The Development or Exacerbation of Eating Disorder Symptoms After Topiramate Initiation

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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.

In 2014, topiramate became the first medication approved for migraine prevention in adolescents by the Food and Drug Administration.\textsuperscript{1} The drug has several proposed mechanisms that include modulatory effects on sodium channels, calcium (L- and T-type) channels, glutamate and \(\gamma\)-aminobutyric acid pathways, carbonic anhydrase isoenzymes, and glutamate subtype \(\alpha\)-amino-3-hydroxy-5-methylisoxazole-5-propionic acid/kainate receptors.\textsuperscript{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.\textsuperscript{5} The specific mode of action behind topiramate's weight-modifying properties is unclear.\textsuperscript{4} Although promising data suggest topiramate may inhibit several carbonic anhydrase isoenzymes, a property shared by zonisamide, a medication with similar weight loss properties,\textsuperscript{6–8} the theory currently remains speculative.\textsuperscript{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 study\textsuperscript{9} to 39% to 40% in 3 independent studies.\textsuperscript{10–12} Although the majority of participants across studies remained on topiramate, several discontinued use due to weight loss/anorexia.\textsuperscript{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.\textsuperscript{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.

abstract

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.


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histories. 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.

RESULTS

Seven female adolescents treated with topiramate (ages ranged from 13 to 18 years, mean = 16.43 years) were diagnosed with EDs (Table 1).

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

MDD, major depressive disorder.
The remaining 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 cases16,17 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. In particular, starvation was shown to produce appetite changes, preoccupation with food, loss of social interest, depression, irritability, poor concentration, and fatigue. 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 symptom of an ED. All 7 patients reported dietary restriction and weight loss/anorexia as their primary ED symptoms. Given that weight loss/anorexia is the second most prevalent symptom of an ED.

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. 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


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