



## How much do we really know about the effectiveness of olanzapine use in patients with anorexia nervosa?



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“Olanzapine binds to various receptors ... which in combination have the potential to influence patient’s anxiety levels, appetite, mood, sleep and cognitions.”

Olanzapine first received US FDA approval for the treatment of psychotic disorders in 1996. Although it has only formally been approved for the treatment of schizophrenia, bipolar disorder and treatment-resistant depression when used in combination with fluoxetine, the drug is used off-label for the treatment of many other disorders, including anorexia nervosa (AN). As with other atypical antipsychotic medications, the exact mechanism of action is not known, but is believed to be the combination of effects on dopamine and serotonin activity. Olanzapine binds to various serotonergic and dopaminergic receptors, as well as to muscarinic, histaminic and  $\alpha$ -adrenergic receptors, which in combination have the potential to influence patient’s anxiety levels, appetite, mood, sleep and cognitions. Major side effects associated with olanzapine include weight gain and sedation. As a result, it is plausible that the medication could facilitate weight gain in AN patients while at the same time helping to decrease their overall food- and weight-related anxiety.

The first case report suggesting that olanzapine might be useful for the augmented treatment of AN appeared in 1999 [1]. In the years that followed, numerous uncontrolled reports were published touting olanzapine’s efficacy as an agent helpful in decreasing anorexic ruminations as well as facilitating weight gain in both adolescent and adult patients. Although these case studies and open trials were useful in raising awareness of olanzapine as a potential treatment for AN, it was recognized that randomized controlled trials (RCTs) were needed. To date, we are aware of five published placebo-controlled RCTs that have since been published investigating olanzapine’s utility in the treatment of AN, four of which were conducted in adult patients [2–6]. Our own experience over the years has been that such trials are extremely difficult to conduct given the host of potential barriers that exist, most notably related to problems with enrollment and consent [7]. The issue of attrition and enrollment difficulties has plagued eating disorder drug

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trials since their inception, with dropout rates of over 50% reported in trials of adults with AN treated with fluoxetine [8].

The first of the adult RCTs was published by Mondraty *et al.* in 2005 [2]. In this small non-blinded trial, the authors set out to compare olanzapine to chlorpromazine in their effects on both weight gain and anorexic cognitions. With 17 female inpatients completing the trial, the investigators found a significant decrease in ruminative thinking as determined by changes on two distinct psychological measures. There were no documented differences in weight between groups. In the second RCT published in 2007 of 15 AN outpatients receiving individual cognitive behavior therapy, Brambilla *et al.* found that olanzapine helped patients to gain weight faster, especially for those with AN–binge/purge subtype; the olanzapine-treated group as a whole showed greater improvement in levels of depression, anxiety, obsessiveness and aggressiveness when compared with the placebo group [3]. Despite these improvements, the study failed to demonstrate any significant differences related to eating habits or more typical AN symptoms. Bissada *et al.* completed the largest double-blinded RCT in which adult females attending a day treatment program were treated with either olanzapine or placebo. The authors showed that olanzapine use resulted in a greater rate of weight gain, earlier achievement of target BMI, and a greater reduction in obsessive symptoms when compared with the placebo-treated group [4]. The study, although well designed, struggled with recruitment issues at every arm of patient entry and ran over a period of 5 and a half years; 28 patients completed the trial. More recently, Attia *et al.*'s placebo-controlled RCT investigating olanzapine's usefulness in an outpatient setting for AN reported higher end-of-study BMIs and greater rates of weight gain in the olanzapine group, although the study failed to distinguish any significant differences on psychological measures [5]. Of the 603 AN patients that inquired about this study, 197 met inclusion criteria, 87 completed the telephone screening and 23 eventually enrolled. Of those, 17 completed the 8-week trial [5]. Of note, the patients in Attia's study received no 'extra' programming or support, unlike the previously cited studies, suggesting that the medication on its own (or in a limited treatment context) could help facilitate weight gain.

Given the complexities associated with clinical trials involving this cohort of patients, it is no wonder that over a decade after the first case

reports appeared we have just five RCTs to help guide our decision-making in this area. It is also not surprising that the evidence base in adolescent patients remains largely nonexistent despite attempts to further our understanding using well-designed studies. These young patients often present in crisis, are psychologically and medically unstable, and not interested in treatment. Typically, parents as well as patients must give consent to join a study. In the only RCT involving adolescents (Kafantaris *et al.*), only 15 patients completed the trial [6]. The authors describe a total of 190 patients screened, of whom 94 met eligibility criteria; of these, 74 declined to participate in the study, and 20 subjects were ultimately randomized to receive medication or placebo. This study ran over a 4-year period, and likely at considerable cost. It is very similar to our own experience, in which after 2 years we had a total of seven patients complete our RCT [9]. The Kafantaris study revealed no observable effect on weight gain or psychological measures resulting from olanzapine use, which is not surprising given the sample size. Given the fact that renourishment is typically controlled in intensive treatment settings, small sample sizes likely prohibit the detection of significant differences in weight gain. As such, investigators might be better served using psychological variables as the primary outcome measure, rather than weight gain in these circumstances. However, this presents other problems as many patients tend to be extremely defensive or in denial of their illness, so that psychological measures frequently show a worsening of depression and anxiety with treatment, as weight gain ensues and body image worsens. One could also argue that large effect sizes might be needed to justify the use of olanzapine for most young AN patients, given increasing concerns around metabolic side effects [10].

Within our own program, we began using olanzapine to help augment treatment-resistant cases of AN 12 years ago. Over the first 5 years, the drug was reserved for cases in which our 'standard' treatment (renourishment plus a combination of Maudsley family therapy and individual therapy) failed. In select cases, we found that the medication helped resistant patients to gain weight more consistently while at the same time decreasing their levels of agitation and anxiety [11]. We knew only of the side effects reported in adult populations at doses used to treat schizophrenia, but found ourselves rarely needing to increase doses beyond 5 mg a day. We found the

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medication useful for helping some especially resistant and agitated patients progress in their treatment. It was these observations that led to our design of a RCT of olanzapine as adjunctive treatment for adolescent AN [9]. As part of our research, we also completed a retrospective study examining our use of olanzapine in inpatient and outpatient treatment settings [12]. As expected, we found that treated patients tended to be more severely ill than those not treated, and to have more comorbid psychiatric illnesses. In an attempt to help further clarify the role of olanzapine across adolescent treatment settings, we are continuing to study the medication, now using an open-label trial design. Our continued experience has also taught us that the medication is not necessarily as benign as we might like, and that our patients, even at low weights, are at a small but real risk for adverse events, including diabetes, elevated liver enzymes, dyslipidemia and prolonged QTc syndrome [12,13].

Taking all of the current published studies into consideration, there is enough evidence to suggest that olanzapine confers a treatment advantage to adult patients with AN, but there is insufficient evidence to recommend it in the pediatric population as a first-line treatment. The challenges for the future involve how to fund, conduct and complete the RCTs needed to determine the efficacy and safety of medications such as olanzapine, especially in children

and adolescents with severe eating disorders. This medication has been used clinically for over a decade now, yet the first RCT in adolescents finally appeared in 2011, and involved just 15 subjects. It would be advantageous for all investigators interested in studying this and similar questions to work collaboratively to standardize methodologies (potentially across different treatment settings). If investigators could agree upon outcome measures, drug dosing and other facets of trial design it could potentially allow for the analysis of multiple data sets across different sites and completed at different times. In an era where grant money is becoming increasingly difficult to access, it is essential that such challenging trials are conducted in a manner which makes not only financial sense, but offers the greatest likelihood of successful completion while at the same time providing results that are generalizable.

#### Financial & competing interests disclosure

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