CASE REPORT

Zonisamide for Weight Loss in Adolescents

Mathew L. Nguyen, MD,[1] Mustafa H. Pirzada, MD,[1] and Michael A. Shapiro, MD[1]

[1]Division of Child and Adolescent Psychiatry, Department of Psychiatry, University of Florida, Gainesville, Florida

Obesity in children and adolescents is a growing epidemic in the United States, and physicians are increasingly looking for safe and effective treatments. In recent years, pharmacologic treatment has been considered for severe and refractory cases of adolescent obesity. We present a case of an obese adolescent who presented to an inpatient psychiatric unit with a body mass index (BMI) of 37.8 (>98th percentile for age). He was started on zonisamide for the purposes of weight loss, and a steady decrease in weight and BMI was noted through 4 months of outpatient follow-up. During this time, the patient's weight decreased from 126.8 kg to 106.2 kg, a 20.6-kg loss, representing a 16.25% reduction in weight. His most recent BMI decreased to 31.7 (96th percentile for age). We discuss the potential use of zonisamide for weight loss in adolescents, considering the potential risks and benefits.

INDEX TERMS adolescents, antiobesity agents, obesity, weight loss, zonisamide

J Pediatr Pharmacol Ther 2013;18(4):311–314

INTRODUCTION

The definition of being overweight for a child (age 2-19) in the Unites States is a body mass index (BMI) between the 85th and 95th percentiles, and obesity is defined as at or above the 95th percentile.[1] The rate of obesity in children has tripled since 1980,[1] with the most recent data indicating that 16.9% of children fall into the obese range.[2] Specifically, over a 12-year period between 1999-2000 and 2009-2010, there has been a significant increase in the rates of obesity and in average BMI in males aged 2 through 19 years.[2] Despite intensive lifestyle modifications, many of these obese children will continue to be overweight and may require concomitant pharmacotherapy. The use of adjunctive medications to help with weight gain has not demonstrated any clear algorithm or medication combinations that are significantly helpful. In recent years, there has been more literature suggesting the usefulness of zonisamide for attenuation of weight gain.[1] We previously documented a case of a 14-year-old adolescent male who lost nearly 100 kg (starting at 301 kg and ending at 202.76 kg) during a 3-month period during which he was in a pediatric hospital and an adolescent psychiatric unit.[3] This patient was treated with zonisamide for the sole purpose of weight loss. However, the 100-kg weight loss that resulted was confounded by several variables that could have influenced the outcome, including the added structure of the hospital and more proportioned meals compared to his usual home diet. Here, we describe a case of a 15-year-old Caucasian male who lost 20 kg during a 5-month period in which he was treated with zonisamide as an outpatient.

CASE REPORT

A 15-year-old Caucasian male initially presented to our inpatient Child and Adolescent Psychiatry unit with worsening depression and anxiety. Symptoms included self-injurious and cutting behaviors as well as suicidal ideation. He had been on multiple medications in the past, including risperidone, haloperidol, escitalopram, topiramate, paroxetine, and lorazepam. He presented on escitalopram (10 mg each morning), topiramate (100 mg at bedtime), and aripiprazole (10 mg every morning). His presenting weight was 120.3 kg (BMI of 35.9), and his fasting triglyceride level was 142 mg/dL. He was stabilized and discharged on escitalopram (10 mg each

morning) and risperidone (1 mg twice daily). The topiramate was increased to 200 mg at bedtime because of concerns of increasing weight.

Despite the increase in the topiramate to 200 mg, his weight continued to range from 121.5 to 128 kg. He had two subsequent hospitalizations, during which time risperidone, quetiapine, and diazepam were each tried to treat impulsivity, agitation, and anxiety while monitoring and minimizing weight gain. During the most recent hospitalization, his presenting weight had increased to 126.8 kg (BMI of 37.8) and his triglyceride level was 275 mg/dL. At this time, his medications included topiramate (200 mg) and escitalopram (10 mg). The treatment team felt that topiramate was somewhat helpful in treating the psychiatric symptoms of impulsivity and anxiety, but larger doses aimed at producing further weight gain led to cognitive dulling. Thus, the decision was made to continue the topiramate at 200 mg.

Risperidone had been discontinued 2 months prior, and he had been on quetiapine for only 1 month, with no noted benefit. A joint decision was made by the treatment team and his guardians to not retry any antipsychotics because he had gained approximately 10 kg during a previous hospitalization while on risperidone 1 mg twice daily. Zonisamide (50 mg nightly) was added to this regimen for the purposes of mood stabilization and weight loss and was increased to 200 mg nightly over the course of 1 month, during which time he spent 2 weeks inpatient and 2 weeks in intensive outpatient therapy. At the time of discharge to intensive outpatient therapy, his weight was 122.6 kg; he had lost about 4 kg while in the hospital. He was continued on zonisamide (200 mg) as an outpatient. At his 1-month follow-up examination, his weight was 116.8 kg; at his 3-month outpatient follow-up visit, he weighed 108.3 kg (BMI of 32.3); and at his 4-month follow-up appointment, he weighed 106.2 kg (BMI of 31.7). His most recent triglyceride level was 112 mg/dL. This represents a 20-kg total weight drop since starting zonisamide and a 16-kg weight drop since being on zonisamide 200 mg and discharged from the hospital. His triglyceride level had also normalized.

DISCUSSION

Zonisamide is an antiepileptic drug approved by the U.S. Food and Drug Administration (FDA) for adjunctive treatment of partial seizures in adults.[4] It currently has no FDA indications for children and adolescents, although there are data suggesting its efficacy in this population as monotherapy or in adjunctive treatment of generalized or partial epilepsy.[5] One of the noted side effects of zonisamide is appetite suppression.[4] In 2009, Wellmer et al[6] performed a retrospective chart review of 103 patients (age 17-68 years) with epilepsy; 35% of patients experienced greater than 5% weight loss. In 2011, Lim et al[7] conducted a systematic chart review focused on the use of zonisamide for weight loss in 82 adult psychiatric outpatients treated with psychotropic medications. The average daily dose of zonisamide was 124.6 ± 53.4 mg, and the mean BMI reduction was 0.8 ± 1.7 kg/m^2. Both of these reviews examined the effects of zonisamide in adults.

Since the time of an earlier literature review,[3] more data regarding the effect of zonisamide on weight loss has emerged. Yang et al[8] reported on 3 adult Korean patients with schizophrenia previously treated with antipsychotics who were then treated with zonisamide. The patients reduced their BMI by an average of 1.75 kg/m^2 after 16 weeks of treatment with an average final dose of 166.7 mg of zonisamide daily. McElroy et al[9] performed a randomized, placebo-controlled study of zonisamide to prevent weight gain in adults treated with olanzapine. In this study, 42 adult patients diagnosed with either schizophrenia or bipolar disorder had a beginning BMI of 22 kg/m^2. Each was randomized to taking olanzapine (5 to 25 mg daily, adjusted for optimal response) with either zonisamide (100 mg) or with placebo. The former group gained a mean of 0.9 kg, while the latter group gained a mean of 5 kg. It should be noted that the zonisamide group also reported greater cognitive impairment. This is a similar side effect that may limit the use of topiramate, another antiepileptic drug that has weight loss as a potential benefit. In our case, the patient tolerated increasing doses of zonisamide despite experiencing cognitive dulling at higher doses of topiramate. Individual patients may preferentially respond to one medication or another. There has not yet been a direct comparison of zonisamide and topiramate.

More recently Gadde et al[10] performed a 1-year, randomized, double-blind, placebo-controlled trial of 225 obese patients. Participants were assigned to one of three arms: placebo, zonisamide

200 mg, or zonisamide 400 mg. Each group also received diet and lifestyle counseling from a dietitian. The study found that the group on 400 mg of zonisamide had the greatest weight loss, while those in the 200-mg group did not statistically differ from the placebo group.[10]

The aforementioned studies were all conducted in adult populations. To our knowledge, there are no such randomized studies in the child and adolescent populations and only a few case reports. Because zonisamide does not yet have any FDA indication in the child and adolescent population, its adjunctive use for weight control is off-label. To this end, its potential side effect profile deserves comment. The most common adverse events include weight loss, sleepiness, cognitive impairment, and dizziness. These tend to be dose- and titration-related and are also noted to be less common in children (24.3%) than in adults (40.1%).[5] Of specific note in children is oligohydrosis, characterized by deficient production and secretion of sweat and elevation in body temperature. This is reportedly very rare (listed at about 13 cases per 10,000 pediatric patient-years).[4] Finally, the zonisamide package insert warns of the potential for psychiatric symptoms, including depression and psychosis.[4] This is particularly important in the child and adolescent population, given the FDA warning on antiepileptic drugs and the associated potential for increased suicidal thinking in patients ages 24 and younger.[11]

As the rate of obesity increases, newer and more varied approaches are needed to combat this growing epidemic. Diet and lifestyle changes remain the cornerstone of treatment; however, in situations in which these options have failed, medication intervention may be warranted.[1] Our patient continued to have elevated triglyceride levels and a BMI in the upper 30s. Significant weight loss was not noted until the addition of zonisamide, and in this particular case, the weight loss was associated with normalization of triglyceride levels. One possible limitation or confounder in this case is that antipsychotics (most recently quetiapine) were also discontinued because of concerns over weight gain. Risperidone had been discontinued 2 months prior to the initiation of zonisamide, and quetiapine was discontinued at the same time zonisamide was started. Therefore, some of the weight loss may have been a result of discontinuation of these antipsychotics, which are associated with an increased risk of metabolic syndrome.[7] Zonisamide may be a reasonable adjunctive agent for weight loss, keeping in mind the potential for adverse effects. More research on this medication's effect and safety in the child and adolescent population is needed.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ABBREVIATIONS BMI, body mass index; FDA, United States Food and Drug Administration

CORRESPONDENCE Michael Shapiro, MD, Division of Child Psychiatry, University of Florida, 8491 NW 39th Avenue, Gainesville, FL 32606, email: mshapiro@ufl.edu

REFERENCES

1. Matson KL, Fallon RM. Treatment of obesity in children and adolescents. *J Pediatr Pharmacol Ther.* 2012;17(1):45-57.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA.* 2012;307(5):483-490.
3. Nguyen ML, Shapiro MA, Rahmani M. Zonisamide for attenuation of weight gain in a morbidly obese adolescent on an antipsychotic. *J Obes Weight Loss Ther.* 2012;2(4):1-3.
4. *Zonisamide* [package insert]. Teaneck, NJ: Esai Inc; 2004. http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020789s019lbl.pdf. Accessed September 3, 2013.
5. Kothare S, Kaleyias J. Zonisamide: review of pharmacology, clinical efficacy, tolerability, and safety. *Expert Opin Drug Metab Toxicol*. 2008;4(4):493-506.
6. Wellmer J, Wellmer S, Bauer J. The impact of zonisamide on weight: a clinical study in 103 patients with epilepsy. *Acta Neurol Scand.* 2009;119(4):233-238.
7. Lim J, Ko YH, Joe SH, et al. Zonisamide produces weight loss in psychotropic drug-treated psychiatric outpatients. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35(8):1918-1921.

8. Yang J, Lee MS, Joe SH, et al. Zonisamide-induced weight loss in schizophrenia: case series. *Clin Neuropharmacol.* 2010;33(2):104-106.
9. McElroy SL, Winstanley E, Mori N, et al. A randomized, placebo-controlled study of zonisamide to prevent olanzapine-associated weight gain. *J Clin Psychopharm.* 2012;32(2):165-172.
10. Gadde KM, Kopping MF, Wagner HR, et al. Zonisamide for weight reduction in obese adults: a 1-year randomized controlled trial. *Arch Intern Med.* 2012;172(20):1557-1564.
11. US Food and Drug Administration. *Suicidal Behavior and Ideation and Antiepileptic Drugs*. 2009 May 5. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm100190.htm. Accessed August 26, 2013.