INTRODUCTION

Despite advances in the number of medication-based studies completed in adolescent patients with eating disorders (EDs) over the last 2 decades, the field remains very much in its infancy. In contrast, emerging research suggests that psychotropic medications are used regularly in clinical care. At present, 3 studies have examined the frequency of use of psychotropics in children and adolescents with EDs at the time of assessment and also at follow-up time points. Monge and colleagues reported that at initial presentation 20.4% of 635 adolescents were taking psychotropic medication, and at 1-year follow-up, 58.7% were taking such medications. In this study, selective serotonin reuptake inhibitors (SSRIs) were the most commonly prescribed medications, and medication use was associated with a need for a higher level of care and psychiatric comorbidity (62.6%). More recently, Mizusaki and colleagues reported that 45% of adolescents and young adults presenting to an academic EDs program...

Disclosure Statement: The authors have no disclosures.

* Corresponding author.

E-mail address: coutur@mcmaster.ca

https://doi.org/10.1016/j.chc.2019.05.005
1056-4993/19 © 2019 Elsevier Inc. All rights reserved.
were taking psychotropic medication. These investigators reported that only a minority of the patients in this sample had diagnosed comorbidity, and that diagnosis of Other Specified Eating Disorders, longer duration of illness, and a history of nonsuicidal self-injury increased the likelihood that a patient would be taking psychotropic medications. Finally, in a different sample, Garner and colleagues reported that 80% of adolescents admitted to an ED residential program were taking psychotropic medication upon admission. Again, antidepressants were the most commonly prescribed medications.

Although by no means a complete picture, these studies provide insight into the prevalence at which medications are being used in this patient population and highlight the need for systematic reviews and clinical practice guidelines to be available to guide clinicians in their practice.

Only 1 North American guideline currently exists specifically focused on the treatment of children and adolescents with EDs. To date, 3 systematic reviews have focused on medication treatments for EDs specifically in children and youth. These reviews have suggested that the greatest body of evidence exists for olanzapine, with some studies showing positive effects on body mass index (BMI), ED symptoms, and function. However, significant limitations, including poor-quality study design, heterogeneity of assessment tools used, small sample sizes, and lack of adequate control groups, limit the ability of reviewers to draw definitive conclusions about the utility of olanzapine.

This article reviews the literature on the efficacy of psychotropic medications used exclusively to treat children and adolescents with primary EDs. Systematic review methodology was used to capture all articles on psychopharmacology for EDs in children and adolescents. A search was performed in the following databases: PubMed, OVID, CIANHL, and Cochrane Database. The search terms “Anorexia Nervosa (AN)”, “Bulimia Nervosa (BN)”, “Binge Eating Disorder (BED)”, “Other Specified Feeding and Eating Disorder (OSFED)”, “Eating Disorder Not Otherwise Specified (EDNOS)”, and “Avoidant/Restrictive Food Intake Disorder (ARFID)” were used, along with treatments such as Selective Serotonin Reuptake Inhibitors, Atypical Antipsychotics, Mood Stabilizers, and Serotonin Norepinephrine Reuptake Inhibitors. All articles up until November 2018 were reviewed. Reference lists were reviewed for any additional articles.

ANOREXIA NERVOSA

Atypical Antipsychotics

Olanzapine

Olanzapine has been the most commonly studied psychotropic medication for children and adolescents with anorexia nervosa (AN). At present, only 1 double-blind placebo-controlled trial in this population has been published. Kafantaris and colleagues examined olanzapine in 20 underweight adolescents being treated in inpatient (n = 9), day treatment (n = 6), and outpatient (n = 5) settings (age range 12.3–21.8 years). In a 10-week pilot study, they found no differences in beneficial effect between the olanzapine and placebo groups in the 15 subjects who completed the trial; however, the treated group showed a trend toward increasing fasting glucose and insulin levels by the end of the study. The mean dose of olanzapine was 8.5 mg daily. Of note, only 21% of eligible patients were recruited into the study, and there was a high rate of attrition. Furthermore, patients were enrolled in each of inpatient, day hospital, and outpatient treatment setting as part of the study design. Although other research teams have also attempted randomized controlled trials using olanzapine in this population, trials have been hampered by a myriad of confounding and recruitment issues.
Several open trials and case series have examined the use of olanzapine in children and adolescents with AN. The most recent of these studies enrolled 38 patients with AN, 22 of whom took olanzapine and 10 who declined medication and were retained as a comparison group. The mean dose of medication was 5.28 mg daily over a 12-week trial period. Those in the medication group demonstrated a significantly higher rate of weight gain in the first 4 weeks, although approximately one-third of participants discontinued olanzapine early due to side effects.10

Leggero and colleagues11 reported a case series of 13 young patients (aged 9.6–16.3 years) treated with a mean dose of 4.13 mg daily of olanzapine. Significant improvements were seen in weight, functioning, ED symptoms, and hyperactivity. Similarly, Swenne and Rosling12 reported 47 adolescents with AN treated with a mean dose of 5.1 mg daily. A mean weight gain of 9 kg was noted. The patients were treated for a mean of 228 days with olanzapine and were followed for 3 months following medication discontinuation. Biochemical side effects were closely monitored and were thought to be more related to refeeding processes than to medication.12

Hillebrand and colleagues13 also reported olanzapine use in 7 patients (mean age 16.0 years) with AN. Most were taking 5 mg of olanzapine, with 1 patient receiving 15 mg once daily. The investigators found reductions in activity levels in the adolescents taking olanzapine in comparison to 11 adolescents not treated with olanzapine. All patients were receiving either inpatient or day hospital care, and there were no significant differences in weight.13

Norris and colleagues14 completed a retrospective chart review of 22 inpatients treated with olanzapine compared with an untreated age-matched group. The rate of weight gain was not significantly different; however, the treated group had more psychiatric comorbidities than those not taking olanzapine and experienced side effects of sedation and dyslipidemia.14

Several smaller case series have also been published. Pisano and colleagues15 report 5 cases of AN treated with 2.5 to 7.5 mg of olanzapine. At 6-month follow-up, these patients demonstrated increased oral intake and improved BMI. Dennis and colleagues16 used olanzapine at a dose of 5 mg daily in 5 adolescent girls with AN and found an increase in BMI, reduction of body concerns, and improvements in sleep and anxiety surrounding food and weight. Another case series involving 4 young patients aged 10 to 12 years reported the use of olanzapine at a dose of 2.5 mg daily to treat AN.17 These investigators reported improvements in compliance and weight gain as well as decreases in agitation. Mehler and colleagues18 reported 5 female patients aged 12 to 17 years on a dose range of 5 mg to 12.5 mg daily of olanzapine. They found improvements in body image distortion and rigidity. La Via and colleagues19 described 2 women with AN who experienced reduction of inner tension and “paranoid ideas” with use of 10 mg daily of olanzapine. Finally, there is a case report using olanzapine 5 mg daily to treat a 17-year-old girl with AN and comorbid pervasive developmental disorder not otherwise specified.20 These investigators reported weight restoration and improvements in eating behavior within 5 months of initiating treatment.

**Risperidone**

Hagman and colleagues21 conducted a double-blind placebo controlled trial of risperidone in adolescents and young adults with AN (age range 12–21 years). These investigators randomized 40 patients to risperidone or placebo. The mean dose of risperidone was 2.5 mg daily over a mean duration of 9 weeks. There were no differences found between the groups at the end of the study.21 Personal communication with the primary investigator indicates that even when the subgroup of patients under
the age of 18 years was examined, no differences were found. These investigators concluded that their results do not support the use of risperidone in the weight restoration phase of treatment of young patients with AN.\textsuperscript{21}

The only other study found of the use of risperidone in the treatment of AN was a case report of a 12-year-old girl with autism and AN who was described as benefiting from treatment with risperidone at a dose of 0.5 mg twice daily.\textsuperscript{22}

**Quetiapine**

Very few studies exist on the treatment of AN with quetiapine. One case series described quetiapine use in 3 subjects, aged 11 to 15 years with severe AN (lengthy hospitalization, use of nasogastric tubes, and BMI 12.3–13.9).\textsuperscript{23} Two of these patients were treated with quetiapine 100 mg twice daily, and 1 patient was treated with 250 mg twice daily. Investigators reported improvements in body image disturbance, weight phobia, and “paranoid ideas.” Sedation and constipation were noted as side effects. In a larger study also involving adults, Powers and colleagues\textsuperscript{24} reported an open-label study of quetiapine. Six of the patients were adolescents aged 14 to 18 years in this study. The dose of quetiapine ranged from 150 mg daily to 300 mg daily. Improvements in anxiety and depression were noted, although the investigators report weight gain was modest at only 0.73 kg.\textsuperscript{24}

**Aripiprazole**

Frank\textsuperscript{25} completed a case series and a retrospective chart review\textsuperscript{26} on the use of aripiprazole in adolescents with AN. The case series reported 4 adolescents who benefited in terms of weight and improved ED cognitions.\textsuperscript{25} The chart review described 22 adolescents with AN taking aripiprazole at a mean dose of 3.59 mg daily compared with an untreated comparison group of 84 adolescents with AN. These investigators found a greater increase in BMI in the treated group.\textsuperscript{26} One other case series reported the use of aripiprazole and included 1 adolescent with AN.\textsuperscript{27} The adolescent received a dose of 5 mg daily. The investigators report an improvement in anxiety and rigidity around eating with aripiprazole.

**Selective Serotonin Reuptake Inhibitors**

There is 1 retrospective study comparing 19 adolescent patients with AN taking SSRIs with 13 patients with AN not treated with SSRIs.\textsuperscript{28} These investigators found no differences between groups in terms of BMI, ED psychopathology, or depressive and obsessive-compulsive symptoms after evaluating patients on admission, discharge, and 1-year follow-up. The SSRIs involved in this study included fluoxetine (n = 7, mean dose 35 mg daily), fluvoxamine (n = 8, mean dose 120 mg daily), and sertraline (n = 4, mean dose 100 mg daily). One other case-control study examined fluoxetine as an adjunct to intensive multidisciplinary inpatient treatment.\textsuperscript{29} No beneficial effect was found on global clinical severity of eating behavior or weight phobia. A case-control study by Wockel and colleagues\textsuperscript{30} predominantly focused on the use of tricyclic antidepressants in 25 adolescents with AN; however, fluvoxamine was also used in 2 of the subjects. Those patients who had comorbid depression seemed to have a more robust platelet serotonin-receptor calcium release in response to antidepressants.\textsuperscript{30} Three adolescent case reports have been published on the use of SSRIs in AN. One on the use of sertraline in an adolescent with AN with symptoms of purging;\textsuperscript{31} another on the use of fluoxetine in an adolescent with AN and depressive features;\textsuperscript{32} and another on the use of fluoxetine for comorbid obsessive compulsive disorder.\textsuperscript{33} All of these cases described a benefit in terms of anxiety, mood, and weight restoration.
**Other Antidepressants**

**Mirtazapine**
To date, 1 case control study as well as 2 case reports involving the use of mirtazapine in AN have been published. Hrdlicka and colleagues\(^3\) examined 9 adolescent patients with AN who had been treated with mirtazapine for anxiety or depression compared with 9 female controls with AN. The 2 groups were matched in terms of age and BMI. The mean dose of mirtazapine was 21.7 mg daily. There were no significant differences in terms of weight or BMI at the end of this study.\(^3\) The first case report described a 16-year-old girl hospitalized for AN and depression treated with mirtazapine.\(^3\) These investigators found positive results in terms of weight restoration and mood improvement and suggested further study of the medication was needed. More recently, Naguy and Al-Mutairi\(^3\) described the case of a 16-year-old boy hospitalized for severe AN who responded well to mirtazapine 30 mg/d in terms of weight restoration.

**Combinations of Medications**
Other case reports have focused on a combination of treatments with antipsychotics and antidepressants, which makes interpretation of the results difficult. For example, Newman-Toker\(^3\) describes 2 cases of adolescents with AN in which risperidone (1.5 mg daily) was added to antidepressant treatment, with improvements in anxiety and weight gain. Similarly, Ercan and colleagues\(^3\) described a case of a 15-year-old girl with severe AN treated with olanzapine, fluoxetine, alprazolam, and thioridazine, demonstrating that polypharmacy is sometimes needed for severe symptoms of AN, including agitation and fear of weight gain. These investigators also reported that once stabilized in terms of agitation, a maintenance dose of 10 mg of olanzapine daily resulted in an increase in BMI, along with a reduction of obsessive-compulsive symptoms, exercising, and anorexic cognitions in this patient.\(^3\)

**BULIMIA NERVOSA**

**Selective Serotonin Reuptake Inhibitors**
SSRIs have shown the most promise for children and youth with bulimia nervosa (BN), although the evidence is scant. One open trial of fluoxetine in 10 adolescents aged 12 to 18 years\(^3\) reported 8 weeks of a titrating dose of fluoxetine (maximum 60 mg daily) along with supportive psychotherapy. Frequencies of binge episodes decreased significantly from a mean of 4.1 to 0 episodes per week, and weekly purges decreased from 6.4 to 0.4 episodes.\(^3\) Seventy percent of patients were rated as improved or much improved on the clinical global impressions-improvement scale. No significant side effects were noted. Whether patients maintained these benefits over the long term is unknown.

**Other Psychotropic Medications**
One case report describes the use of valproate 200 mg twice daily following onset of mania thought to be related to the use of fluoxetine in an adolescent girl with BN. In this report, mood stabilized and binge-eating and purging symptoms resolved once the fluoxetine had been stopped and valproate was initiated.\(^4\)

Finally, 1 paper described the use of stimulants to treat BN with comorbid attention-deficit/hyperactivity disorder (ADHD).\(^4\) The 2 cases of adolescents treated with dextroamphetamine 5 to 10 mg 3 times daily had a rapid response to the medication, including improved concentration and no further binge or purge episodes.
BINGE-EATING DISORDER

No studies could be located that specifically address psychopharmacologic treatment of binge-eating disorder in children and adolescents. Lisdexamfetamine has been approved by the Food and Drug Administration for binge-eating disorder in adults, but has not been studied in child and adolescent populations.

AVOIDANT/RESTRICTIVE FOOD INTAKE DISORDER

Avoidant/restrictive food intake disorder (ARFID) is a heterogeneous diagnostic category often associated with multiple underlying causes for food restriction. In a recent case series, Spettigue and colleagues\(^\text{42}\) described 6 patients with ARFID and comorbid anxiety (median age 12.9 years) who were treated with a combination of family therapy plus pharmacotherapy. All patients were treated with olanzapine in combination with other medications, making interpretation of the results difficult: 3 cases were treated with a combination of olanzapine and fluoxetine; 1 case was treated with olanzapine followed by fluvoxamine, and 2 cases were treated with a combination of olanzapine, cyproheptadine, and fluoxetine. All 6 cases reached their treatment goal weights. Of note, this is the only report in the literature of cyproheptadine for the treatment of ARFID.

Another recent case series reported beneficial effects from olanzapine in the treatment of patients with ARFID.\(^\text{43}\) These investigators completed a retrospective chart review and described a significant increase in weight as well as improvements in anxiety and depressive symptoms in 9 patients with ARFID treated with olanzapine. The mean final dose of olanzapine was 2.8 mg daily. All 9 patients had comorbid mental health diagnoses, including separation anxiety, obsessive-compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder, and social anxiety disorder. Six of the 9 also had significant major depressive symptoms.

In terms of the “posttraumatic” subtype of ARFID whereby there has been a choking event followed by refusal to eat and drink, several medications have been described in case reports as being helpful, including lorazepam,\(^\text{44}\) mirtazapine,\(^\text{45}\) escitalopram,\(^\text{46}\) and fluoxetine.\(^\text{47}\) Of note, Celik and colleagues\(^\text{47}\) reported a case of two 2-year old twins who were treated with fluoxetine 5 mg daily for severe post-traumatic food avoidance, with good effect. Similarly, a case series of 3 children with “severe choking phobias” were successfully treated with low-dose SSRIs (sertraline and paroxetine),\(^\text{48}\) and a case report described the beneficial use of fluoxetine (20 mg daily) in combination with aripiprazole (2.5 mg daily) for a 15-year-old girl with severe choking phobia.\(^\text{49}\)

Pennell and colleagues\(^\text{50}\) described 2 cases whereby significant weight loss occurred with stimulant treatment of ADHD, resulting in the need for hospitalization. These cases were managed by temporarily stopping the stimulant and adding risperidone to help with appetite and behavior.

An additional case report describes a 15-year-old girl with anxiety, somatic symptoms of nausea, and abdominal pain who benefited from treatment with buspirone 7.5 mg twice daily after becoming agitated with a course of sertraline.\(^\text{51}\)

OTHER SPECIFIED FEEDING AND EATING DISORDERS

The authors’ review identified 1 case report of a patient with atypical AN whose depressive symptoms were treated with escitalopram with improvement noted.\(^\text{52}\) She had lost almost 40 kg over a period of 4 months, but remained within a normal weight range.
LACK OF EVIDENCE

No studies could be found on the use of selective norepinephrine reuptake inhibitors for this population. The same was true for mood stabilizers. The only reports found for benzodiazepines are mentioned above for ARFID and in the combination of treatments with other medications for AN.

SUMMARY

Most of the published studies to date on pharmacotherapy of EDs in children and adolescents have focused on the role of antipsychotic medication in AN. Despite progress in recent years, the total number of subjects studied remains small, and there is a paucity of randomized controlled trials. Furthermore, it has become increasingly clear that there are substantive challenges involved with the completion of such studies. As a result, there is still insufficient evidence to recommend medication as a first-line consideration in children and adolescents with EDs. Because of the significant challenges in recruitment and retention in clinical trials to date, large multisite collaborative trials are necessary to move the field forward in determining which young patients with EDs might benefit most from psychotropic medication and in what fashion.

REFERENCES


29. Strober M, Pataki C, Freeman R, et al. No effect of adjunctive fluoxetine on eating behavior or weight phobia during the inpatient treatment of anorexia nervosa: an


