

Aripiprazole in Anorexia Nervosa and Low-Weight Bulimia Nervosa: Case Reports

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ABSTRACT

Objective: There has been much interest in the use of atypical antipsychotics in anorexia nervosa (AN). However, newer, more weight-neutral medications have not been studied in AN, and there are no reports of the use of antipsychotics in bulimia nervosa (BN).

Method: We report on the treatment of eight patients (five with AN and three with BN) with aripiprazole for time periods of four months to more than three years.

Results: All individuals had reduced distress around eating, fewer obsessional thoughts about food, weight and body

image, significant lessening of eating-disordered behaviors, and gradual weight restoration where appropriate. Depression, generalized anxiety, and cognitive flexibility improved as well.

Discussion: In summary, these findings support the need to perform controlled trials of aripiprazole in AN and BN.
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Keywords: anorexia nervosa; bulimia nervosa; atypical antipsychotics; aripiprazole; long-term follow up; dopamine

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Introduction

There has been considerable interest in the use of atypical antipsychotics in anorexia nervosa (AN). Case reports and open trials have described some efficacy for olanzapine,^{1–14} quetiapine,^{15–17} and risperidone.^{18,19} Recently, a controlled trial,²⁰ which randomized 34 day-hospital AN patients to olanzapine 2.5–10 mg/day versus placebo for up to 10 weeks, found increased rate of weight gain and greater reduction in obsessiveness for the olanzapine group. However, there was a high rate of treatment refusal. Although many AN patients resist engagement in any treatment,²¹ the association of olanzapine with weight gain may provide a further deterrent.

It would be useful to determine if other, more weight-neutral atypicals are effective in AN. Only a single case report has been published regarding the relatively weight-neutral atypical antipsychotics aripiprazole and ziprasidone. This report suggested that a 34-year-old female with AN, who was unresponsive to risperidone 1 mg/day, had significant relief of psychotic symptoms related to eating-disordered

themes after a switch to aripiprazole 30 mg/day. The patient's weight, however, remained unchanged at a BMI of 18.²² The author concluded that the tolerability of aripiprazole allowed titration to a more effective dose than was possible with risperidone.

A PubMed search revealed no literature on use of antipsychotics in bulimia nervosa (BN), perhaps due to concerns that these drugs could aggravate binge eating. Clozapine and olanzapine, widely known as the atypical antipsychotics most likely to cause weight gain,^{23,24} have been linked to binge eating in some patients both with and without previous history of eating disorders.^{25–28} Risperidone was associated with exacerbation of BN in one case.²⁹ For aripiprazole and ziprasidone, however, no reports of increased binge eating or purging have been published.

Method

We present a series of case reports regarding our experience in administering aripiprazole to individuals with AN, as well as the first reports, to our knowledge, of response to any antipsychotic in BN.

Case Reports

Table 1 describes the clinical course and response to aripiprazole in eight individuals treated in our clinic. Two individuals are described in greater detail below for illustrative purposes.

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TABLE 1. Aripiprazole case series

Patient #	Age and Gender	Diagnoses	BMI at Initiation of Aripiprazole	Months on Aripiprazole	Average Daily Dose of Aripiprazole	Other Medications and Average Daily Doses	Response
1	52, F	BN (had met criteria for AN-purging for much of her life); MDD-severe, recurrent; GAD; Social phobia; h/o ETOH/meth abuse FSR >20 yrs	26 (significant rebound edema s/p D/C of laxatives after heavy, chronic use)	40	10 mg	Venlafaxine XR 225 mg; Buspirone 30 mg; clonazepam 0.5 mg qam and 1 mg qpm; Trazodone 250 mg qhs	Significant decrease in overall anxiety. Marked decrease in food, weight, body image and exercise obsessions. Ability to tolerate weight/size in high-normal range after > 35 yrs spent underweight. Improved flexibility with food choices and return to 3 meals daily. Increased confidence, initiative, social activity, future planning, mood, and general "peace of mind." First ever significant remission of binge, purge, and restricting behaviors (currently 3.5 yrs). Patient described addition of aripiprazole as both a life-saving and life-changing event. Current BMI 24. See text for further details.
2	33, F	BN; MDD-severe, chronic; OC traits	20	41	7.5 mg	Escitalopram 20 mg; Lamotrigine 200 mg (discontinued after ~18 mos.); Topiramate 75 mg (added after 29 mos.)	Significantly decreased depression, SI, binge/purge (to almost none), rigidity, fears in general and around food. Less rule bound. Increased sense of calm, enjoyment, and future planning. Notably improved ability to make positive changes in multiple areas leading to enhanced quality of life. Stable weight. After 2.5 yrs had mild relapse of binge and occasional purge symptoms, completely remitting with addition of low-dose topiramate. See text for further details.
3	30, F	AN-restricting; Depr NOS; OCD	14	4	10 mg	Fluoxetine 80 mg; Trazodone 50 mg qhs	Entered day-treatment program (five days per wk) and started fluoxetine. Olanzapine was added and eventually titrated to 20 mg/day with benefit for sleep but no change in anxiety with eating or weight. Complained of depressed mood and hopelessness. After 3 mos., switched to aripiprazole. Brightened affect, improved mood and motivation, and increased flexibility of thinking almost immediately apparent. Tolerated gradual wt gain of 23 lbs. over the next 4 mos., to BMI of 17 and return of menses. Able to step down treatment hours and return to graduate school part time. Increased interest in social activity; began dating. Continues weight restoration.
4	28, F	AN-mostly restricting; MDD; GAD	16	~18	10 mg	Citalopram 80 mg	Several prior residential admissions with loss of all restored weight after each discharge. Started aripiprazole at intensive outpatient program. Noted decreased food rituals, rigidity of food choices, and preoccupation with eating-disordered thoughts. Improved ability to tolerate weight gain. With return to residential treatment, achieved greater weight gain than in prior attempts, and further gain, rather than loss, after discharge. Restored to BMI 20, stable for one yr. Improved social life, including resumption of dating. Remission of residual depression and anxiety. Patient then discontinued aripiprazole, moved to a new city, and weight dropped slightly. Without further treatment she eventually returned to a normal-range BMI, got married, and is functioning well at work.

TABLE 1. (Continued)

Patient #	Age and Gender	Diagnoses	BMI at Initiation of Aripiprazole	Months on Aripiprazole	Average Daily Dose of Aripiprazole	Other Medications and Average Daily Doses	Response
5	21, F	BN (prior h/o AN-purging); MDD; OC traits	20	17	15 mg	Escitalopram 40 mg	High-dose SSRI during intensive outpatient program led to improved mood but no benefit for eating disorder. Addition of aripiprazole resulted in decrease in extremely rigid thinking around eating, body shape and weight. Notable decrease in anxiety when eating. Able to follow meal plan. Cessation of binge eating and near cessation of purging. Decreased obsessions about body. Improved capacity for participation in academic and social activities. Significantly increased insight and desire for recovery. Over nearly 1.5 yrs gained to BMI mid-20s. Tapered off aripiprazole, resumed moderate exercise, and at last report had not binged or purged in 3 mos.
6	35, F	AN-restricting; MDD-severe, recurrent; Anxiety NOS	~16	4	10mg	Duloxetine 120 mg	Began on olanzapine but switched to aripiprazole as a result of intolerably ravenous appetite. With aripiprazole, had "normal" appetite and increased ability to tolerate eating "without getting stuck." Reported greatly decreased time spent obsessing about her body. Depression improved. Restored to BMI 19 in residential treatment and to BMI 20 with subsequent intensive outpatient treatment. Eventually discontinued aripiprazole when she noticed increased fatigue after returning to work.
7	15, F	AN-restricting (prior h/o obesity, with BMI in low 30s by age 11); MDD; OCD	17	3+	5 mg	Citalopram (dose unknown)	Extreme anxiety around and rigidity about eating compromised initial attempt at intensive family behavioral therapy. Able to tolerate treatment and weight restoration to BMI 20 with aripiprazole. The medication was discontinued at unknown point thereafter. At 18 months post-treatment, reported BMI 25 with normal eating patterns, improved affect and good social function.
8	55, F	AN-restricting; MDD; GAD	~14	4	5 mg	Duloxetine 60 mg; Quetiapine 50 mg qhs (for insomnia; already had been taking for ~2 yrs at time aripiprazole initiated)	Multiple failures at residential treatment during past 35 yrs. Unable to titrate quetiapine because of daytime sedation; no benefit for eating disorder at 50mg/day. With addition of aripiprazole, noted improved mood. First medication to specifically decrease rigidity of food rules. Able to tolerate decreased exercise. First time able to restore any significant weight outside of residential treatment, currently to BMI 16.

Patient #1

The patient is a 52-year-old female with history of vacillation between low-weight BN and AN-purging type since adolescence, major depressive disorder (MDD), generalized anxiety disorder

(GAD), social phobia and alcohol/methamphetamine abuse in remission for more than 20 years. Her usual BMI ranged from 17 to 19, with a low of 12. Her eating patterns were extraordinarily rigid. She tended toward social isolation. For many years

she had taken 50–200 over-the-counter laxative tablets daily driven by thought distortions of near delusional intensity. After many medical hospitalizations, she truly feared she would die, and was able to discontinue laxatives. She returned to outpatient psychotherapy and described spending many hours daily fighting negative ruminations about her body. The patient's medication regimen had included quetiapine for the past 3.5 years, at a maximum dose of 300 mg/night for the most recent six months. In combination with venlafaxine XR 225 mg, clonazepam 1.5 mg, buspirone 30 mg, and trazodone 250 mg, the patient felt that quetiapine allowed her to “zone out” and escape her painful thoughts and feelings in the evenings, but described her existence as “torture” nonetheless.

Several months after discontinuing laxatives, the patient was switched from quetiapine to aripiprazole 5 mg/day. Within one week, she noticed an increased sense of calm. After titration to 10 mg/day, change in affect was marked. The patient returned to eating three meals per day with expanded food choices, and she was able to enjoy walking while no longer feeling driven to exercise compulsively. The theme of her psychotherapy sessions quickly shifted from food and weight obsessions to handling the intricacies of day-to-day adult life. She was able to initiate plans and social activities where this had been nearly impossible before.

The patient has now taken aripiprazole for 40 months. Her other medications are unchanged. Weight has been stable (BMI 24). She has not used laxatives in more than 3.5 years, and has no acute medical issues or limitations. Depression has remained in remission and anxiety is very manageable. When it was suggested she consider tapering off the antipsychotic, the patient refused, stating, “I have never felt like this before - more accepting of my body. I still would like to weigh less, but I don't feel like punishing myself. I finally have some peace of mind.”

Patient #2

The patient is a 33-year-old female accountant with history of BN, MDD, and obsessive-compulsive traits. She had tightly maintained a BMI of 20 while binge eating and purging four to five times per week for the past 10 years. Her life had been ruled by fears, with rigid, “stuck” thinking about food, weight, and job issues and little capacity for pleasure. While participating in an intensive outpatient eating disorders program the patient was treated with escitalopram 20 mg/day combined with lamotrigine 200 mg/day, but remained chroni-

cally depressed with daily suicidal ideation and no change in eating-disordered behaviors.

With the addition of aripiprazole 7.5 mg/day, the patient reported lessened anxiety, improved mood, and a decrease in binge/purge episodes to eventually less than one time per month. For the first time she noted a loosening of her rigid thought patterns and a reduction in fears. The patient made substantial gains in all areas of her life. She obtained a new job and planned her first true vacation. A new ability to eat outside her “rules” in public led to a more rewarding social life. With decreased negative ruminations about her body, the patient has maintained her first significant intimate relationship.

After about 18 months lamotrigine was discontinued with no change in status. The patient now has been on aripiprazole for 41 months, with lasting benefits in flexibility of thinking and functioning. She initially had a mild weight gain, but has since been stable at a BMI of 21. About 12 months ago, she experienced a slight increase in binge eating with occasional purging, and topiramate 75 mg/day was added to her regimen. The patient subsequently achieved full remission of binge/purge symptoms.

Discussion

These are the first case reports to suggest that aripiprazole may have long-term efficacy and safety in some chronic eating-disordered patients. The medication appears to be well-tolerated in this population, even at moderately-high doses. AN patients may experience severe anxiety with almost any eating, and BN patients may suffer distress when exposed to foods that trigger binge eating. All eight patients described a notable reduction in this eating-specific anxiety with aripiprazole, an effect they had not achieved on antidepressants alone. Also, all patients had a substantial decrease in obsessional thoughts about food, weight, and body image. Three of the AN patients restored weight to a normal-range BMI, and the two others, who were relatively early in treatment, partially restored weight. The two underweight BN patients also gained to more natural body weights. All reported better tolerance of weight gain on aripiprazole. The three BN patients had complete or near-complete cessation of bingeing and purging.

At least seven of the eight patients demonstrated increased cognitive flexibility that both included and extended beyond their eating disorders. They also became more interested and engaged in social

activities. While the improvements in depression and generalized or obsessive-compulsive anxiety that all experienced could have fostered these changes, such an explanation is incomplete, as there appeared to be some alteration in the underlying traits of rigidity and harm avoidance for these patients on aripiprazole. This finding may be significant, as such traits often remain in recovered patients.³⁰

It is important to note, however, that since all patients were taking other medications, it is not clear whether response was due to aripiprazole or combined treatment. AN and BN individuals commonly have co-morbid anxiety and depression, and it is unknown to what extent improved treatment of co-morbidities impacted eating-disordered symptoms. Atypical antipsychotic trial data for efficacy in difficult depressive and anxiety disorders has continued to mount.^{31,32} In late 2007, the US Food and Drug Administration (FDA) approved aripiprazole for use as an augmenting agent in the treatment of unipolar, nonpsychotic depression, the first such indication of its kind. While there is no evidence that aripiprazole has preferential efficacy among antipsychotics as an augmenting agent, its novel mechanism of partial agonism and resulting reputed benefit as a neurotransmitter “system stabilizer” are intriguing.^{33,34}

This article is based on the first and second authors' notes regarding a sample of patients they had treated with aripiprazole who showed substantial clinical improvement. Reviewers asked whether other patients in our clinic had been treated with aripiprazole, and if so, how they had responded. We reviewed our clinic records and found that ~35 total outpatients with AN or BN had been prescribed aripiprazole at the UCSD Center for Eating Disorders Treatment and Research. A review of the charts suggested that perhaps half had a positive response, in terms of some benefits related to reduced depression, anxiety, and eating-disordered signs and symptoms. About a quarter might be considered partial responders, generally with improvement in mood, anxiety, and some eating-disordered thoughts, but a less vigorous impact on behaviors or weight. And about a quarter discontinued aripiprazole after a brief trial, either for potential side effects or a change of mind about medication treatment. Most of this latter group had histories of poor tolerance or acceptance of many medications. Two patients who successfully titrated to a dose of 5 mg/day or more showed no response to aripiprazole. It should be noted that two of the patients had been diagnosed with bipolar-spectrum disorders. None had co-morbid psychotic disorders.

Many AN patients refuse medication, particularly if associated with weight gain. Even those who believe an antipsychotic may help them tolerate weight restoration tend to have tremendous fear of a medication-induced loss of control over the process. We have found that AN patients are more willing to try aripiprazole. This may be because freely available internet searches show that weight gain is not a common side effect. An additional rationale for aripiprazole is its improved overall side effect profile versus predecessor atypicals.^{35,36} Ability to titrate to a higher relative dose could mean greater activation of mechanisms (e.g., dopaminergic versus more heavily serotonergic) that may prove worthwhile for the near-psychotic symptoms not uncommonly seen in AN.

With regard to BN, we have noted a subset of patients who maintain underweight or low-normal BMIs and show little response to high-dose antidepressants and psychotherapeutic treatment. Patients #1, #2, and #5 of our series are representative. For this group, any decrease in binge eating and purging often is met with increased exercising and food restricting, resulting in failure to gain to a more natural weight or even weight loss. They frequently display the extreme rigidity, reduced novelty seeking, obsessionality, and social isolation more typically seen in AN rather than BN. This phenomenological presentation of BN may show treatment overlap with AN, which our early clinical experience with aripiprazole supports. Equally important, aripiprazole did not aggravate binge cravings in these BN patients, as might occur with some other atypical antipsychotics.

If we assume that the two atypical antipsychotics olanzapine and aripiprazole have some clinical efficacy in AN and BN, it would be of value to consider whether a comparison of their pharmacodynamics provided some insight into underlying mechanisms. There is considerable evidence that AN and BN individuals have disturbances in dopaminergic and serotonergic neurotransmission.^{37,38} Thus, it is plausible that the efficacy of atypicals is due to their actions at serotonergic and dopaminergic receptors. While the atypicals have many similar effects, each has a unique pharmacodynamic profile (Table 2).^{39,40} Both aripiprazole and olanzapine exhibit at least moderate inhibitory constants for several subtypes of dopaminergic (D2, D3, and D4) and serotonergic (5-HT_{2A} and 5-HT_{2C}) receptors.

At this time, it is not clear whether there is any common mechanism that accounts for the possible effects of aripiprazole and olanzapine. As we better understand the neurobiology of AN and BN, there is the hope that eventually we can tailor treatment

TABLE 2. Pharmacodynamic profiles of atypical antipsychotics

	D1	D2	D3	D4	5-HT _{1A}	5-HT _{2A}	5-HT _{2C}	5-HTT
Aripiprazole	Lo	Hi/partial	Hi	Mod	Hi/partial	Hi	Mod	Inh
Olanzapine	Mod	Mod	Mod	Mod	Weak	Hi	Mod	—
Ziprasidone	Lo	Hi	Hi	Mod	Hi/ag	Hi	Hi	Inh
Quetiapine	Lo ^a	Lo	Lo	Weak	Lo	Lo	Weak	—
Risperidone	Lo	Hi	Hi	Hi	Lo	Hi	Mod	—

^a Weak per Full Prescribing Information. ⁽⁴⁰⁾ Partial denotes partial agonist; ag denotes agonist. In vitro inhibition constants at each receptor (K_i ⁽³⁹⁾) are denoted as Hi \leq 10 nM; 10 nM < Mod \leq 100 nM; 100 nM < Lo \leq 1,000 nM; Weak > 1,000 nM.

based on a match between drug mechanisms and patient traits. And as noted above, it remains uncertain whether aripiprazole effects are related to augmentation of other drugs. Still, as drug trials of these compounds progress, it is worthwhile paying attention to their effect profiles.

Conclusion

These case reports provide the first evidence that aripiprazole may have efficacy in AN and BN, and provide the preliminary data necessary to support controlled trials of this medication. However, controlled trials of aripiprazole as a monotherapy, as well as augmentation for antidepressants, are needed to prove whether this drug is efficacious in eating disorders.

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