

# Role of antidepressants in the treatment of adults with anorexia nervosa

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## Abstract

**Introduction:** Anorexia nervosa (AN) is a severe psychiatric disorder that is difficult to treat and is associated with frequent relapses and high mortality rates. Psychiatric symptomatology (eg, depression, anxiety, obsessive-compulsive disorder/behaviors) are common comorbidities. This review provides current information about safety and efficacy of antidepressant therapy for management of AN in adults.

**Methods:** A literature review of randomized controlled trials, open-label studies, and case reports with adults or adults/adolescents was conducted. PubMed and Medline were searched using anorexia management and treatment, antidepressants, selective serotonin reuptake inhibitors (SSRIs), fluoxetine, sertraline, citalopram, and mirtazapine in AN, relapse prevention in AN, and psychotropic medications in AN.

**Results:** The role and utility of antidepressants in AN were published in double-blind, placebo-controlled studies; open-label trials; and a retrospective study. Antidepressants should not be used as sole therapy for AN although their use for confounding symptomatology makes discerning efficacy difficult as they are given together with other therapies. Neurobiological changes due to starvation and AN itself complicate results interpretation. For safety, tricyclic antidepressants and monoamine oxidase inhibitors are not recommended, and bupropion is contraindicated. Use of SSRIs during acute treatment lacks efficacy. Use of SSRIs—primarily fluoxetine and to some extent citalopram, sertraline, or mirtazapine—may aid in relapse prevention and improvement of psychiatric symptomatology in weight-restored anorexic patients.

**Discussion:** Health care professionals should use clinical judgment regarding fluoxetine or possibly citalopram, sertraline or mirtazapine as adjunctive treatment to psychotherapy for relapse prevention, improvement of depressive and anxiety symptoms, and/or obsessive-compulsive behaviors unresolved with nutritional rehabilitation and psychotherapy.

**Keywords:** anorexia nervosa, antidepressants, relapse prevention, body mass index, maintenance treatment phase, acute treatment phase, maintenance treatment phase, nutritional rehabilitation

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## Introduction

Anorexia nervosa (AN) is a severe, usually relapsing, psychiatric disorder. It has the highest mortality rate of

any psychiatric disorder with an estimated adult mortality rate of 5% per decade.<sup>1-4</sup> It is most predominant among girls and young women with the average age at onset being 15 years.<sup>4,5</sup> Estimated lifetime prevalence is approximately 2% in females and 0.3% in males although studies have reported rates of up to 4% in females.<sup>2-4</sup> It is characterized by excessive weight loss due to self-starvation, body image distortion, and immense fear of gaining weight or being fat.<sup>6</sup> There are two subtypes: (1) restricting (AN-R), characterized by restricting food intake with or without compulsive exercise, and (2) binge-eating/

purging (AN-BP), characterized by episodes of consuming large portions of food (binging) followed by purging (eg, ipecac- or self-induced vomiting, and/or excessive use of laxatives, enemas, or diuretics).<sup>6</sup> Comorbid psychiatric illnesses (eg, major depression, anxiety disorders, obsessive-compulsive disorder or behaviors) are common among individuals with AN.<sup>7-10</sup>

Anorexia nervosa can result in starvation status and nutritional deficiencies leading to reversible and irreversible medical complications of varying severity (Table 1). These complications can affect nearly every body system and usually directly correlate to severity of the disease, degree of weight loss/starvation and/or purging.<sup>11-16</sup> In adults, the severity of AN is based on current body mass index (BMI) status: BMI  $\geq 17$  kg/m<sup>2</sup> reflects mild severity; BMI of 16.00 to 16.99 kg/m<sup>2</sup> reflects moderate severity; BMI of 15.00 to 15.99 kg/m<sup>2</sup> reflects severe severity; and BMI of  $< 15$  kg/m<sup>2</sup> reflects extreme severity (recommended normal or healthy weight for adults is 18.5 to 24.9 kg/m<sup>2</sup>).<sup>17</sup> There is no US Food and Drug Administration–approved treatment of AN, and available treatments have limited efficacy.<sup>12,18-21</sup> Suicide attempts are very common in AN with lifetime prevalence rates ranging from 3% to 29.7%.<sup>2</sup> Severe medical complications (eg, hypokalemia, arrhythmias) are estimated to be responsible for 54% of all AN deaths, followed by 27% due to suicide and 19% due to unknown/other causes.<sup>22,23</sup> Among surviving anorexic patients, nearly 50% will make a full recovery. Of the remaining half, 40% will continue to improve, albeit not making a full recovery, and 60% will develop chronic AN.<sup>24</sup>

Early clinical detection and diagnosis of AN is crucial for achieving the best outcomes as shorter duration of illness suggests a positive correlation with a positive predictive factor of treatment response.<sup>25,26</sup> Treatment of AN is complex with limited treatment options of documented efficacy or reduced rates or relapse.<sup>1</sup> Treatment plans should be individualized, and treatment goals are (1) weight restoration, (2) normalization of eating patterns/behaviors, (3) correction of biological and psychological complications of malnutrition, (4) management of comorbid psychopathology and psychiatric symptoms, and (5) weight maintenance/relapse prevention.<sup>12,18-21</sup>

Nutritional/weight restoration is first-line treatment in underweight/malnourished anorexic patients.<sup>12,18-21</sup> It improves cognitive function and enhances effectiveness of psychological interventions.<sup>27</sup> In addition, depression and anxiety symptomatology can be triggered or exaggerated by malnutrition and may improve or fully reverse with nutritional rehabilitation and weight restoration.<sup>11</sup> The 2017 National Institute for Health and Care Excellence<sup>18</sup> guideline also encourages daily multivitamin and multi-mineral supplements until dietary intake supplies

necessary daily requirement. Psychological treatment is considered the cornerstone of AN treatment and should be used as primary management for adult anorexic patients.<sup>12,18-21</sup> In addition, medications used to manage medical complications (eg, gastroparesis, constipation, anemia, osteoporosis) may be prescribed based on individual patient needs.<sup>18-21</sup>

Clinical studies of psychotropic medications for AN as adjunctive therapy to weight restoration and/or psychotherapy have produced inconsistent results and lack high-quality evidence.<sup>12,18-21</sup> From a pathophysiologic standpoint, antidepressants merit clinical investigation in AN due to their pharmacologic effects on the serotonin (5-HT) neurotransmitter system as dysfunction of the serotonergic neuronal system is postulated in anorexic patients.<sup>13</sup> Antidepressants are also effective in the treatment of depression, anxiety, and obsessive-compulsive behaviors often present in AN.<sup>7-10</sup>

Current treatment guidelines do not recommend use of antidepressants as sole therapy for AN due to limited efficacy.<sup>12,18-21</sup> In addition, use of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) is not recommended due to limited and unconvincing efficacy data and low safety profiles.<sup>19-21</sup> Bupropion is contraindicated due to increased risk of seizures in anorexic patients.<sup>19,21,28</sup> Garner et al<sup>29</sup> reported that antidepressants are widely prescribed to adults and adolescent anorexic patients despite recommendations in treatment guidelines. Antidepressants were commonly prescribed to 87.9% of studied individuals (n = 287, age = 23.2  $\pm$  10.4 years, BMI = 16.5  $\pm$  1.6) with 79% receiving a selective serotonin reuptake inhibitor (SSRI).<sup>29</sup> This article discusses the safety of different antidepressants in AN and summarizes recent evidence and highlights potential benefits of use of select SSRIs and mirtazapine in adult anorexic patients during acute and maintenance treatment phases.

## Methods

A literature review was conducted using PubMed and Medline databases investigating the safety and effectiveness of SSRIs and mirtazapine in the treatment of AN. The search terms included anorexia management and treatment, antidepressants, SSRIs, fluoxetine, citalopram, sertraline, and mirtazapine in AN, relapse prevention in AN, and psychotropic medications in AN. We limited studies to those that were (1) published in the English language; (2) a randomized controlled trial, an open-label study, case reports, or case series; (3) the study population was adults only or adults and adolescents combined; and (4) acute or maintenance phase research. Race/ethnicity or sex was not a limiter. Efficacy was assessed as weight

**TABLE 1: Medical complications associated with anorexia nervosa in adults<sup>11-16</sup>**

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<b>Neuropsychiatric/Neurological</b>
Cerebral dystrophy/atrophy <sup>a</sup>
Cognitive decline/impairment
Desphoria/depression
Anxiety
Sleep disorders
<b>Endocrine and Metabolic</b>
Amenorrhea
Infertility
Osteopenia/osteoporosis <sup>b</sup>
Thyroid abnormalities
Hypercortisolemia
Low serum albumin
Hypoglycemia
Neurogenic diabetes insipidus
Secondary hyperaldosteronism
<b>Renal, Fluid, and Electrolytes</b>
Dehydration/hypovolemia
Increased BUN
Increased SCr
Decreased GFR
Electrolyte dysbalance <sup>d</sup> (eg, hypokalemia, hyponatremia, hypomagnesemia, hypophosphatemia)
Hypochloremic metabolic alkalosis <sup>d</sup>
Refeeding syndrome
<b>Cardiac</b>
Bradycardia
Hypotension
Orthostatic hypotension
Prolonged QT interval
Arrhythmias
Mitral valve prolapse <sup>b</sup>
<b>Gastrointestinal</b>
Gastroparesis
Constipation
Esophagitis <sup>c</sup>
Dysphagia
Postprandial discomfort
Postprandial bloating
Elevated liver enzymes
Severe acute pancreatitis
<b>Hematologic</b>
Anemia
Neutropenia
Thrombocytopenia
Decreased ESR

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**TABLE 1: Medical complications associated with anorexia nervosa in adults<sup>11-16</sup> (continued)**

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<b>Pulmonary</b>
Aspiration
Pneumonia <sup>c</sup>
Emphysema

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BUN = blood urea nitrogen; ESR = erythrocyte sedimentation rate; GFR = glomerular filtration rate; SCr = serum creatinine.

<sup>a</sup>Data inconclusive whether this is reversed or not reversed after nutrition/weight restoration in anorexic individuals.

<sup>b</sup>Complete reversal unlikely despite nutritional/weight restoration in anorexic individuals.

<sup>c</sup>Complications found only in individuals with anorexia nervosa binge-eating/purging type due to ipecac- or self-induced vomiting.

<sup>d</sup>Secondary to excessive water intake or purging using diuretics, laxatives, enemas or ipecac- or self-induced vomiting.

gain or weight restoration: posttreatment weight gain, BMI improvement, percentage of ideal body weight (IBW), change in percentage of IBW/d, and/or psychiatric symptomatology improvement. We excluded all studies performed with only children or adolescents as well as those studies of TCA and MAOI use as these antidepressant classes are not generally safe in AN populations.

## Results

### Safety of Antidepressants in Anorexic Patients

Tricyclic antidepressants and MAOIs are medications with narrow therapeutic indices and the potential to be lethal when taken in overdose or when mixed with benzodiazepine or alcohol.<sup>30-32</sup> Suicidal ideation and suicide attempts are common among anorexic patients, and self-poisoning with medication as a method of suicide is frequent in females aged 15 to 19 years.<sup>33</sup> Tricyclic antidepressants are also associated with unwanted adverse effects, such as decreased seizure threshold, QT interval prolongation, orthostatic hypotension, and gastrointestinal symptoms (eg, constipation and gastroparesis),<sup>31-32</sup> and thus can worsen preexisting gastrointestinal and cardiovascular conditions inherent to AN individuals. Bupropion decreases seizure threshold, and this risk is even higher in those AN and underweight patients. Bupropion is contraindicated in anorexic patients due to increased risk for new-onset seizures.<sup>19,21,28</sup>

Selective serotonin reuptake inhibitors offer improved safety and tolerability for anorexic patients in comparison with TCAs or MAOIs.<sup>30</sup> Selective serotonin reuptake inhibitors are generally well tolerated when initiated with gradual dose increase. Fluoxetine can be associated with greater potential for drug-drug interactions due to its potent inhibition of CYP2D6 and moderate inhibition of

CYP3A4 enzymes.<sup>34</sup> The lowest effective dose of citalopram should be used as it is associated with dose-dependent QT interval prolongation, and the maximum daily dose should not exceed 40 mg.<sup>35,36</sup> As hypokalemia can prolong the QT interval and increase patient risk for arrhythmias, baseline and follow-up electrocardiogram and serum potassium concentrations should be monitored in those treated with citalopram or TCAs.<sup>31-33,35</sup> Unlike citalopram or TCAs, fluoxetine, sertraline, and mirtazapine, are not associated with increased risk for QT interval prolongation.<sup>34,37,38</sup> In addition, mirtazapine is well tolerated and less likely to cause sexual dysfunction in comparison with SSRIs and TCAs.<sup>37</sup> Antidepressant use may be negatively associated with bone mineral density, especially in adolescent anorexia patients.<sup>39</sup>

### SSRIs and Mirtazapine in Adult Anorexic Patients Undergoing Weight Restoration

Table 2 summarizes studies with SSRIs and mirtazapine in inpatient settings in individuals undergoing a weight-restoration program. Attia et al<sup>40</sup> performed a randomized, double-blind, placebo-controlled study with 31 anorexic women with less than 80% IBW (age = 26.2 ± 7.4 years; weight = 72.5% IBW; *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [DSM-IV] criteria). Subjects were admitted to the inpatient research unit where they underwent individual psychotherapy (3 to 5 times/wk of supportive and cognitive behavioral therapy [CBT]) and weight restoration and were randomly assigned to either fluoxetine or placebo for 7 weeks. Fluoxetine was initiated at 20 mg/d and increased over 1 week to 60 mg/d. In general, fluoxetine was well tolerated as 4 out of 15 (27%) individuals taking fluoxetine vs 4 out of 16 (25%) from the placebo group discontinued the trial before reaching 90% of IBW or completing the full 7 weeks. One patient in the fluoxetine treatment group needed to decrease dosage to 40 mg/daily due to insomnia and agitation and another to 20 mg/d due to blurred vision. The study found no additional benefits regarding weight gain or improvement of psychological functioning with fluoxetine, in comparison with placebo, for subjects with either AN-R or AN-BP. Both treatment groups, placebo- and fluoxetine-treated, experienced statistically significant increases in weight, Clinical Global Impression Subscales for illness and eating disorder, Beck Depression Inventory, Anorexic Behavior Scale, Yale-Brown-Cornell Eating Disorder Scale, Eating Attitudes Test, Symptom Checklist-90 (SCL-90), and Body Shape Questionnaire.<sup>40</sup>

Ruggiero et al<sup>41</sup> conducted a 3-month, single-blind, randomized trial with the antipsychotic amisulpride (n = 12, age = 24.33 ± 5.8), the TCA clomipramine (n = 13, age = 23.7 ± 4.6), and fluoxetine (n = 10, age = 24.5 ± 5.1) at the beginning of the refeeding phase of individuals with AN-R (DSM-IV criteria) enrolled in

standardized inpatient nutritional and psychotherapeutic treatment. Body weight was evaluated initially and at discharge from standardized refeeding hospital treatment. A significant increase in mean weight for amisulpride- ( $P = .016$ ) and fluoxetine-treated ( $P = .045$ ) individuals was reported. However, only the amisulpride-treated group showed a significantly higher but overall modest body weight increase at the end of the trial (BMI increase from 14.4 to 16.0). As individuals completed a feeding program as well as psychoeducational treatment managed by a nutritionist, it is difficult to interpret the efficacy of fluoxetine and amisulpride in weight gain.<sup>41</sup>

Barbarich et al<sup>42</sup> performed a 6-month-long, randomized, double-blinded, placebo-controlled trial with 26 underweight subjects (age = 23.0 ± 6.3 years) with AN-R and AN-BP. They investigated the effect of supplementation with tryptophan, fish oil, minerals, and vitamins on efficacy of fluoxetine (range = 20 to 60 mg/d). The active group (n = 15) received fluoxetine in addition to daily supplements of 2.3 g of tryptophan, 600 mg docosahexanoic acid, 180 mg of arachidonic acid, and a daily multivitamin/mineral capsule while the control group (n = 11) received fluoxetine with an equivalent number of inactive capsules. No significant difference in weekly weight gain was observed between the treatment and control groups (0.27 ± 0.3 kg vs 0.1 ± 0.1 kg). After 3 and 6 months of treatment, psychological testing using the Spielberger State-Trait Anxiety Inventory and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) revealed no significant changes in anxiety or obsessive-compulsive symptoms.<sup>42</sup>

Limited studies were done using mirtazapine in adults undergoing weight restoration to study its effect on cortisol levels. It is postulated that hypercortisolemia, commonly found in anorexic patients, can reinforce decreased eating behavior and behavioral changes associated with AN, possibly due to starvation-induced hyperactivity of the hypothalamus-pituitary-adrenal axis.<sup>43,44</sup> Schüle et al<sup>43</sup> investigated the effect of mirtazapine on salivary cortisol concentrations, BMI, and Hamilton Depression Scale (HAM-D, 21-item scale) in anorexic inpatients. Five hospitalized female subjects between 20 and 29 years of age (age 24 ± 3.67 years; baseline BMI 13.93 ± 1.49 kg/m<sup>2</sup>) with AN-R (DSM-IV criteria) and depressive symptomatology (HAM-D = 20.8 ± 5.97) were initiated on mirtazapine monotherapy with a 3-day titration schedule (mirtazapine 15 mg on Day 0, mirtazapine 30 mg in 2 divided doses on Day 1, and mirtazapine 45 mg in 2 divided doses on Day 2). Subjects were undergoing nutritional rehabilitation, and all meal intake was monitored in the presence of a nurse. After 3 weeks of inpatient treatment with mirtazapine 45 mg/d, there was significant inhibition of salivary cortisol concentration ( $P < .05$ ) and nonsignificant trends for increased

BMI ( $13.93 \pm 1$  vs  $14.79 \pm 1.93$ ;  $P=.063$ ) and decreased HAM-D scores ( $16.40 \pm 4.93$  vs  $20.80 \pm 5.97$ ;  $P=.154$ ).<sup>44</sup>

## SSRIs in Weight-Restored Adult Anorexic Patients

Fluoxetine has been the most-investigated SSRI in AN and seems to have the most evidence for use in treatment of AN in weight-restored individuals (Table 2).<sup>45-48</sup> Gwirtsman et al<sup>48</sup> conducted an open trial investigating fluoxetine in 6 subjects ( $n=5$  women; illness duration = 2–18 years; age = 20–39 years; weight range = 34.5 to 55.9 kg; DSM-III-R [third edition] criteria) with chronic refractory AN-R previously treated with TCAs, trazodone, and/or MAOIs. Fluoxetine  $43 \pm 15$  mg treatment (mean duration = 7.6 months) was associated with significant improvement of depressive symptoms in all studied subjects. In addition, 5 individuals (83.3%) experienced significant weight gain and improvement in obsessive-compulsive symptoms.<sup>48</sup>

A double-blind, placebo-controlled, open-label trial investigating fluoxetine use in 31 weight-restored outpatients (age =  $20 \pm 7$  years) with AN (DSM-III-R criteria) found that 29 subjects (93.55%) who remained on fluoxetine (mean dose =  $38 \pm 18$  mg/d, dose range = 20 to 60 mg/d) for the length of study (mean =  $11 \pm 6$  months) maintained their weight at  $\geq 85\%$  average body weight ( $97\% \pm 13\%$ ).<sup>47</sup> Investigators also rated response in eating behavior, mood, and obsessional symptoms as “good” ( $n=10$ ), “partial” ( $n=17$ ), and “poor” ( $n=4$ ), and reported that individuals with AN-R responded to fluoxetine therapy better than those with AN-BP.<sup>47</sup> A decade later, Kaye et al<sup>46</sup> further demonstrated the potential benefit of fluoxetine for preventing relapses in weight-restored, posthospital discharge AN-R patients ( $n=31$ ) in a 52-week-long, double-blind, placebo-controlled trial. Participants were females (weight = 75% to 90% average body weight) who met DSM-IV diagnostic criteria for AN-R. The goal for weight restoration was set as  $\geq 90\%$  average body weight (ABW) prior to initiation of fluoxetine. A low percentage of patients met this weight goal during hospitalization, and the majority of patients did not seek psychotherapy as outpatients. The initial dose of fluoxetine was 20 mg/d with monthly increases of 20 mg/d to a maximum dose of 60 mg/d. Patients were followed every 4 weeks after the discharge for the duration of the study. Individuals were randomized to the fluoxetine-treatment group ( $n=16$ ; age =  $23 \pm 9$  years; percentage of ABW at entry =  $89 \pm 6$ ; fluoxetine dose = 20 to 60 mg/d) and the placebo group ( $n=19$ ; age =  $22 \pm 6$  years; percentage of ABW at entry =  $89 \pm 7$ ). Ten out of 16 treatment group patients remained on fluoxetine for all 52 weeks while only 3 placebo group patients remained. Those who remained on fluoxetine for the entire length of the study had a

significantly reduced relapse rate and higher weight gain in comparison with those who did not. In addition, they had statistically significant improvement in psychiatric symptomatology (reduced scores of the HAM-D, Hamilton Anxiety Rating Scale, and Y-BOCS compared with those who did not remain on fluoxetine).<sup>46</sup>

In contrast, Walsh et al<sup>45</sup> reported no benefit of fluoxetine treatment over placebo in a 52-week randomized, double-blind, placebo-controlled study investigating fluoxetine use in combination with CBT in outpatient anorexic patients with a minimum BMI of 19 kg/m<sup>2</sup>. No benefit in time to relapse was observed for the fluoxetine group ( $n=49$ ; age =  $22.4 \pm 4.5$  years; mean dose =  $63.5 \pm 15.8$  mg; DSM-IV criteria) compared with placebo ( $n=44$ ; age =  $24.2 \pm 4.5$  years). Among fluoxetine-treatment (26.5%) compared with placebo-treatment (31.5%) subjects remaining in the study for 52 weeks and maintaining a BMI  $\geq 18.5$  kg/m<sup>2</sup> ( $P=.57$ ), there was no significant difference in time to relapse (HR 1.12 95% confidence interval 0.65–2.01;  $P=.64$ ).<sup>45</sup>

Citalopram efficacy was also studied in anorexic patients (Table 2). An open-label trial with 6 female patients with AN-R and AN-BP treated for 8 weeks with citalopram 20 mg/d and psychotherapy (age =  $20.5 \pm 4.7$  years; DSM-IV criteria) concluded that citalopram 20 mg was well tolerated in anorexic patients, and its use was associated with reduced body dissatisfaction (Eating Disorder Inventory-Symptom Checklist [EDI] body dissatisfaction subscale) but no weight changes.<sup>49</sup> Fassino et al<sup>50</sup> randomized 52 weight-restored AN-R female outpatients to either citalopram 20 mg/d ( $n=26$ ; age =  $24.3 \pm 5.4$  years) or a wait-list control group ( $n=26$ ; age =  $25.2 \pm 8.6$  years) in an open-label study. Seven patients (29.6%) in the citalopram group and 6 patients in the control group (30%) did not complete the study. After 3 months of treatment, there was similar weight gain between the 2 groups; however, the citalopram group had significant decreases in Beck Depression Inventory and depressive and obsessive compulsive features on the SCL-90 scale as well as impulsiveness on EDI, and trait-anger on the State-Trait Anger Expression Inventory.<sup>50</sup>

An additional SSRI, sertraline, has limited data regarding its efficacy in AN after weight restoration (Table 2).<sup>51</sup> Santonastaso et al<sup>51</sup> executed an open, controlled trial with 22 individuals with AN-R (age =  $19.3 \pm 4.7$  years; BMI =  $16.1 \pm 1.0$  kg/m<sup>2</sup>; DSM-IV criteria). Subjects were separated into a sertraline group ( $n=11$ ) with sertraline doses ranging from 50 to 100 mg/d and a control group ( $n=11$ ). The researcher used the EDI scale and the short version of the Hopkins Symptom Checklist (SCL-58) for efficacy assessment. Both the sertraline-treated group (baseline BMI  $14.5 \pm 1.2$  kg/m<sup>2</sup> vs 14-week follow-up  $17.1 \pm 1.5$  kg/m<sup>2</sup>;  $P < .005$ ) as well as the control group (baseline BMI  $16.4 \pm 0.9$  kg/m<sup>2</sup> vs

**TABLE 2: Characteristics of studies included<sup>40-43,45-53</sup>**

Intervention/Medication (Daily Dose)	Study Design	Study Length	AN Type	Age ± SD (Years)	Outcome Measure	Finding	Reference
Fluoxetine 60 mg (mean dose 56 ± 11.2 mg) Adjunctive: psychotherapy (individual, family or group therapy, behavior therapy)	Randomized, placebo-controlled, double-blind trial Inpatient setting N = 32	7 wk	AN-R AN-BP (DSM-IV)	26.2 ± 7.4	% IBW Change in % IBW/d CGI BSQ EAT-26 SCL-90	Fluoxetine showed no benefit over placebo	Attia et al <sup>40</sup>
Clomipramine mean dose 57.7 ± 25.8 mg Fluoxetine mean dose 28.0 ± 10.3 mg Amisulpride mean daily dose 50.0 ± 0.0 mg Adjunctive: psychotherapy	Randomized, single-blind trial (3 treatment arms, not placebo controlled) Inpatient setting N = 35	3 mo	AN-R (DSM-IV)	24.2 ± 5.1	Mean weight Body weight increase	Significant increase of mean weight for the fluoxetine- and amisulpride-treated group Significant body weight increase for amisulpride-treated group at the end of trial	Ruggiero et al <sup>41</sup>
Fluoxetine 20 to 60 mg plus supplements (2.3 g tryptophan, 600 mg docosahexanoic acid, 180 mg arachidonic acid, MVI)	Double-blind, placebo-controlled trial Parallel fluoxetine + nutritional supplements vs fluoxetine + placebo Inpatient setting N = 26	6 mo	AN-R AN-BP (DSM-IV)	23.0 ± 6.3	Weight gain STAI-Y Y-BOCS	Nutritional supplementation was ineffective for increasing fluoxetine efficacy	Barbarich et al <sup>42</sup>
Mirtazapine 45 mg	Open-label trial Inpatient setting N = 5	3 wk	AN-R and depressive symptomatology (HAM-D 20.8 ± 6) (DSM-IV)	24.3 ± 3.7	Salivary cortisol Weight gain HAM-D	Significant decrease in salivary cortisol Nonsignificant trends for BMI increase and HAM-D score decrease	Schüle et al <sup>43</sup>
Fluoxetine 20 to 60 mg (mean dose 43 ± 15 mg)	Uncontrolled open trial Outpatient setting N = 6	2 to 5 mo	Chronic refractory AN-R (previously treated with TCA, trazodone, and/or MAOI) (DSM-III-R)	27 ± 9	Weight gain Depressive symptoms Obsessive-compulsive symptoms	Significant improvement in weight, depressive, and obsessive-compulsive symptoms	Gwirtsman et al <sup>48</sup>
Fluoxetine 20 to 60 mg (mean dose 38.0 ± 18 mg)	Double-blind, placebo-controlled, open trial Outpatient setting N = 31	11 ± 6 mo treatment follow-up	AN-R AN-BP (DSM-III-R)	20 ± 7	Weigh maintenance Eating behavior Mood Obsessional symptoms	29/31 (93.6%) patients maintained weight above 85% average body weight Individuals with AN-R responded significantly better than AN-BP	Kaye et al <sup>47</sup>
Fluoxetine 20 to 60 mg Adjunctive: psychotherapy	Double-blind, placebo-controlled Outpatient setting N = 35	52 wk	AN-R (DSM-IV)	22.5 ± 7.5	Trial completion Weight gain Relapse rate HAM-D HAM-A Y-BOCS	10/16 (62.5%) patients remained on fluoxetine while only 4/19 (21.1%) remained on placebo for 56 wk Statistically significant reduction in relapse rate, higher weight gain, and improvement in psychiatric symptomatology (anxiety, depression, obsession-compulsion) in those who remained on fluoxetine in comparison to those who did not	Kaye et al <sup>46</sup>
Fluoxetine 20 to 60 mg Adjunctive: psychotherapy (CBT and family therapy)	Randomized, placebo-controlled, double-blind trial Outpatient setting N = 93 Weight restored individuals (BMI ≥ 19 kg/m <sup>2</sup> )	52 wk	AN-R AN-BP (DSM-IV)	23.3 ± 4.5	Time to relapse Completion of 1 y of treatment	No benefit from fluoxetine in anorexic patients following weight restoration	Walsh et al <sup>45</sup>

**TABLE 2: Characteristics of studies included<sup>40-43,45-53</sup> (continued)**

Intervention/Medication (Daily Dose)	Study Design	Study Length	AN Type	Age $\pm$ SD (Years)	Outcome Measure	Finding	Reference
Citalopram 20 mg Adjunctive: psychotherapy	An open-label trial Outpatient setting N = 6	8 wk	AN-R AN-BP (DSM-IV)	20.5 $\pm$ 4.7	Weight EDI	No significant differences in BMI Significant decrease in mean EDI scores on body dissatisfaction subscale	Calandra et al <sup>49</sup>
Citalopram 20 mg	Prospective, randomized, controlled study (no-drug controls) Outpatient setting N = 52	12 wk	AN-R (DSM-IV)	24.8 $\pm$ 7.0	Weight BDI SCL-90 EDI STAXI-2	Similar weight gain in both groups No significant difference in BMI in treated vs control group Significantly decrease in BDI and depressive and obsessive compulsive features in citalopram-treated group	Fassino et al <sup>50</sup>
Sertraline 50 to 100 mg Adjunctive: psychotherapy	Open-label, controlled trial (drug group vs matched control) Outpatient setting N = 22	14 wk	AN-R (DSM-IV)	19.3 $\pm$ 4.7	Weight EDI SCL-58	No difference in weight gain between treated vs control group (both groups showed significant weight gain) Significantly greater improvement in depressive symptoms, perfectionism, lack of interoceptive awareness, and ineffectiveness in sertraline-treated vs control group	Santonastaso et al <sup>51</sup>
Mirtazapine 30 mg plus olanzapine 10 mg Adjunctive: psychotherapy (inpatient and outpatient), nutritional restoration (inpatient)	Case report 5 wk inpatient and 6 mo outpatient setting N = 1	6 mo	AN with comorbid depression	27	Depression Weight/BMI	Combinational treatment of olanzapine and mirtazapine led to depression remission, weight increased from 24 to 38 kg, and BMI increased from 9.8 to 15.5 kg/m <sup>2</sup>	Wang et al <sup>52</sup>
Mirtazapine 45 mg Adjunctive: psychotherapy	Case report Outpatient setting N = 1	9 mo	Refractory AN with comorbid depression and anxiety (previously treated with sertraline, paroxetine, escitalopram, bupropion, alprazolam)	50	Depression Weight	Improvement of depressive symptoms Weight gain Weight and depressive symptomatology benefits were maintained at 11-mo follow-up	Safer et al <sup>53</sup>

AN = anorexia nervosa; AN-BP = anorexia nervosa binge eating/purging subtype; AN-R = anorexia nervosa restricting subtype; BDI = Beck Depression Inventory; BMI = body mass index; BSQ = Body Shape Questionnaire; CBT = cognitive behavioral therapy; CGI = Clinical Global Impression; DSM-III = *Diagnostic and Statistical Manual*, third edition; DSM-IV = *Diagnostic and Statistical Manual*, fourth edition; EAT-26 = Eating Attitudes Test; EDI = Eating Disorder Inventory-Symptom Checklist; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Scale, 21 items; IBW = ideal body weight; MAOI = monoamine oxidase inhibitor; MVI = multivitamin; SCL-58 = short version of the Hopkins Symptom Checklist; SCL-90 = Symptom Checklist-90; STAI-Y = Spielberger State-Trait Anxiety Inventory; STAXI-2 = trait-anger on State-Trait Anger Expression Inventory; TCA = tricyclic antidepressant; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

14-week follow-up BMI  $17.6 \pm 1.2$  kg/m<sup>2</sup>;  $P < .01$ ) showed significant weight gain over the period of 14 weeks. Individuals treated with sertraline had significantly greater improvement in depressive symptoms using the SCL-58 subscale ( $F_{1,20} = 4.29$ ;  $P = .05$ ) and ineffectiveness ( $F_{1,20} = 4.93$ ;  $P < .05$ ) and perfectionism ( $F_{1,20} = 4.93$ ;  $P < .05$ ) using the EDI scale after 14 weeks of treatment compared with controls. In general, sertraline was well tolerated, and only transient adverse effects (ie, nausea, headache, insomnia) were reported in 8 patients.<sup>51</sup>

### Mirtazapine in Weight-Restored Adult Anorexic Patients

The role of mirtazapine in weight-restored anorexic patients is limited to evidence reported from case studies (Table 2).<sup>52,53</sup> A case report<sup>53</sup> described a 27-year-old female with AN and comorbid major depression with a weight of 24 kg (BMI = 9.8 kg/m<sup>2</sup>) who was hospitalized. Weight restoration was provided via nasogastric tube feeding and total parenteral nutrition for 1 month, which led to a weight gain of 2 kg (BMI = 10.6 kg/m<sup>2</sup>). She was

transferred to a mental health unit, and mirtazapine 30 mg per day was initiated to manage both AN and depressive symptoms. After 1 week of therapy with mirtazapine, olanzapine 10 mg/d was initiated in addition to CBT, family therapy, and dietary intake of 1800 to 2200 calories/d. She experienced continued weight restoration and gained 6 kg over a 5-week hospitalization. Fear of food, distortion of body image, and compulsive ritualistic eating habits improved, and her depression was in remission at that time. She remained on mirtazapine 30 mg/d and olanzapine 10 mg/d for 6 months as an outpatient, and her weight further improved to 38 kg (BMI = 15.5 kg/m<sup>2</sup>) with no adverse effects or recurrence of depression.<sup>53</sup> As olanzapine was given together with mirtazapine, it is very difficult to interpret whether and what efficacy would directly apply to mirtazapine, olanzapine, and/or combinational therapy. In a case report by Safer et al<sup>52</sup> on a 50-year-old female (weight = 39.7 kg; 82.9% IBW) with refractory AN, depression, and anxiety, the use of mirtazapine 45 mg/d plus psychotherapy was associated with 18% weight gain (39.7 kg vs 46.7 kg; 97% IBW) over the course of several months, and she maintained this benefit at an 11-month follow-up.

## Discussion

Treatment of AN is difficult as there is a general lack of effective long-term treatment, and despite successful weight restoration in an acute phase, many patients relapse. The use of TCAs and MAOIs is not recommended, and use of bupropion is contraindicated due to safety reasons and lack of efficacy. Currently, the data for use of SSRIs and mirtazapine in adult anorexic patients are derived from a limited number of small, randomized, controlled trials; prospective and open-label studies; and case studies.<sup>40-43,45-53</sup> Large randomized, controlled trials are currently lacking. Previous studies typically did not control for antidepressant dose or type of adjunctive treatments and usually included only a small sample of AN participants, primarily those with AN-R.

In general, there is a lack of evidence for the use of SSRIs in underweight anorexic patients for specific AN-related symptoms and weight gain.<sup>40,41</sup> These findings are consistent with other published studies utilizing clomipramine, amitriptyline, cyproheptadine, and/or mirtazapine in underweight institutionalized patients with AN, pointing toward a general lack of efficacy of antidepressants to improve BMI or increase weight gain in underweight patients with AN during the acute treatment phase.<sup>54-58</sup> It was suggested that use of 5-HT increasing antidepressants in anorexic patients under starvation or without at least partially restored weight can lead to decrease/loss of antidepressant efficacy due to starvation-related various structural and biochemical/pharmacologic changes in the

brain.<sup>13,59</sup> A 2014 literature review by Phillipou et al<sup>13</sup> summarized neurobiological underpinnings of AN and starvation status. They reported that cortical sulci and ventricle enlargements were commonly seen in anorexic patients along with deficits in volumes of white and gray matter. From a functional standpoint, global brain glucose hypometabolism, especially in cortical areas, specifically the parietal and cingulate cortex, and deficit in serotonergic and dopaminergic systems were commonly identified in anorexic individuals. This is an important consideration as SSRIs' or TCAs' pharmacodynamic effects depend on presynaptic neuronal release of 5-HT and its binding to various subtypes of 5-HT receptors. Pharmacologic effects of serotonergic antidepressants may be compromised in underweight anorexic patients secondary to these structural and function brain changes. In addition, no improvement in fluoxetine efficacy for weight gain and/or improvement of anxiety or obsessive-compulsive symptoms was observed when administered with tryptophan (the precursor of 5-HT) to correct for decreased brain 5-HT levels under starvation.<sup>42</sup> It was reported that glucose hypometabolism and cerebrospinal fluid concentrations of 5-hydroxyindoleacetic acid (metabolite of serotonin) increased or normalized in weight-restored anorexic patients while increased 5-HT<sub>1A</sub> receptors and decreased 5-HT<sub>2A</sub> receptor bindings did not change after weight restoration.<sup>13</sup> These findings potentially explain the insufficient effect of nutritional supplementation with tryptophan on efficacy of fluoxetine in underweight anorexic patients during the acute treatment phase. In contrast, an open-label study demonstrated potential benefit of mirtazapine in a small sample of underweight inpatients undergoing weight restoration, possibly through its ability to reduce cortisol levels.<sup>43,44</sup>

After weight restoration, the major treatment goal is to prevent relapse and provide for weight maintenance in anorexic individuals. The data for SSRIs, especially fluoxetine, as adjunctive therapy for relapse prevention and psychiatric symptomatic improvements in weight-restored adult anorexic patients are somewhat more promising but inconclusive. Selective serotonin reuptake inhibitors, as adjunctive treatment, may offer relapse prevention and/or improvement of concurrent psychiatric symptoms (eg, depression, anxiety, obsessive-compulsive symptoms) and behavior for weight-restored anorexic patients that did not improve or remit after improvement of nutritional and BMI status.<sup>46-51</sup> When fluoxetine is used, the therapy should be slowly titrated to a maximum dose of 60 mg/d to decrease risk of dose-dependent adverse effects and treatment discontinuation. Fluoxetine dose of 20 to 60 mg daily may provide some benefit in relapse prevention, weight maintenance, and mood improvement in weight-restored AN-R while AN-BP individuals were not usually represented in the studies.<sup>46-48</sup> Citalopram 20 mg/



d was well tolerated, and its use was associated with significant improvement of psychiatric symptomatology in weight-restored individuals.<sup>49,50</sup> However, citalopram can be associated with a dose-dependent QT interval prolongation; thus the lowest effective dose should be used, and monitoring of electrocardiogram might be warranted in anorexic patients. This is specifically warranted when citalopram is used in higher doses or under circumstances of risk for hypokalemia and cardiovascular complications or in conjunction with other QT-prolonging therapy.<sup>35</sup> Use of sertraline 50 to 100 mg/d was associated with significant improvement of depressive symptoms, ineffectiveness, and perfectionism among weight-restored anorexic patients.<sup>51</sup> Mirtazapine use lacks strong clinical evidence from randomized, placebo-controlled trials; however, case reports illustrate its possible benefit in adults with AN and comorbid depression or anxiety at doses of 35 to 45 mg/d in conjunction with olanzapine or psychotherapy.<sup>52,53</sup> In addition, its ability to reduce cortisol production can be of potential benefit in anorexic patients.<sup>43,44</sup>

## Conclusion

The use of antidepressants as the sole therapeutic intervention for AN is unsupported, and these agents should only be used as adjunctive treatment to nutritional restoration and psychotherapy. There is a general lack of evidence to support use of SSRIs or mirtazapine during the AN acute treatment phase in underweight individuals. As a result, clinicians should not use antidepressants during hospitalization while patients are undergoing initial weight and nutritional restoration. At this time, the data are inconclusive regarding the place of SSRIs and mirtazapine and for their benefits in individuals with AN during the maintenance treatment phase once the weight is at least partially restored. Health care professionals should use clinical judgment in recommending fluoxetine or possibly citalopram, sertraline, or mirtazapine as adjunctive treatment to psychotherapy for relapse prevention and/or improvement of symptoms of depression and anxiety and/or obsessive-compulsive behaviors that did not to resolve with nutritional rehabilitation and psychotherapy. A combination of psychotherapy and different pharmacologic modalities may be used under the rationale that the efficacy of these treatments might be additive or perhaps synergistic to increase treatment success in weight-restored anorexic patients.

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