Pharmacologic Treatment of Anorexia Nervosa: Where Do We Go from Here?

Introduction

Anorexia nervosa (AN) is a potentially life-threatening disorder, characterized by severe low weight, cognitive distortions about body shape and weight, and amenorrhea in women. AN is associated with a range of psychological symptoms, including depression, anxiety, obsessions, and rituals. The current study summarized findings from randomized controlled trials (RCT) using pharmacologic treatments in patients with AN. We conducted a review of literature using Medline. Several classes of pharmacologic agents have been studied in small samples of patients with acute AN without finding clear benefit to eating, weight, body shape concerns, or associated psychopathology. Studies have been limited by small sample sizes, as well as by research design with most studies adding medication to comprehensive hospital-based treatment programs. Future directions for pharmacologic treatment research in AN should include outpatient trials, rigorous study of atypical antipsychotic medication, and assessment of medication effect for relapse prevention in weight-restored patients.

Medication Studies

Antipsychotics

In the 1960s, Dally and Sargant conducted the first trial of antipsychotic medications in AN. The trial included 30 patients hospitalized for AN who received up to 1,600 mg/day of chlorpromazine and 27 patients who received no medication. Although the patients who received chlorpromazine did show greater initial weight gain and were discharged more rapidly than those who received no medication, they also experienced significant side effects such as seizures and increased purging. The antipsychotic medications pimozide and sulpiride were also examined in double-blind, placebo-controlled studies. Although pimozide resulted in weight gain compared with placebo, sulpiride offered no significant benefit. Neither medication improved patients’ attitudes or behaviors.

The significant side effect profile of traditional antipsychotic medications together with the limited evidence for their clinical benefit have kept these agents from being considered in routine care of patients with AN. The recently developed atypical antipsychotic medications, with their more manageable side-effect profile, have again raised the
question of whether antipsychotic medication may have a role in the treatment of AN. Olanzapine has been described in several case reports\(^5\)-\(^7\) and one open trial\(^8\) as being associated with effective and sustained weight gain and some psychological improvement in AN patients. A controlled clinical trial is the necessary next step in determining whether these novel medications may, indeed, prove helpful to patients with AN.

**Antidepressants**

The common occurrence of depressive symptoms in patients with AN has led to several trials of antidepressants in these patients. Unfortunately, controlled trials of these medications have been consistently disappointing in identifying helpful medication strategies for underweight AN patients. In a placebo-controlled trial of clomipramine conducted by Lacey and Crisp,\(^9\) hospitalized patients receiving active medication showed increased appetite, but gained weight less rapidly than those assigned to placebo. Follow-up assessments at 1 and 4 years found no long-term impact on weight gain in patients taking clomipramine. In two trials, conducted separately by Biederman et al.\(^10\) and Halmi et al.\(^11\) amitriptyline showed no benefit when contrasted with placebo. Patients assigned to amitriptyline in these trials showed neither increased weight gain nor a decreased concern with shape and weight.

Selective serotonin reuptake inhibitors (SSRIs) were believed to hold promise for AN patients, both because of their antidepressant effects and their known benefit for patients with bulimia nervosa.\(^12\) Nevertheless, Attia et al.\(^13\) found that fluoxetine offered no benefit as compared with placebo to inpatients with AN undergoing weight restoration. Discussion of this and other negative medication trials using antidepressants has included the hypothesis that underweight individuals may have neurochemical disturbances that interfere with medication effects. Specifically, groups have proposed that disturbances in serotonin function in the central nervous system may be responsible for poor medication response in patients with acute AN.\(^14\) Barbarich et al.\(^15\) attempted to add nutritional supplementation to fluoxetine in a recent randomized, placebo-controlled study. The investigators assigned patients to receive the supplement, including tryptophan (serotonin’s precursor), and other vitamins, minerals, and oils believed to be involved in serotonin function, or placebo in addition to fluoxetine (dose range 20–60 mg). Among the study’s 26 subjects, the authors found no significant differences in weight gain or psychological measures between active medication and placebo groups.

There are, however, data to suggest that fluoxetine may be helpful in preventing relapse in weight-restored patients with AN. Kaye et al.\(^16\) conducted an open trial comparing fluoxetine and placebo in patients who had restored their weight after hospitalization. Of the 31 women assigned to take fluoxetine, 29 maintained a weight above 85% of ideal body weight at follow-up (11 ± 6 months). Although these data are encouraging, follow-up studies conducted separately by Kaye et al.\(^17\) and Strober et al.\(^18\) are inconclusive as to the utility of fluoxetine in preventing relapse. Strober et al. performed a case-controlled follow-up study in which fluoxetine showed no beneficial effect on the need for rehospitalization or tendency to fall below target weight. Kaye et al. completed a double-blind, placebo-controlled study of patients with AN for 1 year after acute weight restoration. The investigators did not control for dose or additional treatment some patients received while participating in the study, but did find that patients who were assigned fluoxetine were significantly more likely to be at or near normal weight at the conclusion of treatment than those assigned to placebo. A definitive study is necessary to examine the effect of fluoxetine on relapse prevention in weight-restored patients.

**Other Medications**

**Prokinetic Agents**

The prokinetic agent cisapride was hypothesized by Stacher et al.\(^19\) to be useful in patients with AN due to the documented slower motility found in AN patients. The investigators randomized 12 outpatients with AN to 10 mg cisapride or placebo three times daily for 6 weeks, followed by open treatment with cisapride for an additional 6 weeks. The results, although statistically insignificant, showed improvement in patients taking cisapride in outcome measures of gastric emptying, gastric complaints, and weight gain. A subsequent double-blind, placebo-controlled study conducted by Szmukler et al.\(^20\) randomized 29 patients to cisapride or placebo for an 8-week period. Although some subjective measures showed improvement in patients assigned to take cisapride, there was no significant correlation between gastric emptying and either weight gain or subjective measures. Since the completion of these trials, cisapride has been removed from the market.
because of its association with QTc prolongation and reports of torsade de pointes arrhythmia.

**Opiate Antagonists**

Investigation of opiate antagonists in patients with AN has been based on the theory that eating disorders and substance use disorders may have common elements. Small open trials of naloxone infusions and oral naltrexone have in fact shown consistent weight gain in underweight patients with AN, and may deserve further study. Marrazzi et al. did conduct a randomized, double-blind, placebo-controlled study of naltrexone (100 mg twice daily), in which patients receiving active medication showed clinically significant improvement in eating behavior, such as binge eating and purging. The trial was limited, however, by the fact that neither rates nor amounts of weight gain were measured.

**Lithium**

Lithium has been shown in a small placebo-controlled study of short duration to affect weight gain in patients with AN. A controlled trial that included a larger number of patients and a longer duration would be needed to determine the efficacy of lithium in this population.

**Cyproheptadine**

Cyproheptadine is a centrally-acting serotonin antagonist, with neurochemical effects in contrast to those of SSRIs. Cyproheptadine has been used most prominently as an antiallergy agent, and was linked to weight gain. In a placebo-controlled study conducted in 1977 by Vigersky et al. and in the Halmi et al. study comparing amitryptiline, cyproheptadine, and placebo, cyproheptadine showed no benefit compared with placebo. A later study carried out by Goldberg et al., which used a higher dose of medication in a larger sample of patients, found that cyproheptadine was associated with significant weight gain in patients with the restricting subtype of AN. The greater medication effect on one subtype of patients may support the concept that restricting and binge/purge behaviors are associated with hyperserotonergic and hypo-serotonergic states, respectively, and further study would be needed to clarify this observation.

**Tetrahydrocannabinol (THC)**

THC has been studied in AN because of its appetite-stimulating effects. Results of a 4-week randomized, double-blind study of 11 patients with AN that compared oral THC with diazepam showed no benefit of THC on caloric intake, daily weight gain, or psychological symptoms. In addition, THC was associated with negative side effects such as paranoia, sleep disturbance, and interpersonal sensitivity. A number of patients actually dropped out of the study due to the side effects they were experiencing.

**Zinc**

Patients who are zinc deficient may experience appetite change, weight loss, depression, and amenorrhea. It has therefore been theorized that a zinc deficiency associated with the starvation that characterizes AN may contribute to patients’ psychopathology. Three separate double-blind, placebo-controlled studies of zinc supplementation in patients with AN have failed to show conclusive evidence to support zinc supplementation in this population.

---

**Conclusions**

As have most reviews of the literature regarding the utility of medication in AN, the current summary has pointed out several small gaps in an extensive list of interventions considered, and highlighted a few potential pharmacologic treatments that could benefit from larger, more definitive trials. However, a more fundamental question is this: Why have the medication trials conducted to date been so uniformly discouraging? The medication studies in AN conducted heretofore have been driven by two general hypotheses—that appetite stimulation is needed and that symptoms associated with AN such as depression and anxiety can be treated and will thereby improve the core disorder. It is curious for several reasons that these have been the primary avenues of investigation for clinical trials in this population. For example, whereas patients with AN have lower ratings for hunger and higher ratings for satiety on assessment measures, there is a relative lack of evidence for any physiological disturbance in appetite. In addition, the depressive symptoms seen in AN have been shown to be largely reversible with refeeding.

Given these contradictions, it is time to revisit the questions: What is the problem with AN? Or, more precisely: What core features of AN might be amenable to pharmacologic interventions? For example, is it possible that recurring and rigid cognitive processes characteristic of this illness are related both to poor medication response and to high recidivism? Might the recent reports of success with olanzapine derive from this medication’s...
known effect on thought content and process and not any direct effect on appetite or weight? Our limited understanding of the psychobiology of AN and how the biologic disturbances are linked to cognitive-behavioral disturbances hampers our ability to identify promising pharmacologic and psychological interventions.

Additional studies of the psychobiology and treatment of AN are crucial to advance the field and identify successful therapeutic strategies.

References