Low-Dose Olanzapine in the Treatment of Adolescents with Anorexia Nervosa: An Observational Naturalistic Case-Control Study

Title

Low-dose olanzapine in the treatment of adolescents with Anorexia Nervosa. An observational, naturalistic, case-control study

Running title

Low-dose olanzapine for Anorexia Nervosa

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Abstract

Background: Although recent articles have investigated the use of low-dose olanzapine in different psychiatric conditions, only one study so far has assessed this treatment in 13 girls with Anorexia Nervosa (AN).

Methods: Observational, naturalistic, case-control study, aimed at reporting the use and tolerability of low-dose olanzapine in the context of a multidisciplinary hospital intervention for adolescents with AN. Three groups with AN were compared: group 1 was treated with low-dose olanzapine (≤5 mg/day), group 2 with full-dose olanzapine (>5 mg/day), group 3 (control group) was treated without antipsychotics. Psychopathology was assessed at admission (T0) and discharge (T1) with Eating Disorders Inventory-3 Eating Disorders Risk (EDI-3-EDRC), Body Uneasiness Test Global Severity Index (BUT-GSI), Beck's Depression Inventory-II (BDI-II), and Self-administered Psychiatric Scales for Children and Adolescents, Depression subtest (SAFA-D). Possible differences among the 3 groups, concerning clinical and treatment variables, were screened. Then, potential differences of T0-T1 modifications in psychopathological variables among the 3 treatment groups were assessed with ANCOVAs, corrected for baseline psychopathology and potential confounders, including possible concurrent antidepressants.

Results: one hundred-eighteen patients were enrolled (F=94.1%; mean age=15.4+/-1.7 years), including 52 controls, 37 treated with low-dose olanzapine, and 29 with full-dose olanzapine. Low-dose olanzapine was well tolerated and used for a mean of 132.1 (+/-98.6) days, starting with a dosage of 3.4 (+/-1.2) mg/day and increasing to a maximum dose of 4.4 (+/-1.1) mg/day. The multidisciplinary intervention resulted in an improvement of BUT-GSI ($p<0.001$), BDI-II ($p<0.001$), and SAFA-D ($p<0.001$) for the entire sample. Individuals treated with full-dose olanzapine experienced a significantly lower improvement in depressive measures: BDI-II ($F(2,61)=12.653$, $p<0.001$, $\eta 2=0.269$) and SAFA-D ($F(2,57)=7.413$, $p=0.001$, $\eta 2=0.170$), than the other groups.

Discussion: this naturalistic, controlled study expands the existing evidence on the use and tolerability of low-dose olanzapine in adolescents with AN. These results should be assessed in wider and prospective samples.

Keywords

Low-dose, olanzapine, anorexia nervosa, eating disorders, children and adolescents, psychopharmacology

Introduction

Recent guidelines for the treatment of Anorexia Nervosa (AN) in children and adolescents propose the use of atypical antipsychotics (AAP) in the management of low-weight patients in selected conditions (Couturier et al. 2020). Despite a general paucity of data, olanzapine presents the most relevant evidence for the treatment of AN among AAP (Couturier et al. 2020). A randomized-controlled clinical trial documented the use of olanzapine in 15 children and adolescents with AN, showing no significant difference between olanzapine and placebo concerning weight or psychological outcomes (Kafantaris et al. 2011). More promising results have been reported in nonrandomized case-control studies, particularly on hyperactivity (Couturier et al. 2020). Besides its clinical effects, olanzapine has a series of documented side effects in subjects with AN, including increasing fasting glucose and insulin levels (Kafantaris et al. 2011), sedation, and dyslipidemia (Norris et al. 2011), or QTc prolongation (Ritchie and Norris 2009). For this reason, recent studies have focused on the possible effect of antipsychotic treatments with low-dose olanzapine in diverse mental health populations. Concerning the use of low-dose olanzapine in children and adolescents with AN, a single study has been published so far, examining 13 female subjects (Leggero et al. 2010). The final mean dosage was 4.1 (+/-2.9) mg/day, with a wide administration range (1.25–2.5 mg/day in 8 patients, 3.75–12.5 mg/day in 5 patients). The authors reported improvement of both body-mass index (BMI), global functioning, and hyperactivity with minimal side effects (Leggero et al. 2010). Unfortunately, an established definition of “low-dose treatment with olanzapine” is not yet available in the literature. A relevant definition is provided by a recent population-based, longitudinal cohort study, assessing potential associations between off-label low-dose olanzapine or quetiapine and cardiometabolic mortality (Berge et al. 2021). Low-dose olanzapine (reported as olanzapine-equivalents) was defined at ≤5 mg/day (Berge et al. 2021). Conflicting definitions are reported by other studies on schizophrenia (5 mg/day) (Lin et al. 2017), major depressive disorder (1.25 - 2.5 mg/day) (Zhong et al. 2014), or Parkinson’s disease (2.5 to 7.5 mg/day) (Manson et al. 2000).

The primary aim of the present study is to report on the use of low-dose olanzapine in a sample of children and adolescents for AN, in the context of a multidisciplinary hospital treatment. This sample will be compared to a group of similar patients treated with full-dose olanzapine and to a control group of similar subjects receiving no antipsychotic treatment. The secondary aim of this study is to identify possible differences in the variation of eating disorder psychopathology and depressive symptoms among these 3 groups from hospital admission to discharge. In line with the existing literature, we propose that treatment with low-dose olanzapine may be more tolerable than treatment with full-dose olanzapine, without reduction of the global efficacy of the hospital treatment of the psychopathology.

2. Methods

2.1. Study design and participants

This is a case-control, observational retrospective study. The study took place in the context of an observational survey investigating the use of psychopharmacological treatments in a third-level Regional Center for Feeding and Eating Disorders in Children and Adolescents, and was approved by the local ethical committee (Comitato Etico di Area Vasta Emilia Centro della Regione Emilia-Romagna, CE-AVEC) (Protocol code NPI-DAPSIFA2020, study code 9/2021/Oss/AOUBo). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were observed during the planning and execution phases of the study (von Elm et al. 2007). The study was not sponsored or funded by any company.

The study was conducted in December 2021 by retrospectively considering patients only assessed at the study Center between 01/01/2016 and 31/12/2020, and with at least one hospitalization for Eating Disorders (ED) in the same Center. Hospitalization was defined as an inpatient or day hospital treatment. The day-hospital treatment program for patients with ED is comparably structured and as intensive as inpatient treatment. The hospital program adopted in our Center has been described previously (Pruccoli et al. 2021), and entails a multidisciplinary psychological, psychopharmacological, and nutritional intervention. All 3 groups were subjected to the same multidisciplinary program, performed by the same team, in the same Center, following clinical international guidelines (NICE, 2017).

Inclusion criteria were a) a diagnosis of AN according to the DSM-5 criteria; b) either treatment with low-dose olanzapine (defined as maximum reached dosage ≤5 mg/day) (Berge et al. 2021) (case-group 1) or full-dose olanzapine (>5 mg/day) (case group 2), or a hospital treatment completed with no prescription of antipsychotic medications (control group); c) acquisition of informed consent. Exclusion criteria were 1) a concurrent antipsychotic treatment with drugs different from olanzapine (for all the included groups); 2) insufficient clinical documentation. The selection of the 3 groups was performed including all the patients undergoing the same hospital treatment during the selected period, to provide an unbiased and naturalistic observation. Thus, cases and controls were unmatched in this study, and potential confounding variables among the 3 groups were screened and included in multivariate analyses. Given the naturalistic character of the study, concurrent treatments with antidepressants were estimated to be potential confounding factors, consistently with previous studies on this topic (low dose olanzapine + duloxetine in Zhong et al. 2014; low-dose olanzapine +/- antidepressants, Berge et al. 2021). Given the retrospective nature of the study, missing data were not replaced.

2.2. Assessment methods

The primary objective of the study was to report on the use of low-dose olanzapine and its tolerability in a sample of adolescents with AN. Thus, psychopharmacological treatment variables were assessed by thoroughly reviewing clinical documentation, which included the dates and duration of treatment, initial and maximum dosages, any reasons for treatment interruption, and possible emerging adverse drug reactions (ADR). During hospitalization, patients received repeated standard laboratory exams, including blood counts, electrolytes, transaminases, lipid profile (low-density lipoprotein - LDL, high-density lipoprotein - HDL, triglycerides, total cholesterol), and coagulation, as well as electrocardiograms (EKG), before and after the introduction of any antipsychotic. These data were collected for both low- and full-dose treatments with olanzapine and concurrently administered medications, which may represent a potential confounder. Given the exclusion criteria for other antipsychotic interventions, antidepressant treatments

with selective serotonin reuptake inhibitors (SSRI) were considered and documented as dichotomic variables (yes/no). The potential confounding effect of these treatments on the outcome variables was taken into consideration, consistently with previous studies on low-dose olanzapine (Zhang et al. 2014; Berge et al. 2021).

All the patients received an assessment for ED, including psychopathological, nutritional, and biochemical screening at hospital admission. Besides pharmacological treatments, the considered variables included demographics (gender, age), clinical variables (AN subtype, comorbidities, duration of untreated illness, duration of hospitalization), and anthropometric variables (T0 and T1 BMI). Diagnoses of AN, AN subtypes, and comorbidities were performed by pediatric neuropsychiatrists and clinical psychologists trained in the field of ED following DSM-5 diagnostic criteria (APA, 2013). The diagnostic process was supported by the administration of the following tests, all validated for the assessment of children and adolescents with ED in the Italian language. These tests were all administered at both hospital admission (T0) and hospital discharge (T1).

1) The Eating Disorders Inventory-3 (EDI-3), a self-assessment questionnaire routinely used in the diagnosis of ED symptoms, expressed in the form of six Composite scores: Eating Disorder Risk (EDRC), Ineffectiveness (IC), Interpersonal Problems (IPC), Affective Problems (APC), Overcontrol (OC), Global Psychological Maladjustment (GPMC) (Gardner, 2004). These scores are the combination of 12 subscales; ED-specific subscales are Drive for Thinness (DT), Bulimia (B), and Body Dissatisfaction (BD) (Gardner, 2004).
2) The Body Uneasiness Test-A (BUT), a self-report questionnaire for the screening and the clinical assessment of abnormal body image attitudes and eating disorders (Cuzzolaro et al. 2006). A series of disease-specific scales are included in BUT, namely Global Severity Index (GSI), weight phobia, body image concerns, avoidance, compulsive self-monitoring, detachment, and estrangement feelings towards one's own body (depersonalization) (Cuzzolaro et al. 2006).
3) The Beck Depression Inventory-II (BDI-II), one of the most widely used psychological assessments for measuring the severity of depression (Beck et al. 1996).
4) The Self-Administered Psychiatric Scales for Children and Adolescents (SAFA), a validated psychometric instrument used to assess psychiatric comorbidities in children and adolescents with eating disorders (Cianchetti and Fascello, 2001; Franzoni et al. 2009). The test is composed of 6 subtests, assessing specific psychopathological domains: Anxiety (SAFA-A), depression (SAFA-D); obsessive-compulsive symptoms (SAFA-O), ED (SAFA-P), somatic symptoms (SAFA-S), and phobia (SAFA-F) (Cianchetti and Fascello, 2001).

A further objective of the study was the identification of potential differences among the 3 groups as regards changes in psychopathological measures between admission and discharge. Two variables assessing eating disorder psychopathology (EDI-3 EDRC and BUT-GSI) and two variables assessing depressive symptoms (BDI-II and SAFA-D) were considered in order to document modifications between admission and discharge, that is, a potential difference among the 3 treatment groups.

2.3. Statistical analysis

Descriptive analyses were provided for the entire sample and the 3 included groups. The significance level was set at 0.05, and all tests were two-tailed. Shapiro-Wilk's and Levene's tests were used to assess the normality of data distribution and homogeneity of variance. Given the retrospective and non-matched nature of the study, possible

confounders, that is, differences among the 3 groups concerning clinical and treatment variables were investigated with t-tests (Mann-Whitney when required) analyses of variance (ANOVA) for continuous variables (Kruskal-Wallis when required) and chi-square tests for nominal variables. The modification of psychopathological measures between T0 and T1 was studied with paired-sample T-tests for the whole group (Wilcoxon signed-rank when needed).

Then, possible differences among the 3 groups on T0-T1 modifications of psychopathology during the hospital treatment were considered. To this end, multiple analyses of covariance (ANCOVA) were conducted, using each outcome measure at T1 (discharge EDI-3 EDRC, BUT-GSI, BDI-II, and SAFA-D) as a dependent variable, and the treatment-group status (low-dose olanzapine, full-dose olanzapine, controls) as independent variables. All the analyses were controlled for the respective T0 psychopathological measures (admission EDI-3 EDRC, BUT-GSI, BDI-II, and SAFA-D) and potential confounding factors differing among the 3 groups upon univariate analyses. Bonferroni post-hoc tests were conducted. All the statistical analyses were conducted with SPSS 26.0 for Windows.

3. Results

3.1 Selection of the sample

A total of 390 children and adolescents with ED accessed our center during the considered period were identified and included in the study. These included 340 children and adolescents with AN (mean age 16.0 years, F=350, 92.6%), who accessed during the considered period and with a record of hospitalization. Among those, 256 met the inclusion criteria. Then, 138 patients were removed from this sample after applying exclusion criteria. A total of 118 subjects met the selected criteria and were retained for the final analyses.

3.2. Sample characteristics

One-hundred and eighteen adolescents with AN (F=111, 94.1%; M=7, 5.9%) were assessed, with a mean age of 15.4 (+/-1.7) years (range 13-18). AN subtypes were restrictive AN (ANR) (n=105, 89.0%), binge-purging AN (n=11, 9.3%) and atypical AN (n=2, 1.7%). The mean duration of hospitalization was 116.6 (+/-72.7) days. Sixty-six patients were treated with olanzapine; of those, 37 (31.3%) received a low-dose treatment (≤5 mg/day) and 29 (24.6%) received a full-dose treatment (>5 mg/day). A total of 52 (44.1%) patients received no antipsychotic medication and constituted the control group. As for the concomitant treatments, low-dose olanzapine was administered in 82 cases concurrently with sertraline, fluoxetine (34 cases), or fluvoxamine (8 cases). The full characteristics of the 3 groups are reported in Table 1.

3.3. Use and tolerability of olanzapine (primary outcome)

The treatment with olanzapine was well tolerated by 57 (86.4%) of all the patients who were treated with olanzapine, whether low or full dose. Among the 37 patients treated with low-dose olanzapine, 2 (5.4%) developed a mild elevation of total cholesterol levels (reached levels ≤220 mg/dl, reference value <200 mg/dl), while 1 patient (2.7%) showed elevated transaminases. As for the 29 patients treated with full-dose olanzapine, 3 patients (10.5%) presented a mild elevation of total cholesterol levels (reached levels ≤220 mg/dl), 1 patient (3.5%) developed somnolence, 1 patient (3.5%) showed a reduction of blood pressure, and one patient (3.5%) developed an elongation of the PR interval (PR=200 msec); this last effect occurred after sertraline 25 mg/day was added to the ongoing treatment with

olanzapine (7.5 mg/day) and was reduced by the interruption of sertraline (PR=180 msec). Notably, a patient treated with the sole fluoxetine reported the occurrence of panic attacks after the dosage of the drug was increased from 20 to 40 mg, with a reduction of the symptomatology when the previous dosage was restored. No significant difference in the frequency of side effects among the groups emerged (p=0.052). In 5 patients (7.6%) olanzapine was changed to another AAP during hospitalization: in 3 cases, the change was to risperidone, and in 2 cases to aripiprazole. One of these patients reached a maximum olanzapine dosage of 2.5 mg/day, and olanzapine was switched to risperidone, oral solution, due to the suspect of lack of compliance in the assumption of the drug. Two patients reached 5 mg/day, while two patients were in the full-dose group (7.5 and 10 mg/day). For all these patients the reason for the switch was lack of perceived clinical effect. No statistically significant difference in the frequency of switching emerged among the treatment groups (p=0.124) (Table 1).

3.4. Modification of psychopathological measures (secondary outcome)

For the entire sample, a significant T0-T1 improvement was documented for BUT-GSI (p<0.001), BDI-II (p<0.001), and SADA-D (p<0.001), but not for EDI-3 EDRC (p=0.107).

Concerning the 3 separated groups, Table 2 reports the ANCOVA conducted on the T0-T1 modification of the selected psychopathological measures. Given the significant difference among the 3 groups in the distribution of concurrent treatment with sertraline, these analyses were controlled for both baseline psychopathological measures and this confounding variable. ANCOVA conducted on EDI-3 EDRC and BUT-GSI did not show significant differences among the 3 groups. The ANCOVA conducted on BDI-II showed a predictive role of treatment group status for BDI-II at discharge, independent of baseline BDI-II and concurrent sertraline administration. After post hoc Bonferroni comparisons, the full-dose group showed significantly higher BDI-II scores than controls (p=0.025), but not significantly higher than the low-dose group (p=0.057). The ANCOVA conducted on SAFA-D showed a predictive role of treatment group status for SAFA-D at discharge, independent of baseline SAFA-D and concurrent sertraline administration. After post hoc Bonferroni comparisons, the full-dose group showed significantly higher SAFA-D scores than controls (p=0.001) and the low-dose group (p=0.011).

Discussion

The present study provides a naturalistic, controlled observation of treatment with low-dose olanzapine in children and adolescents with AN, and documents the use of this treatment in the context of a multidisciplinary hospital intervention.

In the considered sample, the treatment with low-dose olanzapine was safe and well-tolerated. Similarly, only an increase of transaminases was reported in two cases enrolled in the study by Leggero and colleagues (Leggero et al. 2010). Few studies on AN, in which the different dosages of olanzapine were not compared, demonstrated an elevation in transaminases concurrently with olanzapine (average maximum dose 5.28 mg/day) (Spettigue et al. 2018), and a trend towards increasing fasting glucose and insulin level in patients treated with olanzapine (mean dose 8.5 mg) (Kafantaris et al. 2011). Sedation and dyslipidemia were identified in a matched-groups comparison study of patients treated with olanzapine (median dose 5 mg) when compared to untreated controls (Norris et al. 2011). These ADRs were not confirmed in our study.

No relevant difference was documented concerning admission-discharge modifications in ED psychopathology, differently from Leggero and colleagues, which documented an improvement in eating attitudes in a relevantly different study design (prospective nature, smaller sample of only female patients, lack of a control group, dosages ranging from 1.25 to 12.5 mg/day) (Leggero et al. 2010). Our results expand those reported by Spettigue and colleagues, documenting an increase in body weight in the treated group, without an improvement in ED symptoms. (Spettigue et al, 2018). On the contrary, the only available RCT in young patients with AN documented no specific effect of olanzapine in body weight, ED symptoms, or psychological functioning (Kafantaris et al. 2011).

It is important to notice that in our study, individuals treated with low-dose olanzapine and those treated without any AAP reported better outcomes on depressive symptoms than those treated with full-dose olanzapine. Specifically, a greater SAFA-D improvement was found for low-dose olanzapine and controls than full-dose olanzapine, and a greater BDI-II improvement was observed for controls than for full-dose olanzapine. Similar results were reported in a placebo-controlled trial, with a significant reduction in depression, anxiety, together with an improvement of core ED symptoms and a significant increase in weight (Bissada et al., 2008). In a classical study, Johnson argued that a proportion of patients with schizophrenia may suffer from neuroleptics (antipsychotic) related depressions, possibly 7.5-12.5% (Johnson, 1981). Other authors have described similar findings, (Harrow et al. 1994). Interestingly, evidence of greater D2 receptor occupancy in striatal, temporal, and insular cortex has been linked to negative subjective experience in individuals treated with risperidone or olanzapine (Mizrahi et al. 2007).

Given the naturalistic character of our study, a relevant quantity of the enrolled patients was administered antidepressants with olanzapine. Even though our statistical analyses were controlled for potential confounders, including the administration of antidepressants, future studies should assess the effect of olanzapine on a monotherapy-treated group, as proposed by Leggero and colleagues in a small sample (Leggero et al. 2010).

Our study has a few limitations. It is retrospective. The unmatched control group may present unrecognized confounding factors. The complex nature of any multidisciplinary intervention for AN, and ED in general, may strongly limit the possibility to identify the contributions of specific treatments. A large proportion of our patients were administered sertraline, fluoxetine, or fluvoxamine, concurrently with olanzapine. Olanzapine and low-dose olanzapine treatments are frequently used together with antidepressants, as documented by a recent nationwide study in Sweden by Berge and colleagues, reporting 92.6% of individuals treated with low-dose olanzapine/quetiapine while receiving antidepressants (Berge et al. 2021). Consistently with this study, our results were controlled for the potential confounding effect of concurrent antidepressants (Berge et al. 2021). Finally, clinicians and researchers should consider that pharmacologically, the dose does not equal exposure. This has been pointed out by a large cohort study, conducted in the United States, the daily dose (measured in the study as Defined Daily Dose) to estimate drug exposure duration can result in misclassification This misclassification may depend on the used doses, which may vary according to factors such as age, renal function, and local prescribing practices (Sinnott et al., 2016).

Our study also presents strengths. It has been conducted in a third-level Italian regional Center for ED in the developmental age. The naturalistic quality of this research, for which no financial support was received from any interest groups, points toward an unbiased description of the use of this treatment. Moreover, the presence of 2 control groups may significantly expand the evidence of the few previous studies on this topic. The total size of our sample (118 patients) significantly broadens the scarce existing literature on adolescents with AN treated with

olanzapine and offers a relevant source of information on side effects, which still limit the use of olanzapine in similar populations (Couturier et al. 2020). Finally, in this research, the use of international standardized tests has been associated with assessment measures validated to detect psychiatric comorbidities in children and adolescents with AN, a population characterized by specific and yet undetermined psychopathological features (Franzoni et al. 2009).

In conclusion, the present study provides a naturalistic observation of the role of low-dose olanzapine in the hospital treatment of a wide and controlled sample of adolescents with AN in a third-level Italian Center for ED in Children and Adolescents. Treatment with low-dose olanzapine was found to be relatively tolerable and safe. Even though no specific association between this treatment and the improvement in ED-related psychopathology was found, individuals treated with low-dose olanzapine, as well as antipsychotic-untreated controls, reported significantly greater improvements in depressive symptoms than those receiving full-dose olanzapine. These results should be replicated in prospective and wider samples.

Clinical significance

The present study expands the existing evidence in this field, reporting the use and tolerability of low-dose olanzapine in a naturalistic, controlled sample of 118 adolescents hospitalized for Anorexia Nervosa (AN). The evidence described in this research provides new data on the use and the adverse-drug reaction profile of low-dose and full-dose olanzapine in a sample of metabolically impaired patients of developmental age. These results may promote further, longitudinal investigations on the use of low-dose antipsychotic treatments for young, hospitalized patients with AN.

Declarations

Ethical Standards

The study was approved by the Institutional Review Board of the University of Bologna (reference number NPI-DAPSIFA2020) and was performed in compliance with the Declaration of Helsinki and its later amendments. Parents gave informed consent to the processing of personal data at the time of the clinical evaluation.

Competing interests/conflict of interest/funding

The authors have no competing interests/conflict of interest. The research received no grant from any funding agency

Availability of data and materials

The datasets used and analyzed during the study are available from the corresponding author on reasonable request.

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