# Topiramate in Bipolar and Schizoaffective Disorders: Weight Loss and Efficacy

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***Background:*** Although useful in bipolar disorder, mood stabilizers, such as lithium, divalproex sodium, and carbamazepine, can cause significant weight gain.

***Method:*** We conducted a retrospective chart review of 5 patients with DSM-IV bipolar disorder or schizoaffective disorder who were treated with topiramate as adjunctive therapy or monotherapy.

***Results:*** All 5 patients had a good response to treatment at a mean topiramate dose of 195 mg/day (range, 100–375 mg/day). All patients lost a substantial amount of weight on topiramate treatment. The average weight loss was 22 lb (10 kg; range, 8–56 lb [4–25 kg]). None of the patients discontinued topiramate because of side effects.

***Conclusion:*** Topiramate may represent a valuable alternative to existing mood stabilizers, either as an adjunct or as monotherapy in patients with bipolar disorder or schizoaffective disorder.

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Weight gain is a common and important side effect of many psychotropic drugs. Weight gain puts the patient at risk for hypertension, coronary heart disease, type 2 diabetes mellitus, dyslipidemia, and cancer. Increased weight can lead to noncompliance with an increased risk of relapse and subsequent rehospitalization.[1] Mood stabilizers, including lithium and valproic acid, can lead to weight gain. In a double-blind, controlled study of valproic acid for the maintenance treatment of bipolar disorder, weight gain of more than 7% was reported in 4% of patients taking placebo, 16% of patients treated with lithium, and 23% treated with valproic acid.[2] Atypical antipsychotics, particularly clozapine and olanzapine, are associated with significant weight gain.[3,4] In a recent meta-analysis by Allison et al.,[5] after 10 weeks of treatment, the mean weight gain with clozapine was 4.45 kg and with olanzapine, 4.1 kg. Nemeroff[6] reported that the mean weight gain after 1 year of treatment with olanzapine was 11.8 kg.

Topiramate is a newer antiepileptic drug that blocks sodium channels, similar to carbamazepine and valproate, and also potentiates γ-aminobutyric acid (GABA) neuroinhibition, similar to valproate. Topiramate also antagonizes the glutamate effects at non–*N*-methyl-D-aspartate (non-NMDA) receptors and inhibits certain isoenzymes of carbonic anhydrase.[7] Peak topiramate levels are reached within 1.75 to 4.3 hours after oral administration. The relative bioavailability of the drug from the tablet form is 80% compared with a solution. Food decreases the rate but not the extent of absorption of topiramate. The drug has linear pharmacokinetics and has only 9% to 17% plasma protein binding. Topiramate extensively binds to red blood cells. The average elimination half-life is 18.7 to 23 hours. Seventy percent of an administered dose is excreted in the urine unchanged. Topiramate is metabolized via hydroxylation, hydrolysis, and glucuronidation. No correlation with plasma levels is known, and hence there is no clinical indication to measure them.

Common side effects of topiramate include sedation, fatigue, diplopia, dizziness, ataxia, psychomotor slowing, difficulty with concentration, anorexia, headache, speech problems, memory problems, nystagmus, and paresthesias. Topiramate is classified as a pregnancy category C drug. It may lead to decreased effectiveness of some oral contraceptives. The total daily dosage suggested in epilepsy is 400 mg/day in divided dosages; however, no clear recommendations have yet been given for bipolar disorder. In patients with renal impairment, half the usual adult dosage is suggested.[8]

Several studies have demonstrated the efficacy of topiramate in the treatment of bipolar disorder, including refractory populations, and in the treatment of posttraumatic stress disorder.[7,9–12] Topiramate led to substantial weight loss in patients with bipolar disorders in these studies. The efficacy of topiramate as an adjunct treatment in patients with mood disorders has been demonstrated. Marcotte[7] found that 11 of 18 patients with refrac-

tory bipolar disorder (types I and II) responded to a mean dose of 200 mg/day of topiramate after 8.5 weeks of treatment. Chengappa et al.[10] treated 20 patients with bipolar I disorder or schizoaffective disorder with adjunctive topiramate (mean dose = 210.5 mg/day) over a 5-week period. Twelve patients (60%) responded to topiramate, and the time to response ranged from 2 to 4 weeks. Adverse events included paresthesias, anorexia, slowed thinking, fatigue, sedation, and word-finding difficulty. Fifty-five percent of patients reported no adverse effects. Only 1 patient discontinued the study prematurely because of "acute confusional states." Wooten and Kramer[11] used high-dose topiramate to treat 8 patients with bipolar disorder, schizoaffective disorder, or schizophrenia. The mean dosage was 868 mg/day in divided doses (range, 50–2000 mg/day). Sixty percent of patients responded to topiramate. One patient experienced mild paresthesia, and 2 patients experienced transient delirium at high doses (1600 and 2000 mg/day).

Kusumakar et al.[9] treated 27 female patients with a DSM-IV diagnosis of bipolar I and bipolar II disorder who had been refractory to at least 2 mood stabilizers and who had a weight gain of more than 20% over the previous 24 months with topiramate (100–150 mg/day). Fifteen of the 27 patients showed significant improvement, and only 4 patients discontinued because of adverse events. Fourteen patients lost weight during the 16-week study. Nine patients experienced a weight loss of more than 5%.

We describe a case series of 5 patients who were treated with topiramate either as an adjunct or as monotherapy who experienced improvement in mood symptoms as well as substantial weight loss.

## METHOD

A retrospective chart review was conducted of 5 patients with a DSM-IV diagnosis of bipolar disorder or schizoaffective disorder placed on topiramate treatment. The patients had been placed on topiramate treatment owing to partial response to their therapeutic regimen. This case series includes the first 5 patients placed on topiramate treatment either as outpatients or in the inpatient setting. The efficacy measures included the Young Mania Rating Scale (YMRS),[13] the Brief Psychiatric Rating Scale (BPRS),[14] the Hamilton Rating Scale for Depression (HAM-D),[15] and patient report. A reduction in the rating scale scores was used to determine improvement in symptoms. In the continuing outpatient program, the weight is recorded for all patients. The topiramate was used as adjunctive therapy or monotherapy. The dosage titration was done gradually in a naturalistic fashion without any set protocol following the "start low and go slow" principle. The off-label use of the drug, including its side effects and benefits, was discussed with all patients.

## RESULTS

A detailed discussion was held with each of these patients regarding the use of topiramate to obtain consent for use. They were informed that it was approved by the U.S. Food and Drug Administration (FDA) for epilepsy and not bipolar disorder. All 5 patients responded to adjunctive topiramate for the treatment of the bipolar or schizoaffective disorder. The mean dose of topiramate was 195 mg/day (range, 100–375 mg/day). All patients lost a substantial amount of weight on topiramate. The average weight loss was 22 lb (10 kg; range, 8–56 lb [4–25 kg]). No patient discontinued topiramate because of side effects. We started topiramate at 25 to 50 mg daily and conducted a gradual titration in increments of 25 mg. The slow titration may have been responsible for the lack of significant side effects.

### Case Reports

***Case 1.*** Ms. A, a 58-year-old white woman, had a 37-year history of bipolar affective disorder, manic type with psychotic features. She was admitted to the inpatient unit at the local community hospital because of marked symptoms of mania such as pressured speech and sexual inappropriateness. Ms. A had multiple previous psychiatric hospitalizations. Medical history included Parkinson's disease, 2 seizures, obesity, and urinary incontinence. She had no significant alcohol or drug history. Family history included schizophrenia in her mother.

Ms. A was on treatment with divalproex sodium for several years and recently had compliance problems. She had experienced significant weight gain over several years, resulting in the discontinuation of divalproex. Previous trials of lithium carbonate and divalproex resulted in lack of response to either alone or to the combination; therefore, a trial of topiramate was considered. Laboratory data, including blood count, electrolytes, thyroid studies, serum cholesterol, lithium level, and results of urinalysis and urine drug screen, were within normal limits. Weight on admission was 284 lb (128 kg).

On mental status examination, Ms. A appeared her stated age. She was alert and oriented to all spheres (person, place, time). She had pressured speech and increased psychomotor activity. Ms. A's mood was elevated, and her affect was manic. She had flight of ideas, tangentiality, and decreased concentration. Her judgment and insight were fair. Her YMRS score was 20.

Topiramate was started at 25 mg/day and was gradually adjusted upward in 25-mg increments to 125 mg in the morning and 150 mg at bedtime. Owing to persistence of symptoms, lithium carbonate, 300 mg at bedtime, was added in combination with topiramate and was increased gradually to 1200 mg at bedtime. This addition of lithium resulted in improved sleep and a decrease in manic symptoms. Ms. A's plasma lithium level was 1.0 mEq/L. She

was continued on olanzapine, 20 mg at bedtime. Her other medications included celecoxib, 200 mg/day; furosemide, 40 mg/day; potassium chloride, 20 mEq/day; conjugated estrogen and medroxyprogesterone acetate, 0.625/2.5 mg/day; carbidopa-levodopa 25/250 mg/day, half tablet twice daily; and oxybutynin, 5 mg twice daily. She improved and was discharged to a group home. Her YMRS score was 1, and her BPRS score was 18.

Ms. A was followed up as an outpatient for 2 months, and her symptoms and weight were monitored during visits. She continued to do well, with no reported side effects. Her YMRS score was 0, and her BPRS score was 18. Her weight continues to decline since discharge from the hospital. Her weight before topiramate was 284 lb (128 kg), which decreased to 242 lb (109 kg) at 1-month, 240 lb (108 kg) at 2-month, and to 228 lb (103 kg) at 3-month follow-up. She had a 56-lb (25-kg) weight loss on treatment with topiramate.

***Case 2.*** Ms. B, a 42-year-old white woman with a 27-year history of bipolar disorder, was followed in a continuing day treatment program. Her medical history included obesity, fibromyalgia, and diabetes. Her family history was significant for obesity, cardiovascular disease, diabetes mellitus, multiple sclerosis, and alcoholism, as well as depression with suicide attempts in her mother. Ms. B reported irritability and occasional depressed mood. She also reported concerns about taking divalproex because of weight gain. Her weight was 176 lb (79 kg) before topiramate was added, and she had a DSM-IV diagnosis of bipolar disorder.

On mental status examination, Ms. B was well dressed and groomed and had clear and coherent speech. She had anxious mood and affect. Her judgment and insight were fair. Her YMRS score was 4, and her HAM-D score was 8. Her medications included divalproex, 500 mg in the morning and 1000 mg at bedtime; zolpidem, 10 mg at bedtime; citalopram, 40 mg/day; and lithium carbonate, 900 mg at bedtime.

Various options were discussed, including switching back to carbamazepine (which she had received previously), lowering the dose of divalproex, or trying topiramate. Consent was given, and Ms. B was started on topiramate, 25 mg at bedtime. The divalproex dosage was lowered to 500 mg twice daily. The rest of her medications remained the same.

At 3-week follow-up, Ms. B reported problems at home that caused significant irritability and moodiness. Her weight had decreased to 165 lb (74 kg). Topiramate was increased to 25 mg twice daily for 2 weeks and then was gradually increased in 25-mg increments to 75 mg twice daily. Divalproex was tapered and then stopped. Several weeks later, Ms. B scheduled an intermittent appointment because of increased irritability, decreased sleep, and increased sex drive. Mental status examination revealed that her mood was extremely irritable. Her affect was also irritable. Her judgment and insight were fair. Her YMRS score was 8, and her HAM-D score was 7. Lithium carbonate was increased to 1200 mg at bedtime, and the other medications remained at the same dosages. Laboratory data, including a serum lithium level, serum cholesterol, fasting lipid profile, and complete blood count, were within normal limits.

Six weeks later at follow-up, Ms. B reported decreased irritability and better sleep. No manic symptoms were noted. Her YMRS score was 0, and her HAM-D score was 6. She denied any side effects from the topiramate. Her weight continued to decline. Her weight prior to topiramate treatment was 176 lb (79 kg), which decreased to 165 lb (74 kg) at 1-month, to 162 lb (73 kg) at 2-month, and to 156 lb (70 kg) at 3-month follow-up. She lost 20 lb (9 kg) on topiramate treatment.

***Case 3.*** Ms. C, a 35-year-old white woman with a 22-year history of bipolar affective disorder with rapid cycling, was followed as an outpatient. She had multiple previous psychiatric hospitalizations. Ms. C's medical history included hypothyroidism and weight gain. Her weight was 180 lb (81 kg) before topiramate was added, and her DSM-IV diagnosis was schizoaffective disorder. Her maximum weight had been 199 lb (90 kg). She also had a history of alcohol and cannabis dependence. Family history included a sister who committed suicide and manic-depressive symptoms in a brother. Ms. C had cycles of manic as well as depressive symptoms. Previous medication trials included lithium, risperidone, and olanzapine, with poor results. Lithium in combination with divalproex resulted in minimal improvement, whereas divalproex in combination with lamotrigine resulted in a 30% improvement per patient report.

Ms. C was seen for follow-up. She reported that she had stopped taking the mood stabilizers $3^1/_2$ months earlier. She reported feeling depressed and was concerned about her weight. On mental status examination, she presented with low mood, and affect that was appropriate to the mood with a full range. Her thought process was organized, and her judgment and insight were fair. Her YMRS score was 5.

Because of her numerous previous unsuccessful medication trials, the use of topiramate was discussed. Consent was obtained, and Ms. C was started on topiramate, 25 mg/day. This dosage was gradually adjusted up to 100 mg twice daily. Concomitant medications included levothyroxine sodium, 75 μg/day; zolpidem, 10 mg at bedtime; and bupropion sustained release, 100 mg/day. Laboratory data, including thyroid studies, complete blood count, and liver function test results, were within normal limits. At 2-month follow-up, Ms. C reported improved sleep. She had no manic symptoms. Her YMRS score was 2. She was not experiencing any side effects from the topiramate. Her weight was declining; her weight before topiramate treatment was 180 lb (81 kg), which decreased to 162 lb

(73 kg) by month 3. She lost 18 lb (8 kg) on topiramate treatment.

***Case 4.*** Ms. D, a 43-year-old white woman with an 18-year history of bipolar affective disorder, depressive type, was followed as an outpatient. She had multiple previous psychiatric hospitalizations and had been out of the hospital for 10 years. Her medical history included weight gain. Family history included depression and alcoholism in her father.

At an outpatient follow-up visit, Ms. D reported irritability because of tension in the workplace. She felt out of energy and was also concerned about a 14-lb (6-kg) weight gain. Her affect was anxious, and her mood was irritable. Her YMRS score was 3. Her medications included divalproex, 500 mg in the morning and 1000 mg at bedtime; lithium carbonate, 600 mg at bedtime; and fluoxetine, 20 mg/day. Her serum valproate level was 76 µg/mL, and her plasma lithium level was 0.8 mEq/L. Divalproex was decreased to 1000 mg at bedtime. Lithium carbonate was raised to 900 mg at bedtime, and fluoxetine was continued at 20 mg/day. The possibility of monotherapy such as lithium carbonate alone or the combination of lithium with topiramate was discussed. Dietary management and exercise were also recommended.

Ms. D was seen for follow-up 2 months later. She reported increased irritability and depression. Weight gain was still a concern. Her weight was 196 lb (88 kg). Because of lack of efficacy with previous trials of lithium carbonate and divalproex either alone or in combination, the use of topiramate was discussed and consent was obtained. Ms. D was started on topiramate, 25 mg in the morning, which was gradually adjusted up to 50 mg twice daily. Lithium was continued in the same dose, and divalproex was tapered and stopped. Laboratory data, including a complete blood count and liver function test results, were within normal limits.

At follow-up, Ms. D was alert and oriented to all spheres. Her speech was clear, and her affect was bright, with improved mood. No irritability was noted. She reported that she felt better about herself and that her weight was decreasing. Her YMRS score was 2, her BPRS score was 19, and her HAM-D score was 1. Her weight before topiramate treatment was 196 lb (88 kg). Her weight decreased to 192 lb (86 kg) at 1-month and to 185 lb (83 kg) at 2-month follow-up. She lost 11 lb (5 kg).

***Case 5.*** Ms. E, a 38-year-old Native American woman with a 12-year history of schizoaffective disorder, was seen at a continuing day treatment program. She had multiple previous psychiatric hospitalizations. At a routine visit, she reported concerns of weight gain, difficulty sleeping, and low sex drive. Her YMRS score was 3, her BPRS score was 19, and her HAM-D score was 6. Her weight was 282 lb (127 kg). Ms. E's medications included divalproex, 1000 mg twice daily; risperidone, 6 mg at bedtime; and venlafaxine, 75 mg 3 times daily. A detailed discussion about her medications was held. Risperidone was decreased to 3 mg at bedtime, and the divalproex dosage was changed to 500 mg in the morning and 1500 mg at bedtime.

One month later, Ms. E reported both improved sleep and sex drive, but her weight continued to be a concern. She was started on topiramate, 25 mg twice daily, which was gradually increased to 75 mg twice daily. Divalproex was tapered and stopped. Laboratory data, including a complete blood count, liver function test results, and fasting lipid profile, were within normal limits.

At follow-up a month later, Ms. E was alert and oriented in all spheres. Her affect was bright, and her mood was neutral. Her thought process was organized. Her YMRS score was 1, and her HAM-D score was 2. She reported no side effects from topiramate and denied depressive or psychotic symptoms. Her weight was decreasing; her weight before topiramate was 282 lb (127 kg), which decreased to 274 lb (123 kg) at 3-month follow-up. She had a weight loss of 8 lb (4 kg).

## DISCUSSION

The limitations of our study include lack of a prospective design, absence of randomization, and the limitations associated with a retrospective chart review. We also did not have baseline weight for each subject to know how much weight had been gained on treatment with the mood stabilizer prior to topiramate treatment. This weight gain was ascertained based on patient report and concerns. Other reasons for weight gain such as other medications, diet, and lifestyle were not controlled for. We did, however, have patient weight prior to and after starting topiramate. We also did not calculate body mass index because of lack of record of height in the chart. Another limitation is that the other medications thought to cause weight gain were either stopped or reduced in dosage, which in itself may cause some weight loss, although we doubt that such a loss would be that much and occur so quickly.

A strength of our study is the use of rating scales, such as the YMRS and the BPRS, to quantify improvement in symptoms. The YMRS is an 11-item rating scale used to assess manic symptoms such as elevated mood, increased sexual interest, irritability, sleep, and increased energy in an objective fashion. The BPRS is an 18-item psychopathology rating scale used to assess psychotic symptoms, aggression, thought disorder, and interest level. It is the gold standard for conducting drug trials to assess the efficacy of new antipsychotic compounds.

Topiramate may be a useful alternative to existing mood stablizers in the primary care setting for several reasons. First, many primary care physicians now follow psychiatric patients; weight gain on treatment with psychotropics is an ongoing problem and there is no known drug with efficacy in psychiatric illness that may also

cause weight loss. Second, primary care physicians also have epileptic patients on phenobarbital and divalproex treatment who may have gained weight, and topiramate may be an alternative. Finally, the primary care physician coordinates the care of the patient, and in treating illnesses such as diabetes, heart disease, hypertension, and arthritis, the presence of obesity is an important risk factor. We do not suggest using topiramate specifically as a weight-loss drug, but that it should be considered as an option if there exists an indication to use a drug of its class. Future controlled studies are recommended to replicate these findings in different patient populations.

*Drug names:* bupropion (Wellbutrin), carbamazepine (Tegretol and others), carbidopa-levodopa (Sinemet and others), celecoxib (Celebrex), citalopram (Celexa), clozapine (Clozaril and others), divalproex sodium (Depakote), fluoxetine (Prozac), furosemide (Lasix and others), lamotrigine (Lamictal), levothyroxine (Synthroid and others), lithium carbonate (Eskalith and others), medroxyprogesterone acetate (Amen and others), olanzapine (Zyprexa), oxybutynin (Ditropan and others), phenobarbital (Donnatal and others), risperidone (Risperdal), topiramate (Topamax), valproic acid (Depakene), venlafaxine (Effexor), zolpidem (Ambien).

## REFERENCES


1. Masand PS. Weight gain associated with psychotropics. Exp Opin Pharmacother. In press
2. Sachs GS, Guille C. Weight gain associated with use of psychotropic medications. J Clin Psychiatry 1999;60(suppl 21):16–19
3. Gupta S, Droney T, Al-Samarrai S, et al. Olanzapine: weight gain and therapeutic efficacy [letter]. J Clin Psychopharmacol 1999;19:273–275
4. Cohen S, Chiles J, MacNaughton A. Weight gain associated with clozapine. Am J Psychiatry 1990;147:503–504
5. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686–1696
6. Nemeroff CB. Dosing the antipsychotic medication olanzapine. J Clin Psychiatry 1997;58(suppl 10):45–49
7. Marcotte D. Use of topiramate, a new anti-epileptic as a mood stabilizer. J Affect Disord 1998;50:245–251
8. Topamax (topiramate). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 1999:2249–2252
9. Kusumakar V, Yatham L, Kutcher S, et al. Use of topiramate in rapid cycling bipolar women. Presented at the 11th World Congress of Psychiatry; August 1999; Hamburg, Germany
10. Chengappa R, Rathore D, Levine J, et al. Use of topiramate for bipolar disorder. Presented at the 11th World Congress of Psychiatry; August 1999; Hamburg, Germany
11. Wooten G, Kramer T. Effects of topiramate on mood and global functioning. Presented at the 11th World Congress of Psychiatry; August 1999; Hamburg, Germany
12. Berlant J. Open-label trial of topiramate in post-traumatic stress disorder. Presented at the 11th World Congress of Psychiatry; August 1999; Hamburg, Germany
13. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity, and sensitivity. Br J Psychiatry 1978;133:429–435
14. Overall JE, Gorham DR, The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
15. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62