

The Development or Exacerbation of Eating Disorder Symptoms After Topiramate Initiation

Jocelyn Lebow, PhD^{a,b}, Jeffrey A. Chuy, MD^c, Kyle Cedermark, MD^a, Katlyn Cook, BS^d, Leslie A. Sim, PhD^a

abstract

The Food and Drug Administration recently approved topiramate for migraine prevention in adolescents. Given the well-established appetite-suppressant side effects of topiramate, as well as data suggesting a potential comorbidity between migraine and eating disorders, susceptible young migraine patients may be at a greater risk for the development or worsening of eating disorder symptoms with topiramate therapy. This case series comprises 7 adolescent patients in whom serious eating disorders developed or were exacerbated after the initiation of topiramate therapy. Clinical characteristics of these patients are highlighted. In addition, this case series provides guidelines for providers to use in assessing eating disorders before prescribing topiramate for migraine prevention in adolescents.

Departments of ^aPsychiatry and Psychology and ^bCardiovascular Disease, Mayo Clinic College of Medicine, Rochester, Minnesota; and Departments of ^cPsychiatry and Behavioral Sciences and ^dRadiology, Miller School of Medicine, University of Miami, Miami, Florida

Dr Lebow conceptualized the review, drafted the initial manuscript, referenced the paper, and reviewed and revised the manuscript; Dr Chuy assisted in conceptualizing the review, contributed to the introduction and discussion, and reviewed the manuscript; Dr Cedermark collected and wrote up data related to each of the cases reviewed and critically reviewed the manuscript; Ms Cook assisted with identifying cases for inclusion in the review and gathering relevant data and critically reviewed the manuscript; Dr Sim designed the review, substantially reviewed and revised the manuscript, wrote the abstract, and collected data related to cases reviewed; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-3413

DOI: 10.1542/peds.2014-3413

Accepted for publication Feb 4, 2015

Address correspondence to Jocelyn Lebow, PhD, University of Miami, Miller School of Medicine, 1120 NW 14th St, Suite 1442, Miami, FL 33136. E-mail: j.lebow@med.miami.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2015 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

In 2014, topiramate became the first medication approved for migraine prevention in adolescents by the Food and Drug Administration.¹ The drug has several proposed mechanisms that include modulatory effects on sodium channels, calcium (L- and T-type) channels, glutamate and γ -aminobutyric acid pathways, carbonic anhydrase isoenzymes, and glutamate subtype α -amino-3-hydroxy-5-methylisoxazole-5-propionic acid/kainate receptors.²⁻⁴ Topiramate has been used in the pediatric population to treat epilepsy and episodic and chronic migraines.

Topiramate's age-specific adverse effects are not well known; however, appetite reduction and related weight loss are some of those most commonly reported in both pediatric and adult populations.⁵ The specific mode of action behind topiramate's weight-modifying properties is unclear.⁴ Although promising data suggest topiramate may inhibit several carbonic anhydrase isoenzymes, a property shared by zonisamide, a medication with similar weight loss

properties,⁶⁻⁸ the theory currently remains speculative.⁴

Multiple studies of topiramate treatment of partial-onset and generalized epilepsy in youth describe rates of weight loss/anorexia ranging from 10% in 1 study⁹ to 39% to 40% in 3 independent studies.¹⁰⁻¹² Although the majority of participants across studies remained on topiramate, several discontinued use due to weight loss/anorexia.^{13,14} Authors agree that weight loss and anorexia are not common enough to preclude topiramate use in children, but the side effects merit concern.

It is well established that weight loss, even in individuals with no history of an eating disorder (ED), can lead to the development of behavioral, cognitive, and physical symptoms characteristic of EDs.¹⁵ As such, it is possible that the weight loss side effects of topiramate could trigger the development of an ED, particularly in vulnerable individuals. In fact, case studies have described ED relapse after initiation of topiramate in 2 women with ED

histories.^{16,17} To date, no studies have been published on topiramate use and EDs in youth. The following case series describes 7 adolescents who were diagnosed with EDs after topiramate initiation for the treatment of migraine or chronic headache.

METHODS

This was a retrospective chart review of adolescent patients taking topiramate, evaluated at the Mayo Clinic Eating Disorders Program between November 2008 and June 2013. Demographic data and information regarding ED symptoms, physical sequelae, and chronology of symptom onset were collected. All ED diagnoses were made according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*.¹⁸

RESULTS

Seven female adolescents treated with topiramate (ages ranged from 13 to 18 years; mean = 16.43 years) were diagnosed with EDs (Table 1). Of these patients, 4 were diagnosed with eating disorder not otherwise specified (cases 1, 4, 6, and 7), 2 with anorexia nervosa (cases 2 and 3), and 1 with bulimia nervosa (case 5). All patients had received topiramate for migraine or chronic headache, with dosages ranging from 25 mg twice daily to 150 mg daily. The most common physical comorbidity reported was postural orthostatic tachycardia syndrome (POTS) in 4 patients (cases 2, 4, 5, and 6). The most common psychological comorbidities included major depressive disorder (cases 1, 5, and 6) and various anxiety disorders (cases 1 and 7).

Three patients (cases 2, 6, and 7) estimated that their ED developed before topiramate use. One additional adolescent (case 1) had a history of an ED in remission that recurred after topiramate initiation. The remaining

TABLE 1 Patient Characteristics

Case	Age, y	Gender	Medical/Psychological Comorbidities	Neurologic Diagnosis	Topiramate Dosage	ED Diagnosis	ED Symptoms	Change in Weight, kg	Physical ED Sequelae	Order of Symptom Onset
1	17	F	Postconcussive syndrome, MDD, alcohol/cannabis abuse, trauma	Daily migraine with aura	25 mg, twice daily	ED not otherwise specified	Wt loss; restriction; binge/purge; laxative abuse	-6.8	None reported	History of ED, relapse after topiramate initiation
2	16	F	POTS	Migraine	50 mg, twice daily	Anorexia nervosa	Wt loss; restriction; self-induced vomiting	-22.7	Amenorrhea, cold intolerance, orthostatic intolerance, dizziness, fatigue, abdominal pain, constipation	ED onset first
3	13	F	None	Vein of Galen malformation, treated with coiling, migraine	25 mg, twice daily	Anorexia nervosa	Wt loss; restriction; nighttime binge eating	-11.5	Anergia, amenorrhea, sinus bradycardia, ST and T-wave changes	Topiramate initiation first
4	18	F	POTS, nonepileptic spells	Chronic daily headache	50 mg in the morning, 75 mg at night	ED not otherwise specified	Wt loss; restriction; self-induced vomiting	-9.1	Orthostasis, oligomenorrhea	Topiramate initiation first
5	16	F	POTS, gastrointestinal mastocytosis, MDD	Migraine	150 mg daily	Bulimia nervosa	Wt gain; restriction; binge eating	+32.0	None reported	Topiramate initiation first
6	17	F	POTS, MDD, attention deficit/hyperactivity disorder	Headache	50 mg daily	ED not otherwise specified	Wt loss; restriction; self-induced vomiting	-6.8	Nausea, cold intolerance, oligomenorrhea, dizziness, lightheadedness, abnormal bone density, multiple lower extremity fractures	ED onset first
7	18	F	Obsessive compulsive disorder, generalized anxiety disorder	Chronic daily headache with migrainous features	50 mg daily	ED not otherwise specified	Wt loss; restriction; self-induced vomiting	-5.0	Cold intolerance, fatigue, sleep challenges, oligomenorrhea, poor pain management, bruising	ED onset first

MDD, major depressive disorder.

3 cases (cases 3, 4, and 5) reported no ED symptoms before topiramate usage. All patients reported dietary restriction as their primary ED symptom. Five also reported self-induced vomiting (cases 1, 2, 4, 6, and 7), and 3 reported binge eating (cases 1, 3, and 5). One patient (case 1) reported laxative abuse. Although most patients exhibited unhealthy weight loss, 1 patient (case 5) presented with marked weight gain (32.0 kg). For the remaining 6 patients, weight loss ranged from 5.0 to 22.7 kg. Physical sequelae associated with EDs were numerous and varied by patient (Table 1). Two patients presented with amenorrhea (cases 2 and 3), and 3 reported oligomenorrhea (cases 4, 6, and 7).

DISCUSSION

To our knowledge, this case series is the first describing the development or exacerbation of ED symptoms after topiramate initiation in adolescents with migraine or chronic headache. Migraine and headaches are particularly common conditions seen in individuals with EDs, with one small study finding that at least 74% of patients with EDs also reported migraine.^{19–21} The migraine and ED patient populations share characteristics including frequent symptom onset during adolescence, higher prevalence of female sufferers, common psychiatric comorbidities including depression and anxiety, and personality traits including perfectionism and feelings of ineffectiveness.^{19,21,22} Consequently, several researchers have postulated a pathophysiological overlap in migraine and EDs, such as postsynaptic serotonin dysfunction or catecholamine abnormalities.²³ Of note, patients with POTS have also been found to share many of these clinical characteristics,²⁴ which might account for the high rate of comorbid POTS in this sample.

Although the methodology of this study is insufficient to clarify the

direction of causality, these cases suggest that physicians should be aware of the overlap between migraine and EDs. In particular, it appears that patients who have ED symptoms or who are at risk for an ED should be observed closely after topiramate initiation because the medication might trigger or intensify ED symptoms. In the cases presented, it should be noted that at least 3 individuals (cases 2, 6, and 7) had a distinguishable ED before topiramate use. One additional patient (case 1) had a premorbid history of ED that had resolved by the time topiramate was introduced and relapsed after medication use.

These findings are consistent with previous case studies in which both adult cases had an ED history and relapsed after topiramate initiation.^{16,17} Although an understanding of the prevalence of cases in which EDs either develop or worsen in the context of topiramate prescription is beyond the scope of this article, it is clear that providers should consider the potential that the medication may exacerbate existing EDs and to screen carefully for ED symptoms before prescribing topiramate (Table 2).

It should be noted that, although these 4 cases described clear preexisting ED pathology, none of these patients had received an ED diagnosis or treatment before initiating topiramate. This is in contrast to reported adult cases^{16,17} and is understandable given that the present cases are younger. Perhaps, over time, these patients' ED symptoms would have increased to the point of detection/diagnosis regardless of topiramate use. Nonetheless, because of the potential comorbidity between migraine and EDs,^{19–21,23} it is especially important for providers to remain aware of the possibility of undetected EDs in migraine patients.

In 3 cases, patients endorsed no ED symptoms before topiramate

initiation, although 1 patient (case 3) reported a family history of ED. It is possible that all 3 cases had risk factors and/or subthreshold symptoms of EDs despite not exhibiting clinical levels of symptomatology. Unfortunately, disordered eating and related maladaptive cognitions are not uncommon in adolescents.²⁵ As such, clinicians must remain attentive to the potential development of EDs even in patients with no history of eating issues.

It is also theoretically possible for topiramate-induced weight loss to trigger an ED in a patient with no

TABLE 2 Tips for Assessing EDs in Eligible Adolescents Before Considering Topiramate for Migraine Prevention

1. Obtain collateral information from parent separately from the patient. Do not rely solely on adolescent's self-report.
2. Screen for history of ED symptoms and assess for psychological comorbidities such as mood, anxiety, and behavioral symptoms. Focus on any changes in behavior or affect.
3. Inquire about ED risk factors, such as a history of dieting behaviors.
4. Evaluate exercise habits (look for overexercising or compulsive exercising over and above that of similarly athletic peers) and compensatory behaviors such as vomiting, restrictive eating, laxative abuse, use of medications to control appetite, etc.
5. Assess cognitive symptoms of EDs including weight or shape concerns, fear of gaining weight, drive for thinness, etc.
6. Ask about any recent changes in social functioning, including increased withdrawal or isolation. ED patients may continue to function at a high level academically, but socially they often show behavioral changes.
7. Acquire patient's growth curves and/or assess the adolescent's developmental weight history. Be aware that patients can have dangerous ED symptoms even at higher BMIs if they used to track at a higher BMI percentile than they do currently.
8. Inquire whether patient has any unrealistic or unhealthy goal weights.
9. Evaluate patient's current dietary intake and assess rigid patterns or avoidance of specific categories of foods. Assess preoccupation with maintaining a "healthy diet" or experimentation with fad diets.
10. Use standardized measures, such as the Eating Disorders Examination Questionnaire and the Eating Disorder Test—26 to screen for EDs.

symptoms of disordered eating. The seminal Minnesota Starvation Study showed that, even in healthy subjects, dietary restriction and weight loss can elicit emotional, behavioral, and cognitive symptoms characteristic of EDs.¹⁵ In particular, starvation was shown to produce appetite changes, preoccupation with food, loss of social interest, depression, irritability, poor concentration, and fatigue.¹⁵ In this way, when adolescents decrease their food intake due to topiramate-induced anorexia, it may lead to the symptoms of an ED.

All 7 patients reported dietary restriction as their primary ED symptom. Given that weight loss/anorexia is the second most prevalent category of topiramate adverse effects⁴ and that studies have actually attempted to harness that effect by using topiramate as an intervention for obesity and binge eating,^{26–29} this is unsurprising. Less intuitively, however, 2 patients (cases 3 and 5) also reported the development of binge eating after the initiation of topiramate. Case 5 even experienced overall weight gain as a result of binge episodes. This sort of symptomological drift, in which restrictive eating leads to periodic binge episodes and vice versa, has been well established in the ED literature.³⁰ It does, however, complicate detection, in that clinicians managing patients on topiramate must remain aware that the development of dangerous EDs is possible, even if the patient is not solely restricting and even without weight loss.

Limitations to this study include the retrospective case series design and small number of examined cases. Although it is beyond the scope of this article to make statements regarding broader patterns of ED onset or exacerbation upon topiramate initiation, these cases suggest that this question merits further investigation. In particular, studies are needed to ascertain the

prevalence of ED onset in patients prescribed topiramate, as well as the clinical characteristics and risk factors of patients more likely to exhibit EDs after topiramate prescription. This case series focused on adolescents prescribed topiramate for the treatment of migraine or chronic headache; a further area of study would be to examine whether rates of ED onset are comparable in patients prescribed topiramate for seizure control.

These 7 cases illustrate a need for practitioners prescribing topiramate to be aware of the potential for the medication to either trigger or worsen ED symptoms in young patients. This is particularly important given that topiramate has recently become the first medication approved for use in migraine prevention in adolescents.¹ Providers should carefully screen patients for preexisting EDs and/or ED risk factors before prescribing topiramate (Table 2). Furthermore, careful monitoring of patient weight and eating behaviors should continue after topiramate initiation; weight loss/anorexia should be carefully monitored and not dismissed simply as a side effect of the medication.

REFERENCES

1. Dales M. Topiramate for migraine prevention. *Pediatr News*. 2014;48:7
2. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia*. 2000;41(suppl 1):S3–S9
3. Welch KM, D'Andrea G, Tepley N, Barkley G, Ramadan NM. The concept of migraine as a state of central neuronal hyperexcitability. *Neurol Clin*. 1990;8(4): 817–828
4. Antel J, Hebebrand J. Weight-reducing side effects of the antiepileptic agents topiramate and zonisamide. *Handbook Exp Pharmacol*. 2012;209(209):433–466

5. Levisohn PM. Safety and tolerability of topiramate in children. *J Child Neurol*. 2000;15(suppl 1):S22–S26
6. Dodgson SJ, Shank RP, Maryanoff BE. Topiramate as an inhibitor of carbonic anhydrase isoenzymes. *Epilepsia*. 2000; 41(suppl 1):S35–S39
7. Masereel B, Rolin S, Abbate F, Scozzafava A, Supuran CT. Carbonic anhydrase inhibitors: anticonvulsant sulfonamides incorporating valproyl and other lipophilic moieties. *J Med Chem*. 2002; 45(2):312–320
8. Supuran CT, Di Fiore A, De Simone G. Carbonic anhydrase inhibitors as emerging drugs for the treatment of obesity. *Expert Opin Emerg Drugs*. 2008; 13(2):383–392
9. Ritter F, Glauser TA, Elterman RD, Wyllie E; Topiramate YP Study Group. Effectiveness, tolerability, and safety of topiramate in children with partial-onset seizures. *Epilepsia*. 2000;41(suppl 1): S82–S85
10. Sachdeo RC, Glauser TA, Ritter F, Reife R, Lim P, Pledger G; Topiramate YL Study Group. A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. *Neurology*. 1999;52(9): 1882–1887
11. Uldall P, Buchholt JM. Clinical experiences with topiramate in children with intractable epilepsy. *Eur J Paediatr Neurol*. 1999;3(3):105–111
12. Rosenfeld WE, Doose DR, Walker SA, Baldassarre JS, Reife RA. A study of topiramate pharmacokinetics and tolerability in children with epilepsy. *Pediatr Neurol*. 1999;20(5):339–344
13. Biton V, Montouris GD, Ritter F, et al; Topiramate YTC Study Group. A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. *Neurology*. 1999;52(7): 1330–1337
14. Elterman RD, Glauser TA, Wyllie E, Reife R, Wu SC, Pledger G; Topiramate YP Study Group. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. *Neurology*. 1999;52(7): 1338–1344
15. Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. *The Biology of Human Starvation*. Oxford, UK: University of Minnesota Press; 1950

16. Rosenow F, Knake S, Hebebrand J. Topiramate and anorexia nervosa. *Am J Psychiatry*. 2002;159(12):2112–2113
17. Cailhol L, Rodgers R, Guelfi JD. Prescribing topiramate in patients with borderline personality disorder and a history of anorexia nervosa: A case report. *Prim Care Companion CNS Disord*. 2011;13(2):doi:10.4088/PCC.10101041gre.
18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed., text rev. Washington, DC: American Psychiatric Publishing; 2000
19. Brewerton TD, George MD. Is migraine related to the eating disorders? *Biol Psychiatry*. 1991;29(9):155A
20. Brewerton TD, George MS, Harden RN. Migraine and the eating disorders. *Psychiatry Res*. 1993;46(2):201–202
21. D'Andrea G, Ostuzzi R, Francesconi F, et al. Migraine prevalence in eating disorders and pathophysiological correlations. *Neurol Sci*. 2009;30(suppl 1):S55–S59
22. Seidel S, Karwautz A, Wagner G, et al. Migraine in patients with eating disorders: a study using a sister-pair comparison design. *Headache*. 2011; 51(2):220–225
23. D'Andrea G, Ostuzzi R, Bolner A, Colavito D, Leon A. Is migraine a risk factor for the occurrence of eating disorders? Prevalence and biochemical evidence. *Neurol Sci*. 2012; 33(S1): 71–76
24. Johnson JN, Mack KJ, Kuntz NL, Brands CK, Porter CJ, Fischer PR. Postural orthostatic tachycardia syndrome: a clinical review. *Pediatr Neurol*. 2010; 42(2):77–85
25. Croll J, Neumark-Sztainer D, Story M, Ireland M. Prevalence and risk and protective factors related to disordered eating behaviors among adolescents: relationship to gender and ethnicity. *J Adolesc Health*. 2002;31(2):166–175
26. De Bernardi C, Ferraris S, D'Innella P, Do F, Torre E. Topiramate for binge eating disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(2):339–341
27. Guerdjikova AI, Kotwal R, McElroy SL. Response of recurrent binge eating and weight gain to topiramate in patients with binge eating disorder after bariatric surgery. *Obes Surg*. 2005;15(2): 273–277
28. Tata AL, Kockler DR. Topiramate for binge-eating disorder associated with obesity. *Ann Pharmacother*. 2006;40(11): 1993–1997
29. Verrotti A, Scaparrotta A, Agostinelli S, Di Pillo S, Chiarelli F, Grosso S. Topiramate-induced weight loss: a review. *Epilepsy Res*. 2011;95(3):189–199
30. Fichter MM, Quadflieg N. Long-term stability of eating disorder diagnoses. *Int J Eat Disord*. 2007;40(suppl):S61–S66

The Development or Exacerbation of Eating Disorder Symptoms After Topiramate Initiation

Jocelyn Lebow, Jeffrey A. Chuy, Kyle Cedermack, Katlyn Cook and Leslie A. Sim
Pediatrics 2015;135:e1312

DOI: 10.1542/peds.2014-3413 originally published online April 6, 2015;

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/135/5/e1312
References	This article cites 26 articles, 3 of which you can access for free at: http://pediatrics.aappublications.org/content/135/5/e1312#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Neurology http://www.aappublications.org/cgi/collection/neurology_sub Psychiatry/Psychology http://www.aappublications.org/cgi/collection/psychiatry_psychology_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The Development or Exacerbation of Eating Disorder Symptoms After Topiramate Initiation

Jocelyn Lebow, Jeffrey A. Chuy, Kyle Cedermark, Katlyn Cook and Leslie A. Sim
Pediatrics 2015;135:e1312

DOI: 10.1542/peds.2014-3413 originally published online April 6, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/135/5/e1312>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2015 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

