

## Zonisamide for Attenuation of Weight Gain in a Morbidly-Obese Adolescent on an Antipsychotic

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### Abstract

Obesity is a growing problem in the child and adolescent population. Particularly concerning is the trend of overweight children being increasingly prescribed antipsychotic medications that can lead to further weight gain. We present a case of a morbidly obese adolescent male who had made strides in weight loss with psychopharmacologic aide who was started on an antipsychotic. Weight loss plateaued, and zonisamide was added to further help with weight loss. We discuss the possible risks and benefits of this medication in aiding in preventing weight gain associated with antipsychotic medication.

**Keywords:** Zonisamide; Adolescent; Obesity; Antipsychotic

### Introduction

In recent years there has been an increase in the number of antipsychotics prescribed to children and adolescents [1]. Associated with this, there has also been much discussion about metabolic syndrome and its connection with this medication class, especially in this population. In the adult population, metabolic syndrome is defined by the following parameters: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance, and prothrombotic and proinflammatory states [2]. In children, the parameters for defining metabolic syndrome have been more widely debated. The International Diabetes Federation recently published its guideline criteria [3]:

1. For children ages 6 - 9 years old, obesity is defined as > 90<sup>th</sup> percentile of waist circumference.
2. For children and adolescents ages 10 - 16 years old, obesity is defined as waist circumference > 90<sup>th</sup> percentile, followed by adult criteria for triglycerides, high-density lipoprotein cholesterol (HDL-C), blood pressure, and glucose.

Among other factors, insulin resistance is thought to play a central role in the pathogenesis of metabolic syndrome, though beyond the scope of this article, insulin resistance can lead to increased cardiovascular risks affecting morbidity and mortality rates [3]. A more easily measured parameter is obesity (mean body mass index [BMI] > 33.4 kg/m<sup>2</sup>), which has been strongly associated with insulin resistance. One report indicates that the worldwide prevalence of childhood obesity has increased from 4.2% in 1990 to 6.7% in 2010 [4], with another study indicating that the rates in the United States have tripled in the last 25 years [5]. In addition to insulin resistance, childhood obesity has been associated with elevated blood pressure, elevated triglycerides, low HDL-C, and abnormal glucose metabolism [3].

A major player in the increasing trends of weight gain and obesity in children and adolescents is the use of antipsychotic medications for a wider variety of mental illnesses in this population. As the rates of childhood obesity have increased, so have the rates of antipsychotic prescribing in the child and adolescent population. One study looking at the Texas medicaid population of children and adolescents between 1996 to 2000 showed that, during that 5-year time interval,

an additional 12.25 children and adolescents per 1000 enrollees were prescribed antipsychotics (+160%), and the prevalence of atypical antipsychotics increased by 13.29 per 1000 enrollees (+494%) during that same time period [5]. More recent associations between long-term use of antipsychotics and metabolic abnormalities in children and adolescents have begun to become clearer. Calarge et al. [6] looked at the effects of long-term risperidone in medically healthy children ages 7 to 17. Compared to lean children, overweight and obese children had higher odds of metabolic abnormalities, including increased waist circumference, hypertriglyceridemia, and low, high-density lipoprotein cholesterol (HDL-C) [6].

There is an area for debate whether some or many of these children need to be on long-term antipsychotic medications; however, for those that require antipsychotic treatment, the adverse effects of weight gain and its potential sequelae need to be addressed. In this case, we report on a morbidly obese adolescent who carries the diagnosis of Mood Disorder, Not Otherwise Specified (NOS) and Disruptive Behavior Disorder, NOS.

### Case Report

Johnny, a 14 year-old Caucasian male weighing 301 kg, was admitted to the Pediatrics Hospital to evaluate for pseudotumor cerebri. His home medication of fluoxetine 20 mg prescribed for depression was continued. Child and Adolescent Psychiatry were consulted to help with management of depression and morbid obesity. On day 2 of the hospitalization, we added topiramate for appetite suppression and eventually titrated it to 100 mg qAM and 300 mg qhs by day 50. We also began methylphenidate for appetite suppression, which was ultimately changed and increased to Concerta® 54 mg qAM by day 51. Johnny had a previous psychiatric history of mood lability

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and irritability, so the decision to not increase Concerta® to 72 mg was made so as to minimize the potential for stimulant-induced agitation. Over the course of 3 months during the hospitalization, Johnny's weight decreased to 213.4 kg.

On day 61, aripiprazole 5 mg BID was added to the regimen to address ongoing and worsening mood lability, irritability, and physical agitation with periods of physical aggression. There were periods during which Johnny would yell and tantrum. Other times, he would hit the nurse's hand, causing medication to spill. On rarer occasions, he would "barricade" himself in his room, not allowing staff to enter. Aripiprazole was added because there is some evidence that antipsychotics are helpful with these behaviors, especially with regard to physical agitation and aggression [7]. Aripiprazole was chosen as it is thought of as one of the more "weight-neutral" of the Second-Generation Antipsychotics (SGAs) [8]. Over the course of the next month, Johnny's weight plateaued around 210 kg. He had lost in excess of 80 kgs during the first three months of hospitalization, and the plateau was partially attributed to the addition of the SGA. With his history of aggression and current symptoms, the decision was made to continue the aripiprazole despite its potential negative effect on ongoing weight loss.

On day 90, after about one month of no further weight loss, zonisamide 50 mg was added with the hopes that it might facilitate further weight loss. Zonisamide was eventually increased to 100 mg. We titrated the zonisamide up slowly, monitoring for the potential for Anti-Epileptic Drug (AED)-induced agitation [9]. The previously noted episodes of agitation and physical aggression had been significantly tempered with the addition of aripiprazole. Johnny was in the hospital only for another full month after the dose was increased to 100 mg, and he saw his weight decrease to 202.76 kg at the time of discharge.

## Discussion

More literature regarding the connection between second-generation antipsychotics and obesity and other components of metabolic syndrome (particularly glucose and lipid metabolism) is emerging. One study showed that, in children and adolescents ages 4 - 19 that were treated with SGAs, within the first three months of treatment, the majority showed significant weight gain (> 7% of baseline weight): 58% with aripiprazole, 64% with risperidone, 56% with quetiapine, and 84% with olanzapine [10]. Khan reviewed the effects of olanzapine and risperidone on patients (mean age of 13) over a 27-day duration. They showed that the study group had a significant increase in Body Mass Index (BMI) for both medications with mean increases in weight being 9.1 lbs and 7.4 lbs, respectively [11]. Though the amount of weight gained varies with each SGA and may be person-specific, it is becoming clearer that weight gain in children and adolescents on SGAs is the trend and not the exception.

Efforts to use medications in combination with SGAs to attenuate or ameliorate weight gain have produced modest results at best. Maayan reviewed data on the effectiveness of 15 different medications, looking primarily at their effect on body weight and BMI in adult patients. Results were most robust for metformin, but they were modest and heterogeneous. This analysis did include popular weight loss medications such as topiramate and psychostimulants, which had less of an impact. None of the agents were able to entirely reverse weight gain from antipsychotics [12]. This study did not include zonisamide.

Wellmer et al. did a retrospective chart review analyzing weight changes after beginning zonisamide. Patients' ages were 17-68.

After about 13 months of treatment, 35% of patient showed > 5% weight loss, and weight loss was more prominent in patients who were overweight prior to beginning treatment. The weight loss was reversible after discontinuation of zonisamide [13]. This analysis demonstrated the usefulness of zonisamide for weight loss in patients but did not specifically consider patients whose weight gain had been a consequence of SGA use. In another study, Yang cited three cases of patients with Schizophrenia, ages 28, 31, and 48, each of whom carried the diagnosis of Schizophrenia and treated with multiple antipsychotic medications (both first and second generation). Zonisamide was started at 50 mg daily and titrated up to either 150 mg or 200 mg daily over a period of 16 weeks. Each patient showed a decrease in BMI and waist circumference [14]. A further review of the literature yielded no articles, either anecdotal or evidence-based that commented on the effects of zonisamide augmentation on the parameters of metabolic syndrome.

Zonisamide is an antiseizure medication approved as adjunctive treatment for partial seizures in adults [9]. It currently does not have an indication in children or adolescents, though there have been some studies touting its effectiveness in this population [15]. There are also some reports of oligohydrosis and fever in pediatric patients, leading to hospitalization, though these cases are rare and listed at 13 cases per 10,000 pediatric-years of exposure [16].

The actual mechanism of action for weight attenuation with zonisamide is still unclear. Wallingford attempted to look at this question in looking at the concomitant use of zonisamide with olanzapine, measuring the effects on body weight and feeding behaviors in the Sprague-Dawley rat. They concluded that while olanzapine induced hyperphagia, weight gain, and elevated blood glucose, these outcomes were attenuated and reversed with the concomitant use of zonisamide [17]. For our case, we have a morbidly obese adolescent male who had remarkable weight loss during his first 3 months of hospitalization, going from 301 kg to 213.4 kg. This loss of 87.6 kg could be attributed to many factors, including the addition of appetite suppressing medications (topiramate and methylphenidate) as well as a structured environment and monitored nutritional intake, among other factors. We started with Topiramate and Methylphenidate as they have more data associated with weight loss [12]. Aripiprazole was added to help control episodes of agitation when Johnny would occasionally "barricade" himself in his room; it was not felt this agitation was due to medication effects. With the addition of the SGA, Johnny's weight loss appeared to plateau. We cannot with certainty make this connection, and the timing of the weight plateau and the addition of the SGA may have been coincidental; however, a review of the chart shows no other major changes that could have explained the halt in weight loss. The addition of zonisamide seemed to promote further weight loss over the course of the subsequent month, with a final discharge weight of 202.76 kg. We do not know if his weight loss continued after discharge or if it would have continued had he been in the hospital longer. More research regarding the use of zonisamide as either a single or adjunct agent for weight loss is needed, especially in light of the escalating rates of childhood obesity and antipsychotic prescribing.

It should be noted that the zonisamide package insert warns of three potential neuropsychiatric side effects: "1) psychiatric symptoms, including depression and psychosis, 2) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular,

word-finding difficulties, and 3) somnolence or fatigue. In placebo-controlled trials, 2.2% of patients discontinued Zonégren or were hospitalized for depression compared to 0.4% of placebo patients, while 1.1% of Zonégren and 0.4% of placebo patients attempted suicide [9]". This is particularly important in the child and adolescent population, especially given the FDA warning on Anti-Epileptic Drugs (AED) in patients aged 24 and younger [18]. Johnny did not experience any worsening aggression or agitation with the addition of the zonisamide.

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