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

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1 **Title**

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

4

5 **Running title**

6 **Low-dose olanzapine for Anorexia Nervosa**

7

8 **Authors**

9 Jacopo Pruccoli (1,2), Ilaria Pettenuzzo (1,2), Antonia Parmeggiani (1,2,\*)

10 \*: Corresponding author: Antonia Parmeggiani, Department of Medical and Surgical Sciences, University of Bologna,  
11 Via Massarenti 9, 40138 Bologna, Italy. Email: Antonia.parmeggiani@unibo.it

12

13 **Affiliations**

14 1 IRCCS Istituto delle Scienze Neurologiche di Bologna, Regional Center for Feeding and Eating Disorders in Children  
15 and Adolescents, Child Neurology and Psychiatry Unit, Bologna, Italy

16 2 Dipartimento di Scienze Mediche e Chirurgiche (DIMEC), University of Bologna, Bologna, Italy

17

18 **Abstract**

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

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

31 Results: one hundred-eighteen patients were enrolled (F=94.1%; mean age=15.4 $\pm$ 1.7 years), including 52 controls,  
32 37 treated with low-dose olanzapine, and 29 with full-dose olanzapine. Low-dose olanzapine was well tolerated and  
33 used for a mean of 132.1 ( $\pm$ 98.6) days, starting with a dosage of 3.4 ( $\pm$ 1.2) mg/day and increasing to a maximum  
34 dose of 4.4 ( $\pm$ 1.1) mg/day. The multidisciplinary intervention resulted in an improvement of BUT-GSI ( $p < 0.001$ ), BDI-  
35 II ( $p < 0.001$ ), and SAFA-D ( $p < 0.001$ ) for the entire sample. Individuals treated with full-dose olanzapine experienced a  
36 significantly lower improvement in depressive measures: BDI-II ( $F(2,61)=12.653$ ,  $p < 0.001$ ,  $\eta^2=0.269$ ) and SAFA-D  
37 ( $F(2,57)=7.413$ ,  $p=0.001$ ,  $\eta^2=0.170$ ), than the other groups.

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

#### 40 **Keywords**

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

42

#### 43 **Introduction**

44 Recent guidelines for the treatment of Anorexia Nervosa (AN) in children and adolescents propose the use of atypical  
45 antipsychotics (AAP) in the management of low-weight patients in selected conditions (Couturier et al. 2020). Despite  
46 a general paucity of data, olanzapine presents the most relevant evidence for the treatment of AN among AAP  
47 (Couturier et al. 2020). A randomized-controlled clinical trial documented the use of olanzapine in 15 children and  
48 adolescents with AN, showing no significant difference between olanzapine and placebo concerning weight or  
49 psychological outcomes (Kafantaris et al. 2011). More promising results have been reported in nonrandomized case-  
50 control studies, particularly on hyperactivity (Couturier et al. 2020). Besides its clinical effects, olanzapine has a series  
51 of documented side effects in subjects with AN, including increasing fasting glucose and insulin levels (Kafantaris et al.  
52 2011), sedation, and dyslipidemia (Norris et al. 2011), or QTc prolongation (Ritchie and Norris 2009). For this reason,  
53 recent studies have focused on the possible effect of antipsychotic treatments with low-dose olanzapine in diverse  
54 mental health populations. Concerning the use of low-dose olanzapine in children and adolescents with AN, a single  
55 study has been published so far, examining 13 female subjects (Leggero et al. 2010). The final mean dosage was 4.1  
56 (+/-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).  
57 The authors reported improvement of both body-mass index (BMI), global functioning, and hyperactivity with minimal  
58 side effects (Leggero et al. 2010). Unfortunately, an established definition of “low-dose treatment with olanzapine” is  
59 not yet available in the literature. A relevant definition is provided by a recent population-based, longitudinal cohort  
60 study, assessing potential associations between off-label low-dose olanzapine or quetiapine and cardiometabolic  
61 mortality (Berge et al. 2021). Low-dose olanzapine (reported as olanzapine-equivalents) was defined at  $\leq 5$  mg/day  
62 (Berge et al. 2021). Conflicting definitions are reported by other studies on schizophrenia (5 mg/day) (Lin et al. 2017),  
63 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  
64 et al. 2000).

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

#### 73 **2. Methods**

## 74 2.1. Study design and participants

75 This is a case-control, observational retrospective study. The study took place in the context of an observational  
76 survey investigating the use of psychopharmacological treatments in a third-level Regional Center for Feeding and  
77 Eating Disorders in Children and Adolescents, and was approved by the local ethical committee (Comitato Etico di  
78 Area Vasta Emilia Centro della Regione Emilia-Romagna, CE-AVEC) (Protocol code NPI-DAPSIFA2020, study code  
79 9/2021/Oss/AOUBo). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines  
80 were observed during the planning and execution phases of the study (von Elm et al. 2007). The study was not  
81 sponsored or funded by any company.

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

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

## 101 2.2. Assessment methods

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

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

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

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

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

### 144 2.3. Statistical analysis

145 Descriptive analyses were provided for the entire sample and the 3 included groups. The significance level was set at  
146 0.05, and all tests were two-tailed. Shapiro-Wilk's and Levene's tests were used to assess the normality of data  
147 distribution and homogeneity of variance. Given the retrospective and non-matched nature of the study, possible

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

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

### 159 **3. Results**

#### 160 3.1 Selection of the sample

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

#### 166 3.2. Sample characteristics

167 One-hundred and eighteen adolescents with AN (F=111, 94.1%; M=7, 5.9%) were assessed, with a mean age of 15.4  
168 (+/-1.7) years (range 13-18). AN subtypes were restrictive AN (ANR) (n=105, 89.0%), binge-purging AN (n=11, 9.3%)  
169 and atypical AN (n=2, 1.7%). The mean duration of hospitalization was 116.6 (+/-72.7) days. Sixty-six patients were  
170 treated with olanzapine; of those, 37 (31.3%) received a low-dose treatment ( $\leq 5$  mg/day) and 29 (24.6%) received a  
171 full-dose treatment ( $> 5$  mg/day). A total of 52 (44.1%) patients received no antipsychotic medication and constituted  
172 the control group. As for the concomitant treatments, low-dose olanzapine was administered in 82 cases concurrently  
173 with sertraline, fluoxetine (34 cases), or fluvoxamine (8 cases). The full characteristics of the 3 groups are reported in  
174 Table 1.

#### 175 3.3. Use and tolerability of olanzapine (primary outcome)

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

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

#### 193 3.4. Modification of psychopathological measures (secondary outcome)

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

196 Concerning the 3 separated groups, Table 2 reports the ANCOVA conducted on the T0-T1 modification of the selected  
197 psychopathological measures. Given the significant difference among the 3 groups in the distribution of concurrent  
198 treatment with sertraline, these analyses were controlled for both baseline psychopathological measures and this  
199 confounding variable. ANCOVA conducted on EDI-3 EDRC and BUT-GSI did not show significant differences among the  
200 3 groups. The ANCOVA conducted on BDI-II showed a predictive role of treatment group status for BDI-II at discharge,  
201 independent of baseline BDI-II and concurrent sertraline administration. After post hoc Bonferroni comparisons, the  
202 full-dose group showed significantly higher BDI-II scores than controls ( $p=0.025$ ), but not significantly higher than the  
203 low-dose group ( $p=0.057$ ). The ANCOVA conducted on SAFA-D showed a predictive role of treatment group status for  
204 SAFA-D at discharge, independent of baseline SAFA-D and concurrent sertraline administration. After post hoc  
205 Bonferroni comparisons, the full-dose group showed significantly higher SAFA-D scores than controls ( $p=0.001$ ) and  
206 the low-dose group ( $p=0.011$ ).

#### 207 **Discussion**

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

211 In the considered sample, the treatment with low-dose olanzapine was safe and well-tolerated. Similarly, only an  
212 increase of transaminases was reported in two cases enrolled in the study by Leggero and colleagues (Leggero et al.  
213 2010). Few studies on AN, in which the different dosages of olanzapine were not compared, demonstrated an  
214 elevation in transaminases concurrently with olanzapine (average maximum dose 5.28 mg/day) (Spettigue et al.  
215 2018), and a trend towards increasing fasting glucose and insulin level in patients treated with olanzapine (mean dose  
216 8.5 mg) (Kafantaris et al. 2011). Sedation and dyslipidemia were identified in a matched-groups comparison study of  
217 patients treated with olanzapine (median dose 5 mg) when compared to untreated controls (Norris et al. 2011). These  
218 ADRs were not confirmed in our study.



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

226 It is important to notice that in our study, individuals treated with low-dose olanzapine and those treated without any  
227 AAP reported better outcomes on depressive symptoms than those treated with full-dose olanzapine. Specifically, a  
228 greater SAFA-D improvement was found for low-dose olanzapine and controls than full-dose olanzapine, and a greater  
229 BDI-II improvement was observed for controls than for full-dose olanzapine. Similar results were reported in a  
230 placebo-controlled trial, with a significant reduction in depression, anxiety, together with an improvement of core ED  
231 symptoms and a significant increase in weight (Bissada et al., 2008). In a classical study, Johnson argued that a  
232 proportion of patients with schizophrenia may suffer from neuroleptics (antipsychotic) related depressions, possibly  
233 7.5-12.5% (Johnson, 1981). Other authors have described similar findings, (Harrow et al. 1994). Interestingly, evidence  
234 of greater D2 receptor occupancy in striatal, temporal, and insular cortex has been linked to negative subjective  
235 experience in individuals treated with risperidone or olanzapine (Mizrahi et al. 2007).

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

240

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

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

258 olanzapine and offers a relevant source of information on side effects, which still limit the use of olanzapine in similar  
259 populations (Couturier et al. 2020). Finally, in this research, the use of international standardized tests has been  
260 associated with assessment measures validated to detect psychiatric comorbidities in children and adolescents with  
261 AN, a population characterized by specific and yet undetermined psychopathological features (Franzoni et al. 2009).  
262 In conclusion, the present study provides a naturalistic observation of the role of low-dose olanzapine in the hospital  
263 treatment of a wide and controlled sample of adolescents with AN in a third-level Italian Center for ED in Children and  
264 Adolescents. Treatment with low-dose olanzapine was found to be relatively tolerable and safe. Even though no  
265 specific association between this treatment and the improvement in ED-related psychopathology was found,  
266 individuals treated with low-dose olanzapine, as well as antipsychotic-untreated controls, reported significantly  
267 greater improvements in depressive symptoms than those receiving full-dose olanzapine. These results should be  
268 replicated in prospective and wider samples.

269

#### 270 **Clinical significance**

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

#### 276 **Declarations**

#### 277 **Ethical Standards**

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

#### 281 **Competing interests/conflict of interest/funding**

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

#### 283 **Availability of data and materials**

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

285

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