Anorexia nervosa in adults: Pharmacotherapy

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INTRODUCTION

Standard treatment for anorexia nervosa consists of nutritional rehabilitation and psychotherapy [1,2]. In addition, limited evidence supports augmentation with pharmacotherapy [1,3,4]; specifically, multiple randomized trials suggest that the antipsychotic olanzapine modestly enhances weight gain [5-7]. However, other psychotropic drugs have demonstrated little or no benefit in accelerating weight gain or relieving eating disorder cognitions [1].

Psychotropic pharmacotherapy for anorexia nervosa is reviewed here. The clinical manifestations, diagnosis, other treatments and outcome, and medical complications of anorexia nervosa and their management are discussed separately.

- (See "Anorexia nervosa in adults: Clinical features, course of illness, assessment, and diagnosis".)
- (See "Eating disorders: Overview of prevention and treatment", section on 'Anorexia nervosa'.)
- (See "Anorexia nervosa in adults and adolescents: Nutritional rehabilitation (nutritional support)".)
- (See "Anorexia nervosa in adults: Cognitive-behavioral therapy (CBT)".)
- (See "Anorexia nervosa in adults and adolescents: Medical complications and their management".)

- (See "Anorexia nervosa in adults: Evaluation for medical complications and criteria for hospitalization to manage these complications".)

INDICATIONS

Pharmacotherapy is not an initial or primary treatment for anorexia nervosa [1,4]. However, add-on pharmacotherapy with low dose olanzapine may help acutely ill patients who do not gain weight despite first line treatment with nutritional rehabilitation and psychotherapy. In addition, adjunctive pharmacotherapy may possibly help reduce depressive symptoms. Distorted thinking about body image and food usually does not respond to pharmacotherapy, nor do maintenance medications help delay or prevent subsequent episodes of anorexia nervosa.

GENERAL PRINCIPLES

For patients with anorexia nervosa, standard treatment consists of nutritional rehabilitation and psychotherapy, which are supported by far more evidence than pharmacotherapy [1,4]. Medications are used only for patients who do not respond to initial, standard treatment; if pharmacotherapy is added to the treatment regimen, the focus of treatment needs to remain upon nutritional rehabilitation and psychotherapy.

Many patients with anorexia nervosa refuse pharmacotherapy [8], particularly medications with side effects that include weight gain and the metabolic syndrome. This refusal stems from symptoms of anorexia nervosa that include lack of recognition of the seriousness of the disorder and ambivalence about weight gain [9]. It may be possible to overcome this resistance through negotiation and motivational interviewing (motivating the patient to gain weight by eliciting both the patient's reasons to do so and the patient's ambivalence about change) [10]. Parents of adolescents may also refuse consent due to general concerns about drug safety, which may be allayed with education.

For patients with anorexia nervosa who consent to medications, clinicians should initially prescribe a small dose because low weight patients are at increased risk for side effects [1,4,10]. In addition, depletion of body protein increases the percentage of unbound (free) drug in serum and depletion of body fat decreases the volume of distribution. Pharmacokinetic problems such as poor drug absorption or toxicity can occur because of starvation, vomiting, dehydration, or excess hydration. The antidepressant bupropion should be avoided because it is associated with

a higher incidence of seizures in patients with eating disorders, particularly patients who binge-eat and purge [1,11].

Clinicians should consider the medical complications of anorexia nervosa when selecting a medication. As an example, starvation can cause bradycardia, hypotension, diminished heart rate variability, and the long QT syndrome [12]. Thus, drugs that prolong cardiac conduction (table 1), such as antipsychotics and antidepressants, should be used cautiously in malnourished patients. Tricyclic antidepressants should not be used because of their potential cardiotoxicity. The medical complications of anorexia nervosa are discussed separately. (See "Anorexia nervosa in adults and adolescents: Medical complications and their management".)

We do not use medication combinations in patients with anorexia nervosa because there are no compelling data to support this approach.

EVIDENCE OF EFFICACY

Multiple randomized trials suggest that the antipsychotic olanzapine is helpful in restoring weight [5,6]. However, other psychotropic drugs have demonstrated little or no benefit for weight gain and other therapeutic targets [1,4,13,14].

There are several possible explanations for the general lack of demonstrated efficacy of pharmacotherapy in anorexia nervosa. Starvation and alterations in neurotransmitter function may prevent response to medication [15]. In addition, restrictive eating behavior may become so neurobiologically entrenched that it is impervious to medications [16]. Further, relatively few rigorous trials have been conducted [1,17], and many patients refuse to participate in randomized pharmacotherapy trials or drop-out after enrollment; these problems make it difficult to interpret the results and to demonstrate a beneficial effect [8]. As an example, a one-year randomized trial with 122 patients found that 55 percent dropped out, and much of the attrition occurred within the first five weeks [8]. In a 16-week randomized trial with 152 patients, approximately 45 percent of patients discontinued treatment [7].

Most randomized trials of pharmacotherapy have been conducted within multimodal programs that specialize in eating disorders and are based at academically-affiliated hospitals [10]. For anorexia nervosa patients who do not have access to specialized treatment, pharmacotherapy may conceivably provide greater benefits than those observed in the trials.

Weight gain — The primary goal of treatment in medically stable patients with anorexia nervosa is weight gain [1,4].

Antipsychotics

Olanzapine — For acutely ill patients who receive first line treatment with nutritional rehabilitation plus psychotherapy but do not gain weight, we suggest add-on treatment with olanzapine 2.5 mg to 10 mg per day. Olanzapine has been more widely studied for treatment of anorexia nervosa than any other antipsychotic [18,19], and multiple randomized trials suggest that olanzapine may help restore weight. In addition, the drug is generally well tolerated, with no indication of the adverse metabolic effects frequently observed when olanzapine is prescribed for other disorders. This may be related to olanzapine's modest effect on weight gain in anorexia nervosa, with the largest trial reporting that patients on olanzapine gained only an average of 1.5 pounds per month. Evidence supporting the use of olanzapine includes the following:

- A 16-week trial compared olanzapine (mean dose 8 mg/day) with placebo in 152 outpatients; nearly all of the patients were female, the mean duration of anorexia nervosa was approximately 12 years, and the average number of comorbid psychiatric diagnoses (eg, anxiety disorder or depressive disorder) was two [7]. Improvement of weight was modestly superior with olanzapine than placebo, such that weight gain with olanzapine was approximately 1.5 pounds per month, which exceeded weight gain with placebo by approximately one pound per month. Improvement of obsessional thoughts and eating disorder cognitions (eg, concerns about eating or body shape) was comparable for the two groups. Attrition was high in both groups; during the study, approximately 45 percent of patients in each group discontinued treatment.

- A 10-week trial compared olanzapine (mean dose 7 mg/day) with placebo in 34 female patients attending a day hospital program that included supervised meals and group therapy [5]. The body mass index (calculator 1) at baseline was approximately 16 kg/m^2. More patients treated with olanzapine achieved the target body mass index of 18.5 kg/m^2, compared with patients who received placebo (88 versus 56 percent). In addition, improvement of obsessional thoughts was greater with olanzapine.

- An eight-week trial compared olanzapine (mean dose 8 mg/day) with placebo in 23 outpatients, nearly all of whom were female [6]. Weight gain was more rapid with olanzapine than placebo; however, improvement of obsessional thoughts and eating disorder cognitions (eg, concerns about eating or body shape) was comparable for the two groups.

Nevertheless, the published experience is limited, and there are concerns about the durability of benefits, as well as metabolic complications and other problems that may arise with long-

term treatment. In addition, two small randomized trials found that the benefits of olanzapine and placebo for weight gain in anorexia nervosa were comparable:

- A three-month trial compared cognitive-behavioral therapy (weekly individual sessions) plus olanzapine (5 mg/day) with cognitive-behavioral therapy plus placebo in 30 outpatients [20]. Improvement of body mass index was comparable for the two groups.

- A 10-week trial compared olanzapine (target dose 10 mg/day) with placebo in female, adolescent inpatients, day hospital patients, and outpatients (total n = 20), who were treated at an eating disorder program that included nutritional rehabilitation and different types of psychotherapy [21]. Weight gain for the two groups was comparable.

Other antipsychotics — There are no compelling data that antipsychotics other than olanzapine, such as risperidone, quetiapine, or aripiprazole, help restore weight in anorexia nervosa:

- Risperidone – A randomized trial compared risperidone (mean dose 2.5 mg per day) with placebo for up to approximately 18 weeks in 40 adolescent and young adult females (mean age 16 years) with anorexia nervosa and found no benefit with risperidone [22].

- Quetiapine – A small, eight-week randomized trial (n = 15) found no advantage for quetiapine (mean does 178 mg per day) over placebo [23].

- Aripiprazole – A retrospective study of adolescents hospitalized for anorexia nervosa found that the average increase in body mass index was greater in patients who received aripiprazole (1 to 5 mg/day; n = 22) than in patients who did not (n = 84) [24]. However, no randomized trials of aripiprazole in anorexia nervosa have been reported.

Antidepressants — There are no compelling data that adjunctive antidepressants help restore body weight in patients with anorexia nervosa [4,13,14,17]. As an example, multiple reviews have found that neither tricyclic antidepressants nor selective serotonin reuptake inhibitors helped ameliorate symptoms of anorexia nervosa [25,26].

Other medications — The addition of D-cycloserine to exposure-based therapy (focused upon extinguishing anxiety and fears) for anorexia nervosa showed some evidence of benefit for weight gain in one of two small randomized trials [27,28].

Although some clinical experience and treatment guidelines suggest that an anxiolytic at a low dose may possibly reduce anticipatory anxiety when patients with anorexia nervosa confront a meal [1,10], one study suggests that this practice may not be beneficial. A crossover trial compared a single pre-meal dose of alprazolam (0.75 mg) with placebo on different days in

medically stable patients (n = 17) who were randomly assigned to the order in which they received each study drug [29]. Both mean caloric intake and anxiety were comparable for alprazolam and placebo, but fatigue was greater with alprazolam.

Other randomized trials indicate that cyproheptadine, cannabinoids, lithium, zinc, omega-3 fatty acid supplementation, and testosterone provide little or no benefit compared with placebo [14,17,30-32].

Distorted thoughts about body image and food — Obsessional thoughts and eating disorder cognitions about body image and food generally does not respond to pharmacotherapy. A meta-analysis of five randomized trials compared the effect of antipsychotics with placebo in 114 patients with anorexia nervosa; patients were assigned to olanzapine (n = 30), quetiapine (n = 15), sulpiride (n = 9), placebo (n = 42), or treatment as usual in the one open-label trial (n = 18) [33]. The effects of antipsychotics and placebo/usual care upon distorted thoughts about body image and food were comparable. Additional evidence regarding olanzapine's general lack of efficacy for obsessional thoughts and eating disorder cognitions is discussed elsewhere in this topic. (See 'Olanzapine' above.)

Randomized trials have found that antidepressants provide no benefit for treating eating disorder psychopathology [13,34].

Relapse prevention — After restoration of body weight and normal eating behavior, relapse with substantial weight loss occurs frequently [35]. Patients receiving standard treatment with maintenance psychotherapy do not benefit from adjunctive pharmacotherapy. A one-year randomized trial compared adjunctive fluoxetine (average dose: 63 mg per day) and placebo in 93 adult patients who remitted from an episode of anorexia nervosa [34]. All patients received weekly maintenance cognitive-behavioral therapy, and supplemental family therapy was also available. The proportion of patients who maintained a normal body mass index was similar for fluoxetine and placebo (27 versus 32 percent), and time to relapse was also similar for the two groups.

Comorbid psychopathology — Depressive disorders, anxiety disorders, and obsessive-compulsive disorder are common in anorexia nervosa [1,4]. (See "Anorexia nervosa in adults: Clinical features, course of illness, assessment, and diagnosis", section on 'Comorbidity'.)

Management of comorbid psychopathology depends upon its severity. Standard treatment of anorexia nervosa with nutritional rehabilitation plus psychotherapy often resolves mild to moderate comorbid depressive or anxiety disorders [1,25]. For patients with severe comorbid depression or anxiety that persists despite weight restoration, we use antidepressants, such as a selective serotonin reuptake inhibitor (eg, sertraline, 100 to 200 mg daily); selective serotonin

reuptake inhibitors are generally well tolerated. Tricyclic antidepressants should be avoided because of concerns about cardiotoxicity in malnourished patients, and bupropion is contraindicated in patients with eating disorders because it is associated with a higher incidence of seizures in patients with eating disorders. (See 'General principles' above.)

Weak evidence supporting the use of an antidepressant for severe comorbid depressive syndromes includes a meta-analysis of two small randomized trials that compared an antidepressant with placebo in patients with anorexia nervosa and depressive symptoms (total n = 88) [4]. Improvement of depression was greater in patients who received antidepressants than placebo.

Multiple randomized trials indicate that antipsychotics such as olanzapine do not ameliorate symptoms of depression or anxiety [5-7].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Eating disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient education: Anorexia nervosa (The Basics)")

SUMMARY AND RECOMMENDATIONS

- The standard treatment for patients acutely ill with anorexia nervosa is nutritional rehabilitation plus psychotherapy. However, patients not gaining weight despite standard treatment are candidates for adjunctive pharmacotherapy. (See "Eating disorders: Overview of prevention and treatment", section on 'Anorexia nervosa' and 'Indications' above.)

- Low weight patients treated with pharmacotherapy are at increased risk for side effects and should initially receive a small dose. Bupropion should not be used because it is associated with a higher incidence of seizures in patients with eating disorders. Medical complications of anorexia nervosa should also be considered. As an example, drugs (table 1) that impact cardiac function, such as antipsychotics and antidepressants should be used cautiously in malnourished patients. Tricyclic antidepressants should not be used because of their potential cardiotoxicity. (See 'General principles' above and "Anorexia nervosa in adults and adolescents: Medical complications and their management".)

- For acutely ill patients not gaining weight with nutritional rehabilitation plus psychotherapy, we suggest add-on treatment with olanzapine 2.5 mg to 10 mg per day, rather than other medications (**Grade 2C**). (See 'Olanzapine' above and 'Other medications' above.)

- Obsessional thoughts and eating disorder cognitions about body image and food generally do not respond to pharmacotherapy. (See 'Distorted thoughts about body image and food' above.)

- The treatment of choice for patients who have recovered from an episode of anorexia nervosa is maintenance psychotherapy; adjunctive pharmacotherapy is not beneficial. (See "Eating disorders: Overview of prevention and treatment", section on 'Psychotherapy' and 'Relapse prevention' above.)

- Mild to moderate comorbid depressive or anxiety disorders often resolve with standard treatment consisting of nutritional rehabilitation plus psychotherapy. For severe comorbid disorders that do not respond to standard treatment, it is reasonable to initially try a selective serotonin reuptake inhibitor. (See 'Comorbid psychopathology' above.)

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