

Atypical Antipsychotics in the Treatment of Anorexia Nervosa

Daphne T. Crawford, PharmD, Staff Pharmacist, CVS/Pharmacy, Birmingham, AL

Maisha Kelly Freeman, PharmD, BCPS, Assistant Professor, Drug Information Specialist, McWhorter School of Pharmacy, Samford University, Birmingham, AL

Marshall E. Cates, PharmD, BCPP, FASHP, Professor of Pharmacy Practice, McWhorter School of Pharmacy, Samford University, Birmingham, AL

Abstract

Objective: To review the published literature pertaining to the use of atypical antipsychotics in the treatment of anorexia nervosa (AN).

Methods: PubMed (1966- April 2008), International Pharmaceutical Abstracts (1970– April 2008), and PsychInfo (1966- April 2008) were searched using the terms atypical antipsychotics, olanzapine, risperidone, quetiapine, paliperidone, ziprasidone, aripiprazole and anorexia nervosa.

Results: Effective treatment of AN with atypical antipsychotics has been documented in case reports, a retrospective study, and open trials. Olanzapine, risperidone, quetiapine and aripiprazole improve the psychiatric symptoms (e.g., delusions, depression, anxiety) associated with AN and appear to be well tolerated with a main side effect of mild sedation.

Conclusions: Published literature indicates that atypical antipsychotics may be effective in ameliorating psychiatric symptoms, reducing psychiatric comorbidities, and promoting weight gain in AN, but further investigation to determine the appropriate dosage and duration of these drugs is warranted before implementing atypical antipsychotics into standard practice.

Key Words: atypical antipsychotics, olanzapine, risperidone, quetiapine, paliperidone, ziprasidone, aripiprazole, anorexia nervosa

Introduction

Anorexia nervosa (AN) is a psychiatric condition characterized by refusal to maintain body weight at or above a minimally normal weight for age and height (ie, maintenance of body weight < 85% of that expected); intense fear of gaining weight and becoming overweight even though underweight; altered perception of body weight or shape or denial of the seriousness of low body weight; and amenorrhea, defined as the absence of 3 consecutive menstrual cycles in women who should be experiencing menstrual cycles.¹ Although 90% of reported cases occur in women, this disorder does occur in men.^{2,3} Current estimates indicate that the male to female ratio prevalence of eating disorders ranges from 1:6 to 1:10 and 19-30% of younger patients diagnosed with AN are male. Lifetime prevalence of AN in women ranges from 0.5% to 3.7%.¹ The peak age of onset is between 15 and 19 years and there are increasing cases in younger children. Cases in mid- and late-life have also been reported.^{3,4}

There are 2 subtypes of AN. The restricting type occurs when the patient does not routinely engage in binge-eating or purging behavior. Patients with this subtype of anorexia strictly limit caloric intake to 300-700 kcal per day and often participate in compulsive exercise regimens.^{1,3,5} Patients diagnosed with the binge-eating or purging AN may also participate in self-induced vomiting or misuse of laxatives, diuretics, or enemas.^{1,3} Patients diagnosed with AN often present with comorbid psychiatric illnesses including major depression, bipolar disorder, obsessive-compulsive disorder, social phobias, or substance abuse.^{1,3,5}

Published in:

*The International Journal of
Pharmacy Education and Practice*
Vol 4, Issue 2, Fall 2008

Successful management of anorexia nervosa includes encouraging patients to seek help, weight restoration, addressing negative perceptions of body image, and compulsory treatment, if needed.² Current treatment guidelines recommend: nutritional support, psychological therapy, which include behavioral, family, and cognitive modalities to improve patient self perception, and pharmacotherapy. Pharmacotherapy is typically reserved for weight maintenance, to encourage normal eating behaviors, and to treat psychiatric symptoms associated with the disorder.¹ There are no FDA-approved medications to treat AN; however, the mainstay of pharmacological therapy has been antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs).¹

Results of studies with SSRIs for weight restoration in patients with AN have revealed no benefit;⁶⁻¹⁰ however, SSRIs have been shown to ameliorate relapse rates in patients whose weight was restored prior to SSRI therapy.^{11,12} In addition, due to black box warnings of increased suicide risk for use of SSRIs in depression, determining other treatment alternatives for AN is important.¹³

Atypical antipsychotics, particularly olanzapine, risperidone, and quetiapine, have been evaluated for the treatment of anorexia nervosa and have been shown to induce weight gain and improve symptoms of depression and obsessive thoughts.¹⁴⁻²⁷ The mechanism of action of atypical antipsychotics in weight gain is unknown; however, it has been theorized that the effects of olanzapine on weight gain and appetite may be attributed to 5-HT₂ receptor antagonism. Previous data reports that treatments increasing serotonin reduce food consumption, while decreasing serotonin is associated with weight gain and higher food consumption.²⁸ Studies in animal models have revealed that olanzapine-induced weight gain is due to increased food intake, decreased motor activity, and increased ratio of weight gain to weight of food consumed.²⁹ This article provides insight regarding the efficacy of atypical antipsychotics in the treatment of anorexia nervosa.

Literature Review

Olanzapine Case Reports

A summary of the published literature of olanzapine in the treatment of AN is located in Table 1. Many case reports have documented the use of olanzapine in AN.¹⁴⁻²³ A total of 32 patients, from the ages of 10 to 50 years, with both types of AN were included in case reports. Patients (n=32) included had a variety of psychiatric comorbid conditions including depression,¹⁵⁻²³ obsessive compulsive disorder¹⁶⁻¹⁷ personality disorder,¹⁷ and anxiety.¹⁸ Most patients were initiated on other pharmacotherapeutic regimens prior to and/or during the administration of olanzapine.^{15-17,19,20,22} Patients were initiated on olanzapine doses between 2.5 and 10 mg over the course of 5 weeks¹⁸ to 36 weeks.²¹ All patients experienced weight gain and improvement in psychiatric symptoms while receiving olanzapine therapy. The smallest weight gain was 4.6 kg¹⁹ over 7 weeks and the largest weight gain was 20.1 kg over 28 weeks.²¹ Two patients regressed and consequently lost previous weight gained during treatment with olanzapine.^{19,20} The time frame for regression was not described for one patient¹⁹ and the other patient regressed after 6 months of therapy. One case of hyperglycemia was described in one patient receiving olanzapine for AN.¹⁴

Olanzapine Retrospective Study

Questionnaires were distributed to 18 patients previously treated on an inpatient basis with olanzapine in a retrospective study to determine response to olanzapine therapy.²³ A 10-question, 5-point assessment tool was developed to ascertain patients recollection of the effects of olanzapine on eating disorder behaviors before and after the administration of olanzapine. On average, patients weighed 38 ± 6 kg before treatment and 43 ± 6 kg when surveyed. The average dosage of olanzapine was 4.7 ± 2.4 mg per day (range from 2.5 to 10 mg). Duration of therapy was an average of 17±20 weeks (range from 3-70 weeks). Results indicated a significant reduction in frequency of obsessive thoughts about body image or obesity, reduced anxiety before and during meals, and an increased desire to eat. Subjects were less

Published in:

*The International Journal of
Pharmacy Education and Practice*
Vol 4, Issue 2, Fall 2008

upset for weight gain ($p=.002$), and less reactive in response to stress ($p=.01$), social situations ($p=.001$), and sleeping ($p=.000$). Reported adverse effects included mild sedation. The authors concluded that olanzapine may be an appropriate treatment option for patients with AN.

Olanzapine Open Trials

Several open-label trials involving olanzapine for the treatment of AN have been published.^{24-27,28} These studies were conducted in a small sample of patients and endpoints of weight gain along with several psychological evaluations were evaluated.

The change in BMI (body mass index) was assessed after the administration of 3 months of olanzapine and treatment program of nutritional and weight rehabilitation plus personal cognitive-behavioral therapy (CBT) in 20 patients with AN.²⁴ Patients (mean age 23 ± 4.8 years) participated in the study. Patients discontinued psychotherapeutic or pharmacological treatment at least 3 months prior to the start of the study. The control group consisted of 10 female staff members with a normal BMI. All 20 patients received 3 months of CBT and nutritional rehabilitation. Patients received olanzapine 2.5 mg for 1 month and 5 mg for 2 months. Baseline BMI values were significantly lower than the control group. Although BMI increased in both treatment groups, normal values were not achieved. No statistically significant differences were observed between groups in BMI over all time points. The investigators concluded that olanzapine does not cause a pharmacologic effect on weight.

Investigators of an open-label randomized trial reported the results of treatment with olanzapine and chlorpromazine for 15 patients diagnosed with AN.²⁵ The primary outcome of the trial was impaired control over mental activities subscale of the Padua Inventory (PI). The PI measures intrusive cognitions in a variety of psychiatric disorders, but only the subscale pertinent to AN was used. The tests were administered over the 1-year period of recruiting after randomization and just before discharge from the hospital. Patients in the olanzapine group ($n=8$) received daily doses ranging from 5 to 15 mg with a mean dose of 10 mg. Patients in the chlorpromazine group ($n=7$) received an average dose of 50 mg (range 25-100 mg). The duration of the trial was the length of patient's hospital stay. Patients receiving olanzapine and chlorpromazine had an average length of stay of 46 ± 31 days and 53 ± 26 days, respectively. Patients in the olanzapine group experienced a greater percentage reduction in PI subscale scores. No statistically significant differences in weight gain resulted (5.5 kg average gain in both treatment groups). The Eating Disorders Inventory (EDI-2), containing 3 subscales relating to weight (drive for thinness), eating (bulimia), and shape (body dissatisfaction) was also administered to measure symptoms related to AN and no statistically significant differences were observed between olanzapine and chlorpromazine. Olanzapine was well tolerated by patients in the study, but the incidence of adverse effects was not reported. Investigators concluded that olanzapine may promote cognitive changes in AN patients rather than weight gain during refeeding stages.

A 6-week, non-comparative, open-label trial by Barbarich et al²⁶ included 17 patients hospitalized for AN. Twelve patients had a history of restricting type AN and 5 had binge-purging type AN. All patients discontinued other antidepressants or psychoactive medications before taking olanzapine. Patients were initiated on olanzapine 2.5 – 7.5 mg and the dose was titrated to effect. Cognitive behavioral therapy and dialectical behavioral therapy were also received. Weight was obtained twice a week and psychological evaluations including the Spielberger State-Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI), Yale-Brown Obsessive Compulsive Scale (YBOCS), and the Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS) were performed at baseline and every 2 weeks. A total of 12 of the 17 patients completed the trial, 2 subjects completed only 5 weeks, 2 subjects completed only 4 weeks and 1 subject completed only 3 weeks. The mean age of patients was 20.5 ± 5.1 years. The mean daily dose was 4.7 ± 1.6 mg. Three of the patients were treated with SSRIs after the start of the study, but the specific medications and doses were not provided. A statistically significant increase in weight from baseline to endpoint based on the percentage of patients achieving ideal body weight was observed ($69 \pm 10\%$ vs. $81 \pm 9\%$, $p=.000$). Absolute changes in weight were not reported. Statistically significant decreases on

Published in:

*The International Journal of
Pharmacy Education and Practice*
Vol 4, Issue 2, Fall 2008

the BDI scale, STAI, and YBC-EDS were observed; however, no statistically significant differences were observed with the YBOCS score. Adverse effects experienced included headache (n=5), abdominal pain or bloating (n=5), diarrhea (n=2), ankle edema (n=2), dizziness (n=2), and nausea (n=1). The investigators concluded that olanzapine may be useful in the treatment of AN.

Powers et al²⁷ conducted a 10-week, non-comparative, open-label trial involving 18 patients with AN of both restricting or binge/purging subtypes. The primary endpoint of the study was weight gain at 10 weeks. Patients were excluded if they met the criteria for schizophrenia, schizoaffective disorder, or bipolar disorder. A 7-day wash-out period was included for psychotropic medications. Fluoxetine was discontinued 28 days prior to initiation of olanzapine and lorazepam was allowed for the duration of the study for insomnia. Patients were not allowed to participate in cognitive-behavioral therapy or begin any new therapy during the study. Patients ranged in age from 14 to 56 years with a mean of 26.8 years. Body mass index was an average of 16.4 ± 1.3 (range from 13.7 to 17.8). Of the patients included, 12 had binge/purging AN and 6 had restricting AN. Patients received olanzapine 10 mg per day and were required to attend psychoeducation classes including weekly drug monitoring sessions and weekly group medication adherence sessions. Four patients dropped out of the study at weeks 3, 4, 7, and 7, respectively; however, the last observed weight was carried forward and assessed at endpoint. The mean weight gain at endpoint was 5 ± 7.9 lbs ($p=.0138$) for all patients (n=18) and the mean weight change was 5.75 ± 8.75 lbs ($p=.0315$) for the 14 patients who completed the study. HAM-D scores were significantly lower compared to baseline for the completers (n=14) at week 10. EDI-2 mean scores were significantly lower for all patients between day 1 and week 10 and this statistically significant finding was continued for only patients who gained weight. No statistically significant differences were observed for patients in the PANSS at endpoint; however, patients who gained weight experienced a statistically significant difference PANSS at week 10. CGI scores at baseline were reported at 5.22 (markedly ill) on day 1 and 5 (markedly ill) at endpoint. The most common adverse events reported were sedation (n=13), headache (n=5) and upper respiratory infection (n=5). The investigators concluded that results showed a clinically significant gain in weight in 10 weeks of treatment with olanzapine.

Olanzapine Controlled Clinical Trial

The efficacy of olanzapine therapy in the management of anorexia nervosa was evaluated after 3 months of therapy in a randomized, double-blind, placebo-controlled trial in 30 female outpatients with the restricted (n=18) and binge/purging (n=12) types of AN.²⁸ Patients included in the trial were randomized to placebo (n=15) or olanzapine (n=15) in addition to cognitive behavioral therapy. Patients received olanzapine in escalating doses. Olanzapine was initiated at a daily dose of 2.5 mg for 1 month and 5 mg for the following 2 months. Several parameters were evaluated including homovanillic acid plasma concentration (i.e., the main metabolite of dopamine), EDI-2, Yale Brown Cornell for Eating Disorder Rating Scale and BMI. The mean age of patients was 23.7 ± 4.8 for olanzapine-treated patients and 4.4 ± 3.0 years, respectively. The mean duration of the disease was 6.3 ± 5.0 years and 4.4 ± 3.0 years, respectively. A statistically significant increase in BMI was reported in the olanzapine (15.5 ± 1.9 vs, 17.2 ± 2.0 ; $p=0.0003$) vs, placebo groups (15.8 ± 1.1 vs. 16.9 ± 1.2 ; $p=0.001$), respectively. However, no differences were observed between the olanzapine and placebo-treated patients. A statistically significant decrease in EDI-2 total was observed in the olanzapine (112.1 ± 49.0 vs. 89.6 ± 50.2 ; $p=0.04$) vs. placebo-treated patients (96.7 ± 38.9 vs, 69.2 ± 33.2 ; $p=0.01$); however, no statistically significant differences were found between the 2 groups. No statistically significant differences were observed between group for the Yale Brown Cornell for Eating Disorders Rating Scale (12.6 ± 5.9 vs. 17.0 ± 9.7). HVA plasma concentrations were decreased in patients receiving olanzapine, but not placebo (1.1 ± 1.5 vs, 0.32 ± 0.11). The investigators' concluded that pharmacologic treatment can significantly improve specific aspects of anorexia nervosa.

Risperidone

Risperidone use in 2 patients was documented in a case report.²⁹ A 19-year-old female patient at 70% of her ideal body weight (IBW) and a 5-year-history of restricting AN was hospitalized for bradycardia after failed therapy for weight control and depression with fluvoxamine, paroxetine, fluoxetine, and sertraline. After a 3-month hospitalization, she gained 20 lbs; however, she was unable to maintain her weight after discharge. Risperidone 1.5 mg daily was added to venlafaxine 150 mg twice daily for her delusional thinking about weight. After one week of therapy, the patient's anxiety and obsession about food diminished. The following month she gained 16 lbs (91% of IBW). Risperidone was tapered and discontinued after 10 months. In the second case, a 12-year-old girl with a 2-year history of restricting AN required hospitalization for bradycardia secondary to a body weight of 79% of IBW. Risperidone 0.5 mg daily was added to sertraline 100 mg. Within one week, the patient was more energetic. Risperidone was increased to 0.5 mg 3 times daily and gained 8 lbs in the first month and 4 lbs in the second month to an IBW of 91%. When the risperidone dosage was decreased to 0.5 mg twice daily, her obsessive thoughts returned and improvement was observed with a dosage increase to 1.5 mg daily. Both patients experienced mild sedation initially. The QTc interval was increased from 400 to 421 milliseconds in one patient; therefore, electrocardiographic monitoring may be indicated in these patients.

Quetiapine Case Reports

Treatment with quetiapine was reported in 3 patients by Mehler-Wex et al.³⁰ Patients in the case reports ranged in age from 11-15 years. The first patient had previously received olanzapine 7.5 mg daily, but use was discontinued secondary to leukopenia and increased liver enzymes. After other trials of haloperidol, lorazepam, and nasogastric tube administration, the patient was initiated on quetiapine and the dose was titrated to 100 mg twice daily over 2 weeks. She experienced improvement in restrictive thoughts 3 weeks after medication administration. During week 6, the patient refused the drug and later agreed to receive quetiapine 200 mg daily. Psychotic symptoms improved and she remained stable until follow up (week 20). No adverse effects were reported. In the second case, a 15-year-old patient with a 2-year history of restrictive anorexia nervosa presented with severe body image disturbances and weight phobia. The patient was receiving mirtazapine 30 mg at night for comorbid depressive symptoms, but mirtazapine was discontinued and she began treatment with quetiapine 200 mg daily. The patient's body weight increased by 500 g/week until week 5, but there was no change in her anorexic thoughts. At week 8, her depression began to improve. Due to very low quetiapine plasma concentrations (< 10 ng/mL), the quetiapine dose was increased to 300 mg and later to 500 mg daily. The patient's body image began to improve. Constipation was a possible side effect associated with quetiapine therapy. In the final case, a 14-year-old patient was admitted for anorexia. She was receiving 37.5 mg of melperone daily for anxiety and fluoxetine 20 mg daily for depression. After 3 weeks of therapy, the patient's fear regarding food intake and weight gain was reduced. Shortly after, the patient relapsed. Melperone was discontinued and quetiapine was titrated up to 150 mg. After 2 weeks, the patient was able to achieve a BMI of 17.5; however, she was still experiencing body image disturbances. Quetiapine was increased to 200 mg daily and her body image thoughts decreased. After 3 months of follow up, she maintained her body weight and psychopathological stability.

Quetiapine Open Trial

The effectiveness of quetiapine 150-300 mg daily in 19 patients with AN was assessed in an open-label outpatient pilot study.³¹ Patients were included in the study if they had previously been diagnosed with AN, were between the ages of 14 and 65 years, and had weight at least 15%, but no more than 25% below ideal body weight. The primary endpoint of the study was the mean change in the positive and negative syndrome scale (PANSS) over 10 weeks. All psychotropic drugs were discontinued for 5 half-lives and patients receiving fluoxetine discontinued the medication 28 days before study entry. Quetiapine was titrated using the following schedule: day 1, quetiapine 50 mg; day 2, 50 mg twice daily; day 3, 100 mg twice daily; and day 4 (onward), 150 mg twice daily. The mean age of the patients was

Published in:

*The International Journal of
Pharmacy Education and Practice*
Vol 4, Issue 2, Fall 2008

26.8 years (SD=11.2), 18 patients were female, 12 patients had the restricting type of AN and 8 patients had the binge purge subtype. The mean weight at baseline was 99 lbs and the body mass index was 16.6. Five patients dropped out of the study. A statistically significant decrease in total mean PANSS scores from 56.2 at baseline to 48.4 at week 10 was observed ($p=0.024$). The mean weight gain from baseline to week 10 was 1.6 lbs, but this difference was not statistically significant. The most common adverse drug events that occurred were dizziness, joint/muscle pain, lightheadedness, sleepiness, constipation, paresthesias, headaches, lethargy, dry mouth, and upper respiratory infections. The investigators concluded that quetiapine was well tolerated and improvements in the PANSS score, anxiety, and depression were observed.

Aripiprazole

The beneficial effects of aripiprazole in the treatment of anorexia nervosa was described in a case report highlighting a 34-year-old Caucasian female with a 12-year history of anorexia.³² The patient was also experiencing comorbid psychiatric symptoms such as depression and paranoia. The patient was also diagnosed with generalized epilepsy, chronic renal failure secondary to pyelonephritis, and Raynaud's syndrome. The patient had received a combination of psychopharmacology and psychotherapeutic interventions. The patient was initiated on risperidone 1 mg daily, but the dosage could not be increased secondary to reports of severe asthenia and sedation. The patient refused olanzapine therapy because of the incidence of weight gain. The patient consented to receive gradual aripiprazole therapy, which was initiated at a dose of 5 mg daily and increased to 30 mg daily after 2 months. The risperidone was discontinued after 5 weeks of aripiprazole therapy. Although there was little weight gain over the 6-month treatment period with aripiprazole (51 kg vs. 52.7 kg), improvements were seen in the scales for the assessment of negative (SANS) and positive (SAPS) symptoms. The investigators' concluded that aripiprazole therapy may be useful and well tolerated in psychotic symptoms associated with anorexia.

Discussion

Published literature suggests that there is a modest increase in weight after the administration of olanzapine, risperidone, quetiapine and aripiprazole and these atypical antipsychotics alter delusional thinking,^{19,21-23,28,31,32} depression,^{16,26,31} and anxiety^{14,18,31} in patients with AN. Literature is limited to case reports, one retrospective study, and 5 open-labeled trials and one double-blind, placebo-controlled trial, which makes it difficult to assess how clinically significant the treatment improves the condition.

All of the case reports indicate an increase in weight during therapy with olanzapine, aripiprazole, quetiapine, and risperidone; however, several limitations must be considered including the retrospective design that may be subject to recall bias, absence of a control group, small sample size, and lack of information regarding symptom severity. In addition, differences in psychiatric comorbidities, potential confounding due to additional pharmacotherapeutic (e.g., SSRIs) and behavioral therapies, varying durations and dosage of the atypical antipsychotics, and lack of consistent follow up were also major issues in the studies included in this review.

The results of the open-label studies should be interpreted with caution as well. No control group was used as a comparison; therefore, the true effect of the products is unknown.^{24-27,31} All of the open-labeled studies included a small number of patients; less than 100 patients were included for all the studies combined. In addition, some patients received therapy on an in-patient basis with other therapeutic modalities (e.g., behavioral, medication). Therefore, compliance was less of an issue in this patient population. Although the use of behavioral therapy was not consistent between the studies, a multitude of therapeutic options are appropriate due to the complexity of the disorder. Current therapeutic guidelines indicate that behavioral modification is appropriate for this disorder.¹

Published in:

*The International Journal of
Pharmacy Education and Practice*
Vol 4, Issue 2, Fall 2008

One controlled clinical trial evaluating the use of olanzapine for the treatment of anorexia nervosa was located.²⁸ All patients in the trial were female and the investigators included patients with both the restricted and binge/purging type of AN. All patients received cognitive behavioral therapy in addition to olanzapine or placebo for the total duration of the trial (3 months). The duration of the trial was short and no statistically significant differences were observed between olanzapine and placebo with the rating scales (Yale Brown Cornell for Eating Disorder Rating Scale, EDI-2).

Several other issues remain unanswered. Since the majority of the literature is from case reports, the baseline severity of patients with AN was not reported. The literature does not provide guidance regarding the use of atypical antipsychotics in patients with severe AN. Several different scales were used in the assessment of underlying symptoms associated with AN including obsessive-compulsive disorder, depression, anxiety and eating disorders. For the most part, patients who received quetiapine, risperidone, and olanzapine experienced improvements in these scales of measurements. Clinically significant improvements in the Padua Inventory and EDI-2 eating disorders scales were reported in the trial by Mondraty et al.²⁵ No clinically significant differences were observed in the study by Barbarich in the Yale Brown Cornell Eating disorders scale (22 ± 7 before treatment versus 15 ± 9 after treatment although the authors reported a statistical difference.²⁶ Other investigators failed to report changes in eating disorders scales.^{24,27,31} In addition, it is unclear of the degree in which the scales for the underlying disease processes (e.g., obsessive-compulsive disorder, depression, anxiety) is associated with the improvement in self-perception to enhance weight restoration. Furthermore, it is unknown if the type of AN (i.e., bingeing vs. restrictive) has an effect on the response rate to atypical antipsychotics.

The assessment of weight was made based on the absolute changes in weight or BMI from baseline to the end of treatment. Measures of appropriate nutritional status in patients with AN is variable. Current guidelines indicate that BMI is increasingly being used to assess weight gain in patients with AN.¹ Absolute changes in weight is less reliable because weight must be normalized according to height. One of the goals of therapy is normalization of IBW which correlates with fewer relapses.¹

Dosages of olanzapine utilized in the present review typically ranged from 2.5-10 mg per day, whereas the FDA approved range for treatment of schizophrenia and bipolar disorder is up to 20 mg per day.³³ Risperidone was used in doses up to 1.5 mg daily and quetiapine was administered at doses up to 500 mg daily for AN. Aripiprazole was used in dosages up to 30 mg daily. Doses for risperidone and quetiapine evaluated for the treatment of schizophrenia and bipolar disorder are up to 16 mg daily and 800 mg daily, respectively.^{34,35} Patients with AN could have gained more weight at the higher end of these dosage ranges, but the investigators may have been concerned about overall tolerability of therapy. Regardless, this is a question that remains unanswered given the present data. Additionally, the duration of therapy is not consistent in the literature. The longest duration of olanzapine, risperidone, and quetiapine that patients received in clinical studies were 36 months,²¹ 13 months,²⁹ and 10 months,³¹ respectively. Therefore the duration of therapy associated with the largest increases in weight is unknown.

Weight gain occurs in > 50% of patients receiving atypical antipsychotics.²⁹ Weight gain in patients receiving atypical antipsychotics for schizophrenia is variable (< 2.2 lbs to > 8.8 lbs). Patients with lower BMIs at baseline are associated with greater increases in weight.³⁶ Adolescents have a 3.2 fold higher incidence of weight gain than adult patients receiving olanzapine.³⁶ The onset of weight gain is difficult to pinpoint with olanzapine therapy, but based primarily on the largest case series¹⁷ and 2 of the open trials,^{25,26} it appears that weight gain occurs within the first 6 weeks; however, most of the published literature documents only short-term effects of olanzapine therapy for AN. Only 3 case reports were at least 6 months duration^{15,16,22} and none of the open trials exceeded 10 weeks. One retrospective study,²³ with a mean duration of 17 weeks, suggests sustained benefits of olanzapine therapy. Durations of therapy for the 2 patients who received risperidone for the treatment of AN was 13 and 9 months, respectively. Quetiapine therapy for patients with AN was continued for 10 weeks. No interim analyses were conducted to determine weight gain at varying intervals. Data from pooled studies indicate that

Published in:

*The International Journal of
Pharmacy Education and Practice*
Vol 4, Issue 2, Fall 2008

risperidone and quetiapine were associated with weight gains of 4.4 lbs to 6.6 lbs over the course of 1 year when used for the treatment of schizophrenia.³⁸ Olanzapine was associated with >13.2 lbs over 1 year. Patients who received between 17.5 mg and 22.5 mg experienced greater than a 22 lb weight gain.³⁸ Data from patients with schizophrenia reveal that olanzapine induces the most rapid weight gain within the first 12 weeks of therapy and that weight gain plateaus after 39 weeks of therapy.^{38,39} The time course for a potential plateau of weight gain with risperidone and quetiapine for schizophrenia is controversial and more investigation is needed.³⁶

Appropriate monitoring of patients receiving atypical antipsychotics for the treatment of AN is required. Cardiac abnormalities is one of the physical complications associated with AN.¹ Prolongation of the QTc interval may occur due to the underlying disease state and has been cited as a warning for ziprasidone.⁴⁰ In a case report by Newman-Toker,²⁹ a patient receiving risperidone for AN experienced prolongation of the QTc interval from 400 to 421 milliseconds; therefore, ECG monitoring in this patient population may be warranted.

Glucose monitoring is recommended for patients receiving atypical antipsychotics for the treatment of AN. Atypical antipsychotics have been associated with glucose dysregulation. One patient with no personal or family history of diabetes receiving olanzapine for anorexia nervosa experienced hyperglycemia.¹⁴ The patient's glucose tolerance was measured and remained stable over the course of 10 weeks while receiving olanzapine. There have been several reports in the literature of atypical antipsychotics precipitating or unmasking hyperglycemia.⁴¹⁻⁴⁶ One report indicated that hyperglycemia occurred within 6 months of quetiapine administration.⁴³

Olanzapine, risperidone, aripiprazole, and quetiapine treatment of AN appears to be well tolerated. Mild sedation has been the most frequently reported adverse effect in studies in patients with AN. One patient receiving olanzapine for AN experienced hyperglycemia.¹⁴ However, relatively few AN patients have been studied thus far, and adverse effects have not been systematically determined.

Summary

Novel pharmacotherapeutic regimens are necessary for AN patients, since there is no effective regimen available. Published literature evaluating olanzapine, risperidone, and quetiapine for AN suggests that they may be overall effective in treating the psychiatric manifestations of the disease, psychiatric comorbidities and weight gain. The amount of weight gain for patients with AN appears to be dependent upon baseline BMI measures, age and other factors. Patients have gained as much as 20 lbs with olanzapine therapy, the most studied atypical antipsychotic for this disorder. Further investigation into the dosage, duration, efficacy, and safety of atypical antipsychotics through randomized, double-blinded, controlled, clinical trials is warranted before implementing them into standard practice.

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Table 1. Published Literature of Atypical Antipsychotics for Anorexia Nervosa

Reference	Design	Subjects (N) / Duration	Patient Type	Dosage (mg/day)	Concomitant Therapy (mg/day)	Results
Yasuhara et al ¹⁴ (2007)	Case report	1; N/A	27-year-old female	Olanzapine 5 mg daily	N/A	Resolution of symptoms
Wang et al ¹⁵ (2006)	Case report	1; 6 months	27-year-old female (RAN)	Olanzapine 10	Mirtazapine 30 Cognitive behavioral therapy	Weight gain: 14 kg
Ercan et al ¹⁶ (2003)	Case report	1; 24 weeks	15-year-old female (RAN)	Olanzapine 2.5 titrated to 10	Clomipramine 37.5, fluoxetine 20, thioridazine 75, alprazolam 1	Weight gain: 19 kg increase in BPRS score from 45 to 0 CGI score improved from 7 to 1
Bosanac et al ¹⁷ (2003)	Case series	14; 24.9 days	Females 19-49 years (57% RAN; 42% BAN)	Olanzapine 9.7 (mean)	Fluvoxamine, sertraline, paroxetine, venlafaxine, mianserine	Average BMI increase: 1.1 ($p=.027$) HAM-D: 27.2±4.9 before treatment HAM-D: 23.7±6.8 after treatment
Boachie et al ¹⁸ (2003)	Case series	4; 5-16 weeks	3 Females (RAN)/ 1 male (EDNOS) from 10-12 years	Olanzapine 2.5	Fluvoxamine 75	Case 1: gained 5.7 kg Case 2: gained 10.2 kg Case 3: gained 12.4 kg Case 4: gained 7.5 kg
Mehler et al ¹⁹ (2001)	Case series	5; 6-8 weeks	Females 12-16 years	Olanzapine 2.5 – 12.5	Behavioral Therapy Meperone 175 mg X 1 week, haloperidol 2 mg, chloprotixene 150, levomepromazine 200, diazepam Fluoxetine 30 mg, Paroxetine 30 mg Clomipramine 75 mg	Case 1: gained 12 kg Case 2: gained 11 kg Case 3: gained 11 kg (regressed) Case 4: gained 4.6 kg Case 5: gained 12 kg

Reference	Design	Subjects (N) / Duration	Patient Type	Dosage (mg/day)	Concomitant Therapy (mg/day)	Results
La Via et al ²⁰ (2000)	Case series	2; 22 days – 14 weeks	Females 15 and 27 years (BAN)	Olanzapine 2.5-10	Haloperidol	Case 1: gained 16.8 kg Case 2: gained 5.3 kg (regressed at 6 months)
Jensen et al ²¹ (2000)	Case series	3; unknown	Females 30 – 50 years	Olanzapine 5	N/A	Case 1: gained 19 kg Case 2: gained 9 kg in 9 months Case 3: body image improved
Hansen ²² (1999)	Case report	1; 7 months	49-year-old female	Olanzapine 5-10		Gained 20.1 kg
Malina et al ²³ (2003)	Retrospective study	18; 17± 20 weeks	16-37 years (mean 22 ± 7 years; gender not specified)	Olanzapine 2.5 – 10	SSRIs, benzodiazepines	Gained 5 kg; significant reduction in obsessive thoughts ($p<.001$) Reduced anxiety before and during meals ($p<.001$) Less upset if they gained weight ($p=.002$)
Brambilla et al ²⁴ (2007)	Open-label trial	20; 3 months	Mean age 23±4.8 years	Olanzapine 2.5-5	Nutritional rehabilitation; cognitive-behavioral therapy	No significant change in BMI Olanzapine baseline to 3 months 15.7 ± 2.1 vs. 17.1±1.6 Placebo baseline to 3 months 16.3 ± 0.7 vs.17.5 ± 0.8
Mondraty et al ²⁵ (2005)	Open-label trial	15; Olanzapine 46 ±3 1 days Chlorpromazine 53 ± 26 days	Mean 25.3 ± 7.3 years (gender not specified) RAN = 7; BAN =8	Olanzapine 5-15 (mean 10) Chlorpromazine 25-200 (mean 50)	SSRI (n=5)	Olanzapine change in BMI: 2.5 Chlorpromazine change in BMI: 2 PI mental activities subscale change between olanzapine and chlorpromazine: 54 vs. 9 ($p<.01$)

Reference	Design	Subjects (N) / Duration	Patient Type	Dosage (mg/day)	Concomitant Therapy (mg/day)	Results
Barbarich et al ²⁶ (2004)	Open-label trial	17 (12 completers); 6 weeks	Mean 20.5 ± 5.1 years (gender not specified) BAN = 4; RAN = 12; both BAN/RAN=1	Olanzapine 2.5 – 7.5 (mean 4.7 ± 1.6)	SSRIs (n=3) Behavioral / dialectic therapy	Proportion of ideal body weight at endpoint 81 ± 9; $p=.000$ Beck Depression Inventory score change: +12 ($p=.000$) State-Tait Anxiety Inventory score change: -8 ($p=.014$) Yale-Brown Obsessive Compulsive scale change: -4 (NS) Yale-Brown-Cornell Eating Disorders scale change: -7 ($p=.001$)
Powers et al ²⁷ (2002)	Open-label trial	18 (14 completers); 10 weeks	16 females, 2 males from 14 – 56 years (mean 26.8 years ± 12.3) BAN = 12; RAN = 6	Olanzapine 10	Lorazepam Patients could remain in individual psychotherapy if initiated 1 month prior to enrollment	Mean weight gain: 5 lbs ($p=.0138$) HAM-D score for patients who gained weight: $p=.0343$ EDI-2 ^j score for patients who gained weight: $p=.00377$ PANSS score for patients who gained weight: .0276 CGI score for patients who gained weight: $p=.0072$
Brambilla et al ²⁸ (2007)	Randomized, double-blind trial	30; 3 months	30 females; mean age 23.7 years ± 4.8 and 26.3 years ± 8.5 (RAN=18; BAN=12)	Olanzapine 2.5 mg daily X 1 month; 5 mg for following 2 months	Cognitive behavioral therapy	BMI (olanzapine) 15.5± 1.9 vs. 17.2 ± 2.0; $p=0.0003$ BMI (placebo) 15.8±1.1 vs. 16.9 ± 1.2; $p=0.001$)
Newman-Toker ²⁹ (2000)	Case report	2; 12 months, 6 months	19-year-old female 12-year-old	Risperidone 1.5 mg daily	Venlafaxine 150 mg twice daily; Sertraline 100 mg	Increased BMI ^f from 79% IBW to 90% IBW Gained 20 lb

Reference	Design	Subjects (N) / Duration	female Patient Type	Dosage (mg/day)	Concomitant Therapy (mg/day)	Results
Mehler-Wex ³⁰ (2008)	Case report	3; 20 weeks, 24 weeks, 3 months	Females (11-15 years)	Quetiapine 100 mg twice daily; Quetiapine 500 mg daily; Quetiapine 100 mg twice daily	N/A	Patient 1: stable until 20 weeks Patient 2: BMI increased from 13.4 to 17.5, anorexic thinking reduced Patient 3: body weight and psychopathological stability maintained at 3 months
Powers et al ³¹ (2007)	Open-label trial	19; 10 weeks	14-65 years 18 female	Quetiapine 150-300 mg	N/A	Mean weight gain was 1.6 lbs; not statistically different
Aragona ³² 2007	Case report	1; 3 months	34-year-old female	Aripiprazole 30 mg daily	Risperidone 1 mg daily	SANS/SAPS scores improved, weight maintained at 3 months

Abbreviations: RAN-restricting AN; BPRS-Brief Psychiatric Rating Scale; CGI-Clinical Global Impressions Scale; BAN-binging AN; SSRI-Selective Serotonin Reuptake Inhibitors; BMI-Body mass index; HAM-D-Hamilton Depression Scale; EDNOS-eating disorders not otherwise specified; PI-Padua Inventory; EDI-2-Eating Disorders Inventory-2; PANSS-Positive and Negative Syndrome Scale; IBW-ideal body weight, SANS-Scale for assessment of negative symptoms; SAPS-Scale for assessment of positive symptoms