INVITED COMMENTARY

Olanzapine use for the treatment of adolescents with anorexia nervosa – reflecting on research and clinical practice

Wendy Spettigue MD1,2, Mark L. Norris MD 2,3

Abstract

Anorexia nervosa is a complex and potentially devastating mental health (MH) diagnosis that is recognized as having high rates of non-response to treatment, pronounced medical as well as MH morbidity, and elevated mortality rates. Olanzapine is a second-generation atypical antipsychotic that has demonstrated benefit with weight gain in adults with anorexia nervosa (AN), although controlled research involving children and youth remains limited. In this commentary, the authors provide a brief history and review of research relating to olanzapine for the adjunctive treatment of children and adolescents with AN. Although the medication has been used for more than two decades, its mechanism of action remains incompletely understood and is likely multifactorial. Despite a paucity of research to guide clinical decision making, olanzapine prescription among youth with moderate to severe AN appears to be prevalent among eating disorder specialists in Canada. In addition to commenting on gaps and challenges related to controlled randomized research in this area, the authors reflect on factors likely contributing to olanzapine’s adoption into clinical practice. Moving forward, it is critical that further research involving olanzapine for the adjunctive treatment of AN in youth be undertaken to better understand efficacy, appropriate indications for use, and safety profile.

Key Words: adolescent, olanzapine, anorexia nervosa, treatment, research

Résumé

L’anorexie mentale est un diagnostic de santé mentale (SM) complexe et potentiellement dévastateur qui est reconnu comme ayant des taux élevés de non-réponse au traitement, une morbidité médicale et de SM prononcée et des taux de mortalité élevés. L’olanzapine est un antipsychotique atypique de deuxième génération qui a démontré des effets bénéfiques sur la prise de poids chez les adultes souffrant d’anorexie mentale (AM), bien que les recherches contrôlées impliquant des enfants et des jeunes restent limitées. Dans ce commentaire, les auteurs fournissent un bref historique et une revue des recherches relatives à l’olanzapine pour le traitement d’appoint des enfants et adolescents souffrant d’AM. Bien que ce médicament soit utilisé depuis plus de deux décennies, son mécanisme d’action reste mal compris et est probablement multifactoriel. Malgré le manque de recherche pour guider la prise de décision clinique, la prescription d’olanzapine chez les jeunes atteints d’AM modérée à sévère semble être répandue parmi les spécialistes des troubles de l’alimentation au Canada. En plus de commenter les lacunes et les défis liés à la recherche randomisée contrôlée dans ce domaine, les auteurs réfléchissent aux facteurs susceptibles de contribuer à l’adoption de l’olanzapine dans la pratique clinique. À l’avenir, il est essentiel que d’autres recherches impliquant l’olanzapine pour le traitement d’appoint de l’AM chez les jeunes soient entreprises afin de mieux comprendre l’efficacité, les indications d’utilisation appropriées et le profil d’innocuité.

Mots clés: adolescent, olanzapine, anorexie mentale, traitement, recherche

1Department of Psychiatry, Children’s Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario
2Children’s Hospital of Eastern Ontario Research Institute, Ottawa, Ontario
3Department of Pediatrics, Children’s Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario

Corresponding E-mail: mnorris@cheo.on.ca

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In 2021 the Ontario Student Drug Use and Health Survey revealed that 46% of high school respondents reported not being able to stop worrying about their weight or shape, 49% reported binge eating or uncontrolled eating, and 36.5% reported skipping meals or going most of the day without eating (1). Taken together, these statistics help provide context for the high numbers of adolescents requiring acute services for eating disorders (EDs) across Canada (2). Concerns relating to rates of disordered eating and EDs are not isolated to Canada. A recent systematic review helped highlight the global scale of the issue by demonstrating a worldwide incidence of disordered eating of 13%, based upon self-reported answers to screening instruments among high school students across 25 different countries (3). In addition to these troubling statistics, numerous studies have described increases in emergency room presentations, hospital admissions, and severity of EDs since the COVID-19 pandemic began (2, 4-6).

This means that most child and adolescent psychiatrists will be faced with adolescents suffering from EDs such as anorexia nervosa (AN) or bulimia nervosa, whether in the emergency department, on hospital wards, or in outpatient consultations. Common symptoms endorsed by patients with EDs include struggles with severe body image concerns, nutritional restriction, binge eating, and engaging in behaviors that promote weight loss, including compulsive over-exercising, purging, or abuse of laxatives or diet pills. In addition to being aware of the core criteria for EDs, it is critical that clinical providers have knowledge and understanding of the secondary mental health effects of weight loss. Those suffering from the effects of malnutrition will often experience irritability, low mood, emotion dysregulation, anxiety, obsessive eating disorder cognitions, rigidity, preoccupation with food, insomnia, difficulties concentrating, and cognitive impairment (7-8).

Despite the increase in prevalence and severity of EDs in adolescents in recent years (9), there have been no recent advances in treatments. Family Based Treatment (FBT) remains the most evidence-based treatment for adolescent AN, despite reported recovery rates of only 21-49% depending on length of follow up studied (e.g. end of treatment, 6 month or 12 month follow up) (10-11). Individual cognitive behavioral therapy for EDs (CBT-E) or adolescent-focused therapy has demonstrated comparable rates of efficacy as compared to FBT across trials (although a randomized controlled trial (RCT) has not been completed), for adolescents who are motivated for treatment (12-13). However, many adolescents are unable to access specialized treatment for AN, and there is a lack of evidence-based treatments for those with chronic, severe, or treatment-resistant AN, or with potential contra-indications to FBT (e.g. minors living independently or without support, family observed to be highly critical, etc.). There also remains a lack of evidence for pharmacological treatments for EDs. Overall, ED treatment outcomes are often poor, with reported rates of recovery for AN varying, depending on study design, from 18% of participants enrolled in a large genetic study of risk for EDs (14) to 63% of individuals interviewed 22-years following enrollment into a longitudinal study of ED recovery (15).

In addition to challenges associated with poor treatment response, medical and psychological morbidity is common, and patients with EDs (including AN) have demonstrated mortality rates five to seven times higher for patients diagnosed in hospital settings compared with the overall population (16-18).

Given all of this, ongoing efforts to advance treatments, including further exploration of effective pharmacological treatments for adolescent AN, are urgently needed. As it stands, the only medication with any meaningful evidence for effectiveness in AN is olanzapine, although the majority of evidence has been drawn from studies on adults. Olanzapine is a second-generation atypical antipsychotic (SGA) that was recognized early as contributing to weight gain in patients with schizophrenia (19). Thus, it is not surprising that this medication has been intensively studied for the treatment of AN. Although not completely understood, proposed mechanisms of action for weight gain observed in patients taking olanzapine are multifactorial and include alterations in glucose metabolism, antihistaminergic effects, hypothalamic activation, changes in the production of cytokines, adipokine regulation, changes in the microbiome, as well as the impact of genes (20-22).

The first cohort study of olanzapine for AN was published by Powers et al in 2002 and used an adult sample (23). In that study, twenty outpatients were enrolled in an open label study of olanzapine 10 mg/day plus psychoeducation for ten weeks. Of the 14 patients who completed the study, 10 gained an average of 4 kilograms and 4 lost weight. Although there was no comparison group, this was the first study to demonstrate possible utility of olanzapine as a treatment adjunct for adults with AN. Over the last two decades, several additional studies with varying methodological designs conducted across varying treatment settings have been completed in adults (24-28). In the largest RCT to date, Attia et al. (2019) studied the efficacy of olanzapine versus placebo in 152 adult outpatients with AN from five eating disorder programs in North America, over a period of 16 weeks (29). There was a greater increase in body mass index (BMI) over time for those on olanzapine compared
Unfortunately, the evidence for efficacy of olanzapine in adolescent AN is less robust. Following two case series suggesting potential benefits of olanzapine for pediatric AN (30-31), the first cohort study to include adolescents was a 6-week open trial by Barbarich et al. (2004) of 17 adolescent and adult patients (mean age 20 years). In this study, patients taking olanzapine experienced significant reductions in depression, anxiety, and ED symptoms, and significant weight gain, with no major adverse effects observed (32). Another case series of 5 adolescents followed in 2006, which suggested that patients receiving 5 mg and above reported decreased eating-related anxiety and rumination, improved sleep, and decreased body concerns (33). Leggero et al. (2010) published a prospective study of 13 patients (mean age 13.7 years) with AN who were treated with adjunctive olanzapine (mean dose 4 mg/ day) and followed up at 1 and 6 months (34). They reported significant improvements in BMI and on psychological measures, with minimal adverse effects. In contrast, the first randomized placebo-controlled trial of olanzapine in adolescents conducted by Kafantaris et al. in 2011, reported that after 10 weeks, there was no difference in ED symptoms or cognitions or weight gain for 7 patients with AN on olanzapine compared to 8 patients taking placebo (35). Of note, 79% of eligible patients (n=74) declined enrollment in this study, and of 20 patients that initially enrolled, only 15 completed the study, raising concerns that the study itself may have been underpowered to detect meaningful differences in those taking olanzapine as compared to those taking placebo.

A retrospective chart review by our team compared 43 adolescents with AN treated with olanzapine (2.5–7.5 mg/day) to a comparison group of 43 patients (36). Olanzapine-treated patients demonstrated greater illness severity and higher rates of comorbidity compared to those not treated with olanzapine, and weight gain was not statistically different between groups. Mild adverse effects were reported in 56%, including abnormal lipid profiles in 29%. In 2018, our team also published the results of an open-label trial in which adolescents with AN were invited to take olanzapine at study enrollment (37). Twenty-two participants took olanzapine (medication group) and ten participants did not (comparison group). Participants in the medication group demonstrated a higher rate of weight gain after four weeks compared to those who did not receive olanzapine (p = .012).

Most recently, Pruccoli et al., in 2022, reported on a naturalistic study of 118 adolescents who had been hospitalized (inpatient or day program) for AN, and divided them into three groups: those treated with low dose olanzapine (≤ 5 mg/ day) (n=37), those treated with high dose olanzapine (> 5 mg/ day) (n=29), and those who were not on any antipsychotic medications (n=52) (38). Olanzapine was well tolerated with minimal adverse effects by 86% of all the patients who were treated with the medication, whether low or high dose. Improvement in body uneasiness and depression scores were noted for the entire sample, although those treated with high dose olanzapine experienced less improvement in depression compared to other groups.

There have been numerous reviews that have synthesized the research data relevant to olanzapine for AN. Most recently, based on a review of trials completed to date, olanzapine is considered to have demonstrated efficacy in improving weight for patients with AN and is stated to have ‘category grade B evidence’ (implying recommendation) for use in adults (39-40). In the most recent systematic review and meta-analysis of the literature, Han et al. (2022) determined that for adults, the olanzapine groups showed a significant increase in BMI of 0.68 kg/m² compared to the placebo groups in four double blind randomized controlled trials (RCTs) that ranged from 8-16 weeks in duration. Only two prospective studies (one RCT, one open label study) examined the effect of olanzapine as adjuvant treatment in adolescents, which showed an increase in BMI of 0.66 kg/m² although this finding did not reach statistical significance and the RCT included only 15 patients (40). As noted in the most recently published systematic scoping review of the efficacy and tolerance of SGAs for AN, the overall number of available studies exploring the utility of olanzapine for AN treatment remains low, have low power, and have not been uniform in their results (41). This reality has likely contributed to heterogeneity regarding international guideline recommendations, as recommendations vary widely from country to country, with some countries (i.e. France) only mentioning SGAs in treatment decision trees and others (i.e. the United States of America) indicating level of evidence as well as specific limitations of available studies (41). Other countries (including Canada) have provided weak recommendations for olanzapine as a reasonable treatment option for certain populations of children and adolescents with AN if monitored carefully (42).

The lack of research on olanzapine for adolescent AN may reflect the multitude of challenges associated with conducting RCTs on adolescents with EDs, including difficulties in procuring funding, obtaining regulatory and research ethics board (REB) approvals, procuring placebo, consent procedures, completing and collecting measures, and difficulties associated with recruitment and retention of patients (43-44). For example, for Attia’s 2011 trial, the authors report that of the 603 AN patients who inquired about this study,
Despite our own best efforts to complete a gold standard placebo controlled RCT of olanzapine for adolescent AN, the study closed prematurely due to an insufficient number of patients recruited (45). In hindsight, although our 2011 case-comparison chart review failed to demonstrate a statistically significant difference in weight between those who took olanzapine compared to those who did not, weekly weight gain of 1.14 kg (SD 0.32 kg) was observed for those on olanzapine compared to those who did not take the medication (0.79 kg, [SD 0.52 kg]) (with only 11 patients in each group). This difference in weight gain has relevance given that the olanzapine-treated group exhibited greater illness severity, including higher scores of depression, longer lengths of stays in hospital, and higher rates of readmission (36). Finally, the study’s finding that 36% of patients (95% CI, 23% to 50%) restarted the olanzapine after initial discontinuation due to either increased psychological distress or pronounced weight loss offered further insight into the potential utility of the medication when used as adjunctive treatment for a proportion of patients.

Despite the limited evidence for olanzapine as a treatment option for AN in adolescents, anecdotal conversations among ED specialists suggest that the medication is used widely by clinicians working in specialized ED programs in Canada. Thorey et al.’s review (2022) also suggested that the medication appears to be prescribed regularly in clinical practice (41). Our own clinical experience and that within our large specialized ED program would suggest that olanzapine is used in a number of situations, including as an adjunct to treatment to help facilitate recovery and weight gain, to help decrease agitation and distress at and after mealtimes, and to help aid sleep and settle patients in the evening who struggle with intrusive thoughts relating to the ED. Clinically, within our program, olanzapine is typically started at 2.5 mg qhs (1.25 mg for younger i.e. < 12 years old) or very low weight patients (i.e. < 70% treatment goal weight), and increased as needed and tolerated by increments of 1.25-2.5 mg (with typical doses ranging from 2.5 to 10 mg/ day, although dosing is titrated based upon perceived effect and tolerability). Although the medication is generally prescribed at bedtime (owing to its sedative effects), a proportion of patients appear to benefit from divided doses to help combat daytime agitation, although this has not been studied formally. As noted, available research evidence mainly demonstrates that olanzapine is effective for improving weight; improvements in psychological functioning have not been consistently demonstrated. Despite this, our own clinical experience has been that for some patients, olanzapine helps to facilitate acceptance of nutrition by decreasing resistance to taking nutrition, but also by decreasing overall degree of distress and ED rumination. Of note, olanzapine does not have a formal indication for adolescent AN by Health Canada or the United States Food and Drug Administration (FDA) and as such its use remains off-label.

In addition to these considerations, pharmacogenetic testing may aid in decision-making related to pharmacotherapy. Within our own center, rates of pharmacogenetic testing have increased in the last decade (whether through private means or participation in various studies that have provided such results), which allows clinicians access to information about cytochrome (CYP) p450 gene and allele activity. This information can in turn help guide prescription choice as well as dosing of psychotropic medication. As olanzapine is metabolized primarily through CYP 1A2 but also CYP 2D6, having knowledge of personalized gene and allele activity allows experienced clinicians to better determine whether olanzapine might be a reasonable drug to consider for their patient, and can also help guide dosing strategies (46). As a hypothetical case example, a patient who reports previous attempts to augment treatment using SGA medications as “failed trials,” may in fact be an ultrarapid CYP 1A2 metabolizer and therefore require higher doses than considered “typical.” Although this case example highlights the potential utility of having added precision health information, we are unaware of any studies that have used pharmacogenetic testing to better assess how olanzapine might confer benefit to patients with EDs. In an editorial published in 2016 concerning the utility of pharmacogenetic testing for patients with EDs, Smith and Woodside suggested that ongoing genetic research into the etiology of AN is necessary to further our understanding of how this information may better inform options for treatment (47).

In addition to genetic findings relevant to diagnoses and symptom clustering, information on genetic variations in serotonin, dopamine, and other systems relevant to mental health will also gain relevance to EDs and their treatments. As an example, the serotonin 2C receptor (HTR2C) has been implicated in adverse metabolic effects, including weight gain from SGAs. This could have potential application if olanzapine was being considered in a patient recognized to be homozygous for the C allele of HTR2C variant rs3813929 and therefore at potential greater risk of olanzapine-induced weight gain. (Or alternatively, in a patient heterozygous for HTR2C rs3813929 and thus protected from the weight gain effects of olanzapine)(48-49).

Importantly, given the obvious distress that would be associated with unwanted added weight gain in patients
with EDs, we begin tapering olanzapine as the patient approaches their treatment goal weight (TGW) (usually > 95% TGW) (50). Not uncommonly, patients with distress related to anxiety and depression are concurrently started on selective serotonin reuptake inhibitors (SSRIs) as a means of targeting these conditions. Although studies have not suggested benefit to SSRI use in malnourished patients, our own experience is that medications such as SSRIs can be helpful to help treat patients that are approaching their TGW (i.e. more than 90%) or have reached weight restoration targets. Importantly, studies that have explored these anecdotal observations have not been completed. We have learned that tapering off olanzapine can at times be difficult for patients and result in a rebound or escalation of anxiety and ED-mediated distress. Although we have not examined this in recent years, as previously noted our retrospective study published in 2011 found that 36% of patients struggled as the olanzapine was tapered off (36). As a result of this pattern, our current approach is to taper the medication slowly (e.g. decreasing by 1.25 mg-2.5 mg every 2-3 weeks) as tolerated. While research suggests that olanzapine is reasonably well tolerated in most patients, bloodwork (i.e. metabolic blood work consisting of fasting glucose, fasting insulin, lipid panel, liver function tests, and prolactin) should be monitored at regular intervals in adolescents taking olanzapine (51).

Anecdotally and in summary, clinical practice involving treatment of moderate to severe AN in youth appears to rely heavily on olanzapine, despite the lack of sufficient evidence from research trials demonstrating its effectiveness in the treatment of pediatric AN. The significant challenges associated with clinical trials in adolescents with AN as well as an overall paucity of researchers in the field has resulted in a situation in which the scope of available research does not align with current clinical practice. Although olanzapine is not likely indicated for every patient with AN, there may be a subset of patients who benefit from this treatment, although further research is required. Moving ahead, innovative research trials using qualitative as well as quantitative methods are required to help answer clinical questions in a variety of ‘real life’ treatment environments. More research and oversight is clearly needed, to not only determine the efficacy of olanzapine in the treatment of AN, but also to try to determine factors involved with individual patient response and dosing, in order to improve outcomes for this difficult and complex illness.

Conflicts of Interest
The authors have no relevant financial disclosures or conflicts to declare.

References


36. Spettigue and Norris
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