed with topiramate use in our study, it may be suggested that topiramate only attenuate the ongoing weight gain from lithium and risperidone. This suggests a protective role for topiramate.

Interestingly according to the weight and BMI z-score changes across normal weight and overweight/obese categories, most weight gains were observed among those with normal weight when compared with the overweight/obese subgroup. In particular, subjects with normal weight in the Li+Ris/Valproate sodium group showed significant weight gain defined as ≥ 0.5 increases in BMI z-score (22).

At the initiation of the study, the mean of TG was above normal (145.33± 29.22 mg/dl). In addition, the proportion of participants with TG ≥110 mg/dl was also high in both intervention groups. In line with our findings, Sicras et al. (6) demonstrated higher prevalence of high TG levels in BD patients over 16 years of age who received one drug or more for at least three weeks when compared with general population. In the above study, 30% and 19.6 % of patients were receiving lithium and risperidone respectively at any time during the research period. Medications may also have a role in causing lipid abnormalities. To our knowledge, the effect of lithium therapy on lipids in adolescents with BD has not been reported in the literature yet. Increased appetite and weight gain are common reported side effects of lithium therapy (1) ,and could probably result in complications of overweight including hypertriglyceridemia (44). One study on an adult with BD showed that lithium increases atherogenic lipids (45). Regarding antipsychotics, hypertriglyceridemia among adult users of second generation antipsychotics with prevalence greater than general population has also been demonstrated (3). As noted earlier, data on the effects of atypical antipsychotic on lipid profile in children and adolescents is not conclusive yet (34).Nonetheless, Patel et al. demonstrated that dyslipidemia was a common finding in hospitalized adolescents exposed to atypical antipsychotics (25). Genetic predisposition has also been mentioned to be a probable cause for cardiovascular illnesses in BD patients (8). Thus, given the vulnerable nature of adults with BD to develop dyslipidemia (5), elevated TG at baseline may be explained by the illness itself, unhealthy lifestyle habits and /or the medications.

At the initiation of our study being overweight was prevalent among 35.7% and 33.3% of children before randomization to topiramate and valproate sodium, respectively. At the end point of the study, the percentage of overweight subjects in Li+Ris/Valproate sodium was 26.7% that was greater than the estimation of 16% for general children population reported by National Health and Nutrition Examination Survey (NHANES) IV documents (from the 1999-2002) (44). However, as mentioned earlier, data are sparse for mood stabilizers in pediatric population with BD for this side effect. Goldstein et al. have noted a 42% prevalence of obesity among adolescents with BD (9). Patel et al. found that 53% of hospitalized adolescents exposed to atypical antipsychotics were overweight (25). A recent pooled analysis of antipsychotics and mood stabilizers trials which followed adolescents with BD for 4-48 weeks concluded that weight gain was relevant in 75% of these trials (14). Thus, our finding highlights the need for monitoring this metabolic risk factor in children and adolescents with BD.

This study has a number of limitations. The study was not designed as a double-blind trial. The short duration of this study and small sample size set limit to observe more clinically significant effects. Data on participants with a family history of obesity, atherosclerotic or

metabolic diseases were not gathered. Besides, we did not have fasting lipid profile and weight before Li+Ris initiation; the participants were heterogeneous regarding duration of illness, duration of prior lithium and /or risperidone treatment (prior to the 4 weeks) and previous bipolar medication treatments. Finally lithium and risperidone co medication could have influenced our results.

Despite the above limitations, our finding highlights the importance of cardiometabolic monitoring in children and adolescents with BD on mood stabilizers and/or antipsychotics. At this time, the body weight and lipid dysregulation associated with atypical antipsychotics or mood stabilizers either as monotherapy or as add-on therapy in children and adolescents with BD is non conclusive.

Conclusion

As add on therapies to lithium and risperidone, topiramate and valproate sodium act alike on lipid milieu of children and adolescents with BD when they are taken for 6 weeks. All of the participants in the normal weight subgroup showed greater weight gain potential during the 6 week trial than the overweight/obese subgroup.

It should be noted that topiramate may only attenuate the ongoing weight gain and may not necessarily cause weight loss in patients taking lithium and risperidone.

High proportion of elevated triglyceride, total cholesterol and overweight among children and adolescents with BD, which remained elevated throughout the course of this study, warrant cardiometabolic monitoring of children and adolescents with BD on mood stabilizers and/or antipsychotics.

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