The Role of Mood Stabilizers in Children and Adolescents with Anorexia Nervosa: A 1-year Follow-Up, Propensity Score-Matched Study

Title

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Running title

Mood stabilizers in Anorexia Nervosa

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Abstract

Background: The existing literature on the use of mood stabilizers (MS) in children and adolescents with Anorexia Nervosa (AN) is limited, for the most part, to small case studies.

Methods: Observational, naturalistic, propensity score-matched study. Subjects treated and not-treated with MS were compared by being matched via propensity score on age, sex, concurrent atypical antipsychotics, concurrent antidepressants. General and AN-specific psychopathology was assessed with SCL-90-R, BDI-II, EDI-3, BUT. Potential differences in admission-discharge modifications (BMI, psychopathology) among the 2 groups were assessed. Finally, re-hospitalizations after 1-year follow-up were assessed with Kaplan-Meier analyses.

Results: The study enrolled 234 hospitalized patients (15.9+/-3.3 years; 26, 11.1% receiving MS). After propensity-score matching, 26 MS patients matched 26 MS-not-treated subjects. MS were used for a mean of 126.1 (+/-87.3) days; two cases of side effects were documented (alopecia and somnolence with valproate). No significant difference between MS-treated and not-treated patients emerged concerning admission-discharge improvements of BMI, AN-specific or general psychopathology. The cumulative survival from re-hospitalization at 12 months was 64.4% (95%-CI, 31.3-97.5) for MS and 58.7% (95%-CI, 22.2-95.2) for

MS-not-treated subjects. No significant difference in survival rate emerged (hazard ratio, 0.04; Log-rank test: p=0.846).

Conclusions: this propensity score-matched study expands on the scant existing evidence of the use and side effects of MS in children and adolescents with AN. These results should be assessed in wider longitudinal samples.

Keywords

Mood stabilizers, lithium, valproate, anorexia nervosa, eating disorders, children, adolescents

Introduction

Anorexia Nervosa (AN) is currently classified among the Feeding and Eating Disorders (FED) in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [1]. This condition is characterized by A) a restricted intake of energy, which leads to low body weight; B) a fear of body weight and fat; and C) a disturbed experience of body weight and body shape, with an inappropriate influence of these features on self-evaluation and insufficient recognition of the current body weight [1]. AN may be linked to several medical and psychiatric complications and comorbid diseases, such as cardiovascular [2], nutritional [3], and neurodevelopmental disorders [4].

Current clinical guidelines identify Family-Based Treatment and the least intensive treatment environment as the preferred interventions for the treatment of AN in children and adolescents [5]. Weaker recommendations may support Multi-Family Therapy, Cognitive Behavioral Therapy, Adolescent Focused Psychotherapy and Yoga. Weak recommendations are available for atypical antipsychotics (AAP), since olanzapine and aripiprazole may represent relevant interventions for specific conditions and clinical settings upon careful monitoring. The same guidelines state that mood stabilizers (MS) are not indicated in the treatment of children and adolescents with AN, due to a lack of evidence [5].

The evidence for the use of MS in the treatment of AN is scarce. The most important available evidence is provided by a past DSM-III-based trial, comparing lithium carbonate in 8 patients with AN to controls [6]. The study showed an increased weight gain in the treatment group at weeks 3 and 4 [6]. A former case series assessed the use of lithium in 2 adults with AN, showing relevant weight gain, which was maintained for a year during follow-up [7]. In another case report, lithium played an important role in the clinical course of an individual with AN [8].

The available evidence on the use of valproate in patients with AN is even more scarce. The widest documented sample is represented by a case series of 14 subjects, which was recently published by our group and documenting an improvement in target symptoms for 71.4% of the examined patients, with minor side effects [9]. Further evidence comes from previous smaller case series, with a role in the management of treatment-emergent mania [10,11].

Fewer studies have investigated the use of other antiepileptic drugs such as MS in the treatment of AN. Trunko and colleagues assessed the effect of adjunctive lamotrigine in a sample of 5 individuals with mixed FED diagnoses, including binge-purging AN (AN-BP), and documented an improvement in disordered eating behavior and psychopathology [12]. The use of carbamazepine for AN was documented in two case reports (one in combination with lithium), with a description of fulminant hepatic failure in response to concurrent acetaminophen [13,14]. Given its pro-anorectic effect, the role of topiramate in the treatment of FED is mainly limited to Bulimia Nervosa and Binge Eating Disorder [15]. Two case reports document the use of topiramate in AN, for comorbid Bipolar Disorder (BD) [16] or epilepsy [17]. In the last case, a recurrent episode of AN was possibly triggered by the use of topiramate [17].

As this brief review of the existing literature shows, clinical evidence documenting the use of adjunctive MS in the treatment of AN is significantly limited, and mainly represented by small case series, conducted before the current diagnostic criteria for AN were established. Even less evidence is available concerning the use of these drugs in children and adolescents with AN, and individuals without a comorbid BD. Studies intended to report on the use of specific psychopharmacological interventions in children and adolescents with AN are greatly needed, since this sub-population shows peculiar tolerability issues, as documented by a systematic review [18]. The present study aims to describe the use of mood stabilizers in the naturalistic context of a multidisciplinary intervention for children and adolescents with AN, with no concurrent BD.

2. Methods

2.1. Study design and participants

This is a propensity score-matched, 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 (code NPI-DAPSIFA2020). The Center in which the study was conducted is a third-level service for the treatment of FED in children and adolescents. The Center services a metropolitan area of nearly 900.000 inhabitants and represents one of the few public hospital centers for FED in the developmental age in Italy. Patients with a FED as the only diagnosis, but marked comorbid psychiatric symptoms are referred to this Center from pediatric and mental health services of this metropolitan area and other regions in Italy, frequently after previously attempted therapeutic interventions have failed. Given these reasons, a relatively high percentage of the included patients is subjected to protracted hospitalizations and treated with off-label psychotropic medications, for the management of comorbid impairing symptoms in a limited time interval. The use of off-label psychiatric medications, thus, was explicitly discussed with the patients and their legal representatives before any clinical action. Written informed consent was obtained at the start of hospitalization after all the specific potential clinical interventions were disclosed.

The guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were observed during the planning and execution phases of the study [19]. The evidence here reported focuses on the included hospitalized individuals with AN, who represent the largely preponderant group of patients referring to our Center and undergoing a standardized protocol of assessments during the treatment. The study was not sponsored or funded by any company.

The study was conducted in February 2022 by retrospectively considering patients assessed at the Center between January 1, 2016 and January 31, 2021, 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 [20] and consists in a multidisciplinary psychological, nutritional, and psychopharmacological intervention. All the included patients were subjected to the same multidisciplinary program, performed by the same team, in the same Center, following clinical international guidelines [21].

Inclusion criteria were a) diagnosis of AN according to the DSM-5 criteria; b) either treatment with MS in monotherapy or an adjunct therapy (lithium, valproate, lamotrigine, topiramate, carbamazepine, lamotrigine, oxcarbazepine) (case-group) or a hospital treatment completed with no prescription of MS (no-MS group); c) acquisition of informed consent. Exclusion criteria were 1) a concurrent diagnosis of Bipolar Disorder (both type I and II), according to the DSM-5 criteria; 2) insufficient clinical documentation. The selection of the 2 groups was performed including all the patients undergoing the same hospital treatment during the selected period, to provide an unbiased and naturalistic observation. Patients included in the 2 groups were then matched by conducting a Propensity Score Matching. To address the potential confounding effect of clinical variables and concurrent treatments, the 2 groups were matched for the following variables: age, gender, concurrent selective serotonin reuptake inhibitors (SSRI), and concurrent atypical antipsychotics (AAP). Given the naturalistic 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 MS and the potential side effects from the use of these drugs in a sample of children and 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, liver enzymes, lipid profile, coagulation) and repeated electrocardiograms (EKG). These data were collected for both groups.

All the patients received an assessment for FED, 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 child and adolescent neuropsychiatrists and clinical psychologists trained in the field of FED following DSM-5 diagnostic criteria (APA, 2013). The diagnostic process was supported by the administration of tests that are all validated for the assessment of children and adolescents with ED in the Italian language. The tests, which were all administered at both hospital admission (T0) and hospital discharge (T1), included:

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, including an Eating Disorder Risk (EDRC), and a Global Psychological Maladjustment (GPMC) scores [22];
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, expressed in a series of disease-specific scales, including a Global Severity Index (GSI) [23];
3) The Symptom Check List-90-R (SCL-90-R) [24,25], a self-report questionnaire assessing the severity of 90 psychiatric symptoms during the last week, expressed in a series of scales, including a Global Severity Index (GSI), Somatization (SOM), Obsessive-Compulsive (O-C), Interpersonal Sensitivity (I-S), Depression (DEP), Anxiety (ANX), Hostility (HOS), Phobic Anxiety (PHOB), Paranoid Ideation (PAR), and Psychoticism (PSY) [24,25].
4) The Beck Depression Inventory-II (BDI-II), one of the most widely used psychological assessments for measuring the severity of depression [26];

The diagnostic process was supported by the administration of The Self-Administered Psychiatric Scales for Children and Adolescents (SAFA), a psychometric instrument used to assess psychiatric comorbidities in children and adolescents [27], and specifically tested to detect psychiatric comorbidities in children and adolescents with eating disorders [28].

A further objective of the study was the identification of potential differences between the 2 groups as regards the occurrence of new hospitalizations for FED in the 12 months following hospital discharge. Thus, clinical data on the 12 months following hospital discharge were systematically collected.

2.3. Statistical analysis

Descriptive analyses were provided for the entire sample and the 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. Propensity score matching was adopted to adjust for

potential confounders between subjects treated and not treated with MS. The propensity score was estimated using a logistic regression model, considering four covariates (age, sex, concurrent use of AAP, and concurrent use of SSRI). We performed a nearest-neighbor matching algorithm without replacement using a caliper width equal to 0.2 of the standard deviation of the propensity score. We matched the MS and the no-MS group in a 1:1 ratio according to these covariates. The balance of the covariates between MS-treated and MS-not-treated subjects was assessed using the standardized mean difference (SMD), with <10% being considered well-balanced.

The two treatment groups were compared for anamnestic, clinical and treatment variables. Chi square tests (Fisher's exact test where needed) were adopted to compare categorical variables, and t-tests (non-parametric tests where needed) were used to compare continuous variables. Effect sizes were reported.

Then, possible differences among the two groups regarding T0-T1 modifications of BMI and psychopathology during the hospital treatment were considered. To this end, multiple analyses of covariance (ANCOVA) were conducted, using each BMI/each psychopathological measure (EDI-3-EDRC, BUT-GSI, BDI-II, SCL-90-GSI) at T1 as a dependent variable, and the group status (MS-treated, MS-not-treated) as independent variables. All the analyses were controlled for the respective T0 BMI/psychopathological measures. Bonferroni correction was applied for multiple comparisons.

The rate of further hospitalizations for the MS-group and the MS-not-treated group was calculated with the Kaplan–Meier method, and the Log-rank test was performed to assess potential differences between the two groups. The Cox proportional hazards model was used to calculate the hazard ratio and the 95% confidence interval for mood stabilizers as compared with that for MS-not-treated subjects. The sample size was determined from the number of subjects enrolled within the study period. All the statistical analyses were performed using R 4.1.2 (The R Foundation for Statistical Computing) for Windows.

Results

3.1 Patients' Characteristics

A total of 346 children and adolescents with FED (mean age 15.9 years +/- 2.1 years, F=277, 92.0%) came to our Center during the considered period and were identified and included in the study. Among them, 300 children and adolescents had AN and a record of hospitalization. Among those, 248 met the inclusion criteria. However, 14 patients were removed from this sample on account of the exclusion criteria. A total of 234 (mean age 15.9 +/- 3.3 years) subjects met the selected criteria and were retained for the final analyses. One-hundred fifty-three (65.4%) of the included patients received atypical antipsychotics (olanzapine: n=83, 35.5%; aripiprazole: n=52, 22.2%; risperidone: n=35, 15.0%; quetiapine: n=19, 8.1%). One hundred fifty-four (65.8%) of the included patients received treatment with a SSRI (sertraline: n=151, 65.5%; fluoxetine: n=60, 25.6%; fluvoxamine: n=16, 6.8%).

Among the 234 included patients, 26 patients were in the MS group (mean age ± standard deviation, 16.2 ± 2.5 years; females, 92.3%) and 208 were in the MS-not-treated group (15.9 ± 3.3 years; females, 93.3%). After propensity score matching, 26 mood stabilizer cases matched with 26 MS-not-treated subjects. The SMD was less than 10% for all covariates. Thus, the covariate balance in the matched data met the "well balanced" criterion. Since MS were used as adjunctive treatments, concurrent use of SSRI and AAP were included among propensity score matching criteria, and resulted well balanced and not significantly different in the two groups. Moreover, the assessment of all specific concurrent psychopharmacological medications revealed no

significant difference between the two groups. The patients' characteristics at baseline are summarized in Table 1.

3.2 Use of mood stabilizers

MS were used for a mean of 126.1 (+/-87.3) days. Among the 26 patients in the mood stabilizers group, 24 (92.3%) were treated with valproate, and 2 (7.7%) were treated with lithium. None of the patients received more than one mood stabilizer at a time. One patient treated with lamotrigine was identified during the enrollment phase, and was excluded due to a concurrent diagnosis of Bipolar Disorder, type I. Reasons for the introduction of MS included unstable mood (19 cases, 73.1%), lack of compliance (9 cases, 34.6%), and aggressive behavior (5 cases, 19.2%). "Lack of compliance" was targeted with the use of MS when compliance with psychological interventions was specifically hampered by unstable mood or aggressive behavior.

Lithium was used at a mean starting dose of 225.0 ± 106.1 (range 150.0 – 300.0 mg/day) to a maximum dose of 525.0 ± 106.1 mg/day (range 450.0 – 600.0 mg/day). Valproate was used at a mean starting dose of 295.8 ± 172.5 mg/day (range 100.0 – 600.0 mg/day), up to a mean maximum dose of 472.9 ± 203.8 mg/day (range 200.0 - 1000 mg/day). Mild side effects were documented in 2 patients treated with valproate (somnolence, 1 case; alopecia, 1 case). As previously described in a smaller case series (Pruccoli and Parmeggiani, 2021), reduced levels of concurrent AAP were documented in three patients treated with valproate. Namely, one patient showed a decrease in olanzapine levels (from 41 to 29 mcg/L, reference 20–80 mcg/L, despite an increase of the daily dose of olanzapine); one patient presented non-measurable quetiapine levels, despite 3 months of continuous quetiapine up to 75 mg/day; last, low levels of risperidone (10 mcg/L, reference: 20–60 mcg/L) after one month of treatment up to 1 mg/day. No other side effects were documented, including hematological variations and EKG modifications.

3.3. Modification of weight and psychopathological measures

Patients treated and not treated with MS were compared for potential differences in T0-T1 modifications of BMI, EDI-3 EDRC, BUT GSI, BDI-II, and SCL-90 GSI. Significance was corrected (Bonferroni) for multiple comparisons ($p = 0.05/5 = 0.01$). Subjects treated with MS did not present a different T0-T1 increase of BMI than MS-not-treated ($F(1,48)=4.140$, $p=0.047$, $\eta2=0.026$). Similarly, no statistically significant difference in T0-T1 modifications of psychopathological parameters was documented between subjects treated with MS and MS-not-treated subjects. In particular, cases treated with MS did not show a greater improvement than MS-not-treated cases concerning EDI-3 EDRC ($F(1,36)=0.183$, $p=0.671$, $\eta2=0.004$), BUT GSI ($F(1,14)=0.523$, $p=0.482$, $\eta2=0.026$), BDI-II ($F(1,11)=0.350$; $p=0.561$, $\eta2=0.026$), and SCL-90 GSI ($F(1,9)=0.042$, $p=0.843$, $\eta2=0.003$).

3.4. Survival analysis for re-hospitalization

Kaplan Meier curves for MS-treated and MS-not-treated groups are reported in Figure 1. The mean survival time from re-hospitalization was 309 (95% CI, 228.4 - 389.5) days for the MS group and 315 (95% CI, 246.6 - 383.6) days for the MS-not-treated group. The cumulative survival from re-hospitalization at 12 months was 64.4% (95% CI, 31.3 - 97.5) for the MS group and 58.7% (95% CI, 22.2 - 95.2) for the MS-not-treated group. MS subjects did not have a significantly different survival rate than MS-not-treated (hazard ratio, 0.04; Log-rank test: $p = 0.846$).

4. Discussion

The present study reports on the use of MS in the hospital treatment of a group of children and adolescents with AN, followed up for 1 year. This is the widest sample of patients reported so far in a population treated with MS.

Across our sample, the analyzed MS (lithium and valproate) were linked to mild side-effects (somnolence and alopecia) in two patients treated with valproate. The use of MS in children and adolescents is currently not recommended by the available guidelines due to a lack of evidence [5]. Moreover, the administration of these drugs has been limited by relevant potential adverse drug reactions, including altered liver function, polycystic ovarian syndrome (PCOS), bleeding and unintended weight gain [29]. The teratogenic nature of both lithium and valproate represents an ulterior limitation in the use of these drugs in women and girls of childbearing potential [30]. Previous studies on the use of these drugs in subjects with FED showed good tolerability, despite being conducted on a case series basis. Among the 3 FED patients (2 with AN) treated with valproate by Tor and Colleagues, no relevant side effects were reported with the exception of a transitory concern for gaining weight in a subject with Bulimia Nervosa [11]. No specific side effects were reported in a previous case report describing the use of valproate to treat comorbid epilepsy in a subject with AN [31]. Although infrequent side effects emerge from the comprehensive evidence resulting from these data, the potential teratogenic risk for women of childbearing potential should always be acknowledged before starting these interventions in girls with AN, considering the possible future resumption of menses and fertility, and their actual use should be strongly limited.

When considering potential differences in admission-discharge modifications of weight measures between the two groups, subjects treated with adjunctive MS did not present a different improvement in BMI from not treated cases. Conversely, in the only available controlled trial in this field, lithium was associated with a greater weight gain in the first weeks of treatment than placebo [6]. A notable difference between the research conducted by Gross and colleagues and the present research is represented by the prevalent frequency of use of valproate in our sample. Both valproate and lithium may induce weight gain in pediatric samples, particularly when administered concurrently with antipsychotics [32]. Even though this could represent a potential clinical advantage in the treatment of restrictive FED, our naturalistic data did not support the evidence of a clear improvement for underweighted patients treated with MS. Nonetheless, given the existence of transdiagnostic psychopathological mechanisms in the development of FED [33], we alert clinicians to strictly monitor weight gains in subjects with AN, to prevent potential shifts to binge or binge-purging conditions.

As for the potential modification of psychopathological measures or the risk of rehospitalization and variations in measures, no statistically significant differences were documented in our study between the group treated with MS and the not treated group. Patients' rehospitalization rates at one year represent a key element to evaluate the clinical effect of MS [34-36]. In a study comparing the effect of MS versus an MS plus an antipsychotic in subjects with Bipolar Disorder, no significant differences in rehospitalization rate or time to rehospitalization between groups were documented [34]. Kim and colleagues, conversely, reported that for bipolar patients treated with MS, adjunctive aripiprazole was associated with a longer time before hospitalization than ziprasidone, olanzapine, quetiapine, or risperidone [35]; these results were expanded by Niu and colleagues more recently [36]. Overall, follow-up data on the use and tolerability of MS in children, despite promising [37], are still scarce. No study so far has assessed the role of MS in preventing rehospitalization in subjects with AN or other FED, and the results presented here demand new longitudinal research in this field. No significant differences emerged between the treated and not-treated groups according to psychiatric symptoms measured at admission by the SCL-90-R. However, it should be noted that the patients here considered frequently presented a high, FED-related burden of disease, in terms of

psychopathological and medical instability, low compliance, and scarce insight. This may have limited the possibility for the self-report questionnaire to fully reveal and measure the intensity of psychiatric symptoms. Thus, a prudent interpretation of differences and similarities arising from comparisons of the two groups should be made.

Clinicians and readers should consider that international guidelines do not indicate the use of MS in the treatment of FED and AN [5]. Nevertheless, these interventions could reasonably represent adjunctive treatment addressing specific comorbid psychopathological symptoms in selected cases, but not single interventions for children and adolescents with AN. Consistently, in this study, the use of MS represents an adjunctive treatment to concurrent psychopharmacological and psychological interventions, which were systematically reported. This study has some limitations. Its retrospective nature and the specific setting (a third level Center for FED in developmental age) may reduce the chances to make comparisons with other studies in this field. Despite the inclusion of a comparison group without treatment with MS, no specific control group treated with placebo was available. Lastly, the follow-up period was limited to 12 months. This study also presents some strengths. The sample of AN patients treated with MS and with a 1-year follow up represents the widest one available in literature so far. The real-world nature permitted the thorough description of psychopharmacological, nutritional, and psychopathological parameters. The use of propensity matching permitted to drawing of two directly comparable treatment groups.

In conclusion, this study reports the broadest sample available so far of subjects with AN treated with mood stabilizers and compares the rehospitalization rates of these individuals to matched cases. While infrequent side effects were reported, the treatment with MS was not associated with improved weight restoration, psychopathology or reduced rehospitalization rates in the included samples. Future studies should systematically assess the potential impact of MS in the treatment of specific psychopathology and psychiatric comorbidities in subjects with AN. The relevant risk for women of childbearing age and the extremely scarce evidence on MS use with AN available so far, however, strongly recommend that these interventions be limited to selected, monitored clinical settings.

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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