Topiramate Treatment for SSRI-Induced Weight Gain in Anxiety Disorders

Michael Van Ameringen, M.D., F.R.C.P.C.;
Catherine Mancini, M.D., F.R.C.P.C.; Beth Pipe, B.Sc.N., B.Ed.;
Mira Campbell, B.A.; and Jonathan Oakman, Ph.D., C.Psych.

Background: Antidepressants, including selective serotonin reuptake inhibitors (SSRIs), have been associated with significant weight gain, a problem that frequently leads to noncompliance and premature discontinuation of treatment. Topiramate is a novel anticonvulsant that has also been used as a mood stabilizer and augmentation agent in mood disorders. Topiramate has been observed to have an interesting side effect of weight loss in some individuals. In this study, topiramate was added to the treatment regimen of patients with a primary DSM-IV anxiety disorder who had experienced substantial SSRI-induced weight gain, in an attempt to induce weight loss.

Method: Topiramate was added to SSRI treatment in 15 anxiety disorder patients, starting at a dose of 50 mg/day and titrating up to a target daily dose of 100 mg/day, with a maximum dose of 250 mg/day. Subjects' weight was measured at baseline and after 5 and 10 weeks of treatment.

Results: Before topiramate treatment, SSRI-treated subjects in this sample had gained a mean of 13.0 ± 8.4 kg (28.6 ± 18.5 lb). After the addition of a mean dose of 135.0 ± 44.1 mg/day of topiramate for approximately 10 weeks, subjects lost a mean of 4.2 ± 6.0 kg (9.3 ± 13.3 lb).

Conclusion: Topiramate may have a role in managing SSRI-induced weight gain in anxiety disorder patients.

(J Clin Psychiatry 2002;63:981–984)

Received Oct. 10, 2001; accepted March 13, 2002. *From the Anxiety Disorders Clinic, McMaster University Medical Centre (Drs. Van Ameringen and Mancini and Mss. Pipe and Campbell); the Department of Psychiatry and Behavioural Neurosciences, McMaster University (Drs. Van Ameringen and Mancini), Hamilton, Canada; and the University of Waterloo, Waterloo, Canada (Dr. Oakman).*

Dr. Van Ameringen is a consultant for Wyeth-Ayerst; has received grant/research support from Pfizer, Lundbeck, Lilly, GlaxoSmithKline, Solvay, Janssen-Ortho, Bristol-Myers Squibb, AstraZeneca, and Wyeth-Ayerst; and has been a speakers/advisory board member for GlaxoSmithKline, Novartis, Solvay, and Pfizer. Dr. Mancini has received grant/research support from Lundbeck, GlaxoSmithKline, Lilly, Janssen-Ortho, Bristol-Myers Squibb, Pfizer, Wyeth-Ayerst, AstraZeneca, and Solvay and has been a speakers/advisory board member for GlaxoSmithKline. Dr. Oakman is a consultant for Pfizer and has received grant/research support from Pfizer, Bristol-Myers Squibb, GlaxoSmithKline, and Janssen-Ortho. Mss. Pipe and Campbell report no financial association or other relationship relevant to the subject matter of this article.

Corresponding author and reprints: Michael Van Ameringen, M.D., Anxiety Disorders Clinic, McMaster University Medical Centre, Hamilton Health Sciences, 1200 Main St. West, Hamilton, Ontario, Canada L8N 3Z5 (e-mail: vanamer@mcmaster.ca).

Antidepressant medications are currently the mainstay of pharmacologic treatment for both anxiety and mood disorders. Treatment with antidepressants, particularly tricyclic antidepressants (TCAs), is frequently associated with weight gain.[1–3] Patients have been reported to gain 20 pounds during a year or more of treatment with a TCA,[2] and many patients will continue to gain sizable amounts of weight for the duration of treatment. Weight gain can be a major cause of antidepressant noncompliance.[4,5]

It is a widely held belief that TCAs are much more likely to cause weight gain than the selective serotonin reuptake inhibitors (SSRIs).[2–4,6] However, findings from a recent study by Rigler and colleagues[6] indicate that TCAs may not facilitate weight gain any more than other antidepressant groups.

Several mechanisms have been invoked to explain TCA-induced weight gain, such as stimulation of appetite via blockade of the histamine H_1 receptors, altered food preference toward calorically dense foods and carbohydrates, and alterations in the metabolism of nutrients.[3,5,7] Other hypothesized mechanisms that may account for antidepressant-induced weight gain include neurotransmitter modulation at the hypothalamic level that leads to a change in the regulation of body fat stores, increased energy efficiency, and, in some cases, clinical improvement in anxiety and depressive symptoms.[7]

SSRIs were initially considered to be weight neutral; some were even believed to contribute to weight loss.[4] However, long-term treatment with SSRIs has been associated with weight gain.[4,7,8] Sussman and colleagues[8] recently analyzed data from 6 completed clinical trials comparing nefazodone with SSRIs and with TCAs in terms of effects on weight. Patients treated with SSRIs demonstrated more weight loss than those treated with nefazodone in the acute phase of treatment, but significantly higher rates of weight gain during long-term therapy.[8]

Potential mechanisms contributing to SSRI-induced weight gain may include the presence of comorbid disorders, such as hypothyroidism, and recovery from depression, as well as possible changes in serotonin 5-HT_{2C} receptor activity.[5,7] Increased appetite may also play a role in SSRI-induced weight gain, although weight gain has

also been observed in patients who exercise and carefully monitor food intake.[5,7] According to Fava,[7] there have been no definitive studies that describe the pathophysiology of weight gain induced by either SSRI or TCA therapy.

Pharmacologic agents have proven useful for managing some weight and appetite issues. Stimulants, including methylphenidate and amphetamine, have been used to counteract antidepressant-induced weight gain, as have histamine H_2 receptor antagonists, bupropion, phentermine, sibutramine, liothyronine, and naltrexone.[5,7] These agents are typically added to the patient's current SSRI treatment.[7]

Topiramate is approved as an anticonvulsant and has a chemically novel structure.[9,10] It has been used in clinical practice, off label, as a mood stabilizer. In a retrospective chart review of 58 patients who received 16 weeks of topiramate treatment for mood disorders and who were refractory to previous therapies (including lamotrigine and gabapentin), 62% of patients showed moderate or marked improvement as evidenced by qualitative assessments.[11] Data from recent literature indicate that topiramate has been used both as an augmenting agent and as an alternative mood stabilizer in treating bipolar disorder,[12] refractory depression,[11] and, recently, binge-eating disorder.[13] Topiramate has been noted to have an interesting side effect of weight loss in some patients[12,14–19] and, for this reason, has been used in treating patients with comorbid psychiatric disorders and obesity.[12,13,15,16] Most of the available data are in the form of case studies. In these studies, which involved patients with mood disorders, topiramate was added to patients' pharmacologic regimen[12,15] or, alternatively, replaced their regular mood stabilizer (primarily valproic acid).[11,16] Shapira and colleagues[13] published an open-label trial of topiramate treatment of 13 female patients with binge-eating disorder in which topiramate was added to existing pharmacotherapy. The treatment period in the studies reporting weight loss with topiramate ranged from 8 to 20 weeks, with weight loss ranging from 0.7 to 56.5 kg (1.6–124.3 lb) and topiramate daily dose ranging from 200 to 1400 mg.[12,13,15,16]

Topiramate appears to have several mechanisms of action. It is thought to work by enhancing GABA-A receptors at nonbenzodiazepine sites, by inhibiting glutamate via the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate subreceptors and by blocking voltage-gated sodium channels. Topiramate is also a weak inhibitor of the carbonic anhydrase isoenzymes CA2 and CA4.[9–11] The mechanism of the alleged weight loss that occurs with topiramate is unknown. However, it has been postulated that the weight loss may be mediated through first or second messenger systems and augmentation of 5-HT_{2C} receptors, as well as possible effects on dopamine, norepinephrine, and glutamate.[12]

Several preclinical studies carried out in various strains of rats have attempted to characterize the effects of topiramate on energy balance regulation. The results of these studies indicate that topiramate may reduce protein gain, decrease the activity of lipoprotein lipase, reduce food intake, and enhance regulatory thermogenesis.[20,21]

In clinical practice, patients treated with SSRIs have been reported to have a high incidence of weight gain. We elected to add topiramate to current SSRI treatment to evaluate its potential as a weight loss or weight control agent.

METHOD

Fifteen patients with a primary DSM-IV anxiety disorder diagnosis (panic disorder with or without agoraphobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, or generalized anxiety disorder) entered an open-label trial of topiramate treatment in addition to their current SSRI treatment. Written informed consent to participate in the study was obtained from all subjects by the study nurse.

The sample comprised 11 women and 4 men with a mean age of 41.5 ± 12.7 years. Primary diagnoses are listed in Table 1. The mean weight gain on SSRI treatment was 13.0 ± 8.4 kg (28.6 ± 18.5 lb) with a range of 4.5 to 30.0 kg (10.0–66.0 lb). Five (33.3%) of 15 patients gained weight on SSRI treatment within a month of initiation, while 10 (66.7%) of 15 gained weight gradually. Thirteen (86.7%) of the patients were still gaining weight when they were started on topiramate, and in 2 patients (13.3%), weight gain had plateaued. None of the patients in this study had used specific weight loss strategies or agents prior to topiramate initiation. The mean duration of the SSRI treatment that induced the weight gain was 12.9 ± 14.0 months.

Topiramate was started at 25 mg twice daily and increased by 25 mg/week to a target dose of 100 mg/day. Further increases in the dose were made on the basis of weight loss effect and the absence of adverse events. Patients were seen twice at intervals of approximately 5 weeks. At each visit, patients were weighed and the presence of adverse events was evaluated.

RESULTS

All 15 patients were able to tolerate the dose titration schedule to the target dose, and all completed the trial. The mean weight loss at week 10 was 4.2 ± 6.0 kg (9.3 ± 13.2 lb), although 4 patients gained weight during the trial. There was a significant weight loss from baseline to week-10 endpoint (mean baseline weight = 89.7 ± 25.9 kg [197.8 ± 57.1 lb]; mean endpoint weight = 85.3 ± 24.7 kg [188.1 ± 54.4 lb]; $F = 8.3$, $df = 1,14$; $p = .01$). There was a significant change in body mass index (BMI) from

Table 1. Demographic Variables and Patient Weights and BMIs[a]

Patient	Age (y)	Sex	Primary Diagnosis	Pre–SSRI Treatment BMI	SSRI	Duration of SSRI Treatment Before Topiramate Initiation (mo)	Weight Gain on SSRI Treatment (kg)	Baseline BMI	Baseline Weight (kg)	BMI Change With SSRI Treatment	Week 5 Topiramate Dose (mg/d)	Week 5 BMI	Week 5 Weight (kg)	Week 10 Topiramate Dose (mg/d)	Week 10 BMI	Week 10 Weight (kg)	Total Weight Change (kg)
1	38	F	GAD	33.7	Paroxetine	3	23.4	43.3	105.4	9.6	200	43.3	105.4	250	42.4	103.1	–2.3
2	17	M	OCD	28.6	Fluvoxamine	5	11.4	32.3	99.0	3.7	200	31.6	96.7	150	31.6	96.9	–2.3
3	61	F	PDAG	20.9	Sertraline	28	9.1	24.4	62.5	3.6	50	23.5	60.2	100	24.6	63.1	+0.6
4	52	F	PDAG	24.4	Paroxetine	13	6.4	27.0	66.6	2.6	100	25.6	63.0	125	23.9	59.0	–7.6
5	47	M	PTSD	37.7	Citalopram	4	8.2	40.3	127.7	2.6	150	41.0	130.0	150	41.2	130.4	+2.7
6	53	F	PDAG	18.2	Paroxetine	46	15.9	25.1	57.9	6.9	100	24.8	57.2	150	25.4	58.6	+0.7
7	60	M	PDAG	30.4	Paroxetine	9	5.5	32.7	80.5	2.2	100	31.8	78.4	100	32.3	79.5	+1.0
8	32	F	SP	20.3	Citalopram	7	6.6	22.7	64.0	2.3	50	21.9	61.9	100	21.9	61.9	–2.1
9	50	F	OCD	24.9	Paroxetine	4	9.1	27.9	83.5	3.0	100	27.9	83.5	100	27.4	82.0	–1.5
10	34	F	PDAG	22.2	Paroxetine	4	4.5	23.9	63.6	1.7	100	23.2	61.6	100	22.6	60.0	–3.6
11	37	F	PDAG	44.7	Paroxetine	10	30.0	56.4	144.5	11.7	100	54.7	140.0	100	53.9	138.0	–6.5
12	41	F	SP	27.2	Citalopram	6	5.9	28.9	99.0	1.7	150	27.2	93.0	150	25.2	86.4	–12.6
13	22	M	OCD	25.0	Citalopram	13	11.4	28.3	97.0	3.3	100	27.3	93.3	150	26.5	90.6	–5.9
14	40	F	SP	31.8	Fluoxetine	1	27.3	41.9	114.0	10.0	100	38.5	104.9	200	34.3	93.5	–20.5
15	38	F	OCD	24.8	Fluvoxamine	41	20.5	33.3	80.0	8.5	100	31.8	76.5	100	31.8	76.5	–3.5
Mean	41.5	NA	NA	27.7	NA	12.9	13.0	32.6	89.7	4.9	113.3	31.6	87.0	135.0	31.0	85.3	–4.2
SD	12.7	NA	NA	7.1	NA	14.0	8.4	9.3	25.9	3.4	44.2	9.2	25.6	44.1	8.9	24.7	6.0

[a]Abbreviations: BMI = body mass index, GAD = generalized anxiety disorder, NA = not applicable, OCD = obsessive-compulsive disorder, PDAG = panic disorder with or without agoraphobia, PTSD = posttraumatic stress disorder, SP = social phobia, SSRI = selective serotonin reuptake inhibitor.

baseline to week-10 endpoint (mean baseline BMI = 32.6 ± 9.3; mean endpoint BMI = 31.0 ± 8.9; F = 8.5, df = 1,14; p = .01). The mean change in BMI from baseline to week-10 endpoint was 1.6 ± 2.1. The mean dose of topiramate at week 10 was 135.0 ± 44.1 mg/day, with a range of 100 to 250 mg/day.

Topiramate was generally well tolerated. Seven patients (46.7%) reported no adverse events. Numbness and tingling in the extremities were reported by 3 individuals (20.0%), and 2 patients (13.3%) reported blurred vision. Other adverse events occurred with the following frequency: insomnia, N = 1 (6.7%); nausea, N = 1 (6.7%); fatigue, N = 1 (6.7%); headache, N = 1 (6.7%); and myalgia, N = 1 (6.7%).

DISCUSSION

SSRI-related weight gain is a significant problem in clinical practice. In addition to the associated health risks, weight gain frequently leads to noncompliance and premature discontinuation of treatment. The results of this study suggest that topiramate may be a useful strategy to combat SSRI-related weight gain. Actively treating the side effects of a drug to which the patient has shown an otherwise good response may have significant benefits over switching to an alternative treatment with which the patient's response and tolerance may be uncertain.

Norton and colleagues[19] reported a mean weight loss of 11% in patients remaining on topiramate treatment for 6 months. Findings from a retrospective trial by Rosenfeld and colleagues[18] indicated a significant mean weight loss of 8 kg (18 lb) for those patients receiving concomitant valproic acid treatment. In another study that examined the effect of weight loss with topiramate, Lin and colleagues[17] found that dose of topiramate and age were not related to the degree of associated weight loss. The results of these studies lend support to our findings of significant weight loss with topiramate use.

Although quantitative measures of anxiety were not elicited in this study, the majority of patients reported a reduction in their anxiety symptoms, including panic attacks, social and performance anxiety, and obsessive-compulsive symptoms. These observations suggest that topiramate may also have a role as an anxiolytic agent, but this role warrants further study.

Most of the adverse events noted in previous topiramate studies were reported as minor central nervous system effects including paresthesias, somnolence, fatigue, and impaired concentration and memory.[11–13,15] The literature contains 2 reports of gastrointestinal disturbances.[11,13] Also documented in the literature are adverse psychiatric symptoms, including 1 report of increased anxiety and irritability[16] and 2 cases of exac-

erbation of comorbid manic symptoms.[13] The adverse events in our study were comparable to those previously reported in the literature, with the exception of a lack of cognitive side effects. The lack of cognitive side effects in this study was most likely attributable to the use of lower doses of topiramate than were used in other studies.

Both investigator and patient bias are limitations inherent in the open-label trial design of this study. We did not control for changes in diet or physical activity. In addition, participating in a study focused on weight loss may have induced individuals to adhere to their own weight reduction strategies.

This study supports further investigation, using a control design, of topiramate as a weight-loss agent in antidepressant-induced weight gain. Other unanswered questions raised by this study include the following: (1) Is weight loss with topiramate maintained when topiramate is withdrawn and SSRI monotherapy is resumed? (2) How long do people need to be treated to maintain the weight-loss effect? (3) What is the optimal topiramate dose that needs to be achieved in order to obtain the weight-loss effect? and (4) As 4 of our patients gained rather than lost weight during the study, what are the predictors of topiramate response?

Drug names: amphetamine (Adderall and others), bupropion (Wellbutrin and others), citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), gabapentin (Neurontin), lamotrigine (Lamictal), liothyronine (Cytomel, Triostat), methylphenidate (Ritalin and others), naltrexone (ReVia), nefazodone (Serzone), paroxetine (Paxil), phentermine (Adipex-P), sertraline (Zoloft), sibutramine (Meridia), topiramate (Topamax), valproic acid (Depakene and others).

REFERENCES

1. Shioiri T, Kato T, Murashita J, et al. Changes in the frequency distribution pattern of body weight in patients with major depression. Acta Psychiatr Scand 1993;88:356–360
2. Frank E, Kupfer DJ, Bulik CM, et al. Imipramine and weight gain during the treatment of recurrent depression. J Affect Disord 1990;20:165–172
3. Fernstorm MH, Kupfer DJ. Antidepressant-induced weight gain: a comparison study of four medications. Psychiatry Res 1988;26:265–271
4. Fava M, Judge R, Hoog SL, et al. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. J Clin Psychiatry 2000;61:863–867
5. Zajecka JM. Clinical issues in long-term treatment with antidepressants. J Clin Psychiatry 2000;61(suppl 2):20–25
6. Rigler SK, Webb MJ, Redford L, et al. Weight outcome among antidepressant users in nursing facilities. J Am Geriatr Soc 2001;49:49–55
7. Fava M. Weight gain and antidepressants. J Clin Psychiatry 2000;61 (suppl 11):37–41
8. Sussman N, Ginsberg DL, Bikoff J. Effects of nefazodone on body weight: a pooled analysis of selective serotonin reuptake inhibitor– and imipramine-controlled trials. J Clin Psychiatry 2001;62:256–260
9. Biton V, Edwards KR, Montouris GD, et al. Topiramate titration and tolerability. Ann Pharmacother 2001;35:173–179
10. Schneiderman JH. Topiramate: pharmacokinetics and pharmacodynamics. Can J Neurol Sci 1998;25:S3–S5
11. Marcotte D. Use of topiramate, a new anti-epileptic as a mood stabilizer. J Affect Disord 1998;50:245–251
12. Dursun SM, Devarajan S. Accelerated weight loss after treating refractory depression with fluoxetine plus topiramate: possible mechanisms of action? [letter] Can J Psychiatry 2001;46:287–288
13. Shapira NA, Goldsmith TD, McElroy SL. Treatment of binge-eating disorder with topiramate: a clinical case series. J Clin Psychiatry 2000;61: 368–372
14. Sabers A, Gram L. Newer anticonvulsants: comparative review of drug interactions and adverse effects. Drugs 2000;60:23–29
15. Teter CJ, Early JJ, Gibbs CM. Treatment of affective disorders and obesity with topiramate. Ann Pharmacother 2000;34:1262–1264
16. Gordon A, Price LH. Mood stabilization and weight loss with topiramate [letter]. Am J Psychiatry 1999;156:968–969
17. Lin M, Michell WG, Chang C, et al. Topiramate (TPM) and weight loss [abstract]. Epilepsia 1999;40(suppl 7):130
18. Rosenfeld WE, Schaefer PA, Pace K. Weight loss patterns with topiramate therapy [abstract]. Epilepsia 1997;38(suppl 3):58
19. Norton J, Potter D, Edwards K. Sustained weight loss associated with topiramate [abstract]. Epilepsia 1997;38(suppl 3):60
20. Picard F, Deshaies Y, Lalonde J, et al. Topiramate reduces energy and fat gains in lean (Fa/?) and obese (fa/fa) Zucker rats. Obes Res 2000;8: 656–663
21. Richard D, Ferland J, Lalonde J, et al. Influence of topiramate in the regulation of energy balance. Nutrition 2000;16:961–966