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BRIEF REPORT

Inpatient treatment of anorexia nervosa with adjunctive valproate: a case series of 14 young and adolescent patients

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Abstract

Background The use of valproate in the treatment of Anorexia Nervosa (AN) in children and adolescents is currently not recommended by clinical guidelines, due to lack of evidence. Nonetheless, valproate is used to treat a series of psychiatric and neurologic conditions. To date, only six cases of patients with Feeding and Eating Disorders (three with AN) have been described.

Methods Case series of 14 children and adolescent patients hospitalized for AN and treated with valproate as an adjunctive treatment. Reasons for introduction, dosages, plasma levels, adverse drug reactions (ADR) and modifications of liver enzymes, platelets levels, abdominal and pelvic ultrasounds, and concurrent drugs plasma levels were assessed.

Results Reasons for the introduction of valproate included unstable mood (57.1%), lack of compliance (50%) and aggressive behaviour (21.4%). In 71.4% of patients an improvement on target symptoms was observed. Valproate was started at 241.7 (±73.3) mg, up to 521.4 (±204.5) mg; the most frequent scheme was twice-daily. The mean plasmatic concentration was 66.3 (±25.0) mg/L. One patient (7.1%) experienced side effects (somnolence). No major modifications of liver enzymes, platelet levels, abdominal and pelvic ultrasounds emerged after the introduction of valproate. Low concurrent olanzapine and quetiapine levels were documented.

Conclusions This is the largest sample of patients with AN treated with valproate. Valproate was administered to improve psychiatric symptoms impairing compliance with inpatient treatment programs. The majority of patients experienced an improvement on target symptoms after being administered valproate, with minor ADR. These data should be investigated in wider populations and controlled studies.

Level of evidence Level IV, case series.

Background

Anorexia Nervosa (AN) is an increasingly widespread mental health condition, which is defined by restriction of food intake, fear of gaining weight and disturbed self-perception of body weight or shape [1].

According to the most recent guidelines, treatments for AN in young patients encompass family-based treatment, multi-family therapy, cognitive behavioural therapy, adjunctive yoga, adolescent focused psychotherapy, and psychopharmacotherapies [2]. Among psychopharmacological treatments, mood stabilizers, such as lithium and valproate, are not viewed as recommended treatments for AN, and Feeding and Eating Disorders (FED) in general, in children and adolescents, due to lack of evidence on efficacy and tolerability [2].

Valproate is a mood stabilizer and an anti-epileptic drug (AED) with diverse pharmacokinetic and clinical properties. The mechanisms of action of valproate include blockade of sodium channels, enhancement of GABA transmission, and effects on cellular signalling pathways [3]. Valproate is currently adopted in the treatment of multiple epilepsy types, of manic and mixed episodes in bipolar disorders, and for migraine prevention [4]. Weight gain represents a relevant side effect of treatment with valproate; altered liver function and polycystic ovarian syndrome (PCOS) may occur;

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use in patients with thrombocytopenia is not recommended, since bleeding has been reported [4]. Since valproate is a major teratogen, its use in women and girls of childbearing potential is avoided according to a series of guidelines; exceptions should be considered on a case-by-case basis [5]. Problems could arise while treating patients concurrently with valproate and hormone replacement therapy (HRT), since a dose-related increase in seizure frequency has been documented in women treated with HRT and a series of AEDs, valproate among them, with a decrease in plasmatic levels of lamotrigine but not valproate [6].

Despite its extensive usage in mental health, evidence of a possible role of valproate in the field of FED remains scarce. The most developed description to date of the use of valproate in FED is offered by a small case series of three patients with different diagnoses (AN and Bulimia Nervosa), who experienced antidepressant treatment-emergent mania (TEM). Valproate was started at 200 mg/die and increased, achieving the remission of TEM in each patient [7]. A case report describes an adolescent with AN and epileptic seizures, who was treated with valproate and clonazepam, with a good outcome on seizures and EEG abnormalities [3]. The authors reported a positive effect of the treatment on ED symptoms as well, with an improvement in compliance, and food and weight acceptance. A last case report describes a rapid resolution of refractory bulimia and affective symptoms in a young woman [8]. This evidence was collected in a review of McElroy and colleagues, who concluded that AEDs associated with weight gain, such as valproate, may be useful in the treatment of patients with AN [3].

Based on these data, evidence in favour of the use of valproate remains considerably scarce. Our study documents treatment with valproate in a case series of 14 children and adolescents with AN, who were hospitalized in a FED specialized centre.

Methods

Patients

This study is a retrospective chart review of patients, who were hospitalized between 01/01/2013 and 31/12/2019 in the Regional Centre for Feeding and Eating Disorders in children and adolescents in Bologna, Italy. Inclusion criteria were a) a diagnosis of Anorexia Nervosa according to the Diagnostic and Statistical Manual of Mental Disorders-fifth edition (DSM-5) criteria [1]; b) a treatment with valproate during hospitalization in our centre; c) acquisition of informed consent. Patients without complete clinical documentation were excluded from the study. Diagnoses of AN were performed by clinicians trained in the field of FED. Demographic and clinical data were obtained for all patients. Concerning the treatment with valproate, we recorded: the length of treatment, the dosage at introduction, the maximum dosage, the frequency of dosing (once daily (OD), twice daily (BDS), three times per day (TDS)), and formulation (non-chrono, Chrono). Reasons for the administration and for the interruption of the treatment, if it became necessary, were documented as well. Clinical evidence of adverse-effect reactions (ADR) was also recorded. Plasma levels of platelets (PLT), alanine transaminase (ALT) and aspartate transaminase (AST) were recorded before and after the start of valproate. The results of abdominal and pelvic ultrasounds were reported. Blood levels of valproic acid and concurrent drugs were considered as well. All the psychopharmacological treatments, which were administered concurrently with valproate, were noted, as well as the use of Naso-Gastric Tube feeding (NGT) when deemed necessary. Body mass index (BMI) of the patients at hospital admission and discharge was recorded.

Statistical analysis

All statistical analyses were performed using JASP, version 0.14.1 for Windows. Given the specific nature of the study (case series) and the small sample size ($n = 14$), only descriptive statistical analyses were performed.

Results

Demographic and clinical variables

Of 195 inpatients hospitalized between 01/01/2013 and 31/12/2019, 14 patients with a diagnosis of AN and receiving treatment with valproate were enrolled in the study. The main characteristics of the patients are reported in Table 1. The sample consisted of 13 females (92.9%) and one male (7.1%). The mean age at admission was 15.9 (± 1.6) years. The mean duration of hospitalization was 111.9 (± 77.59) days. Concerning body measures, the mean BMI at admission was 14.1 (± 1.3), and the mean BMI at discharge was 15.5 (± 1.3). The mean difference between admission and discharge was + 1.4 (± 1.0), (range + 0.030– + 3.5). Considering only female patients, 1 (7.7%) presented primary amenorrhea and 9 (69.2%) showed secondary amenorrhea, with a mean duration of 15.1 (± 10.8) months before the first administration of valproate.

Treatments with valproate

The mean dosage at the start of the valproate treatment was 241.7 (± 73.3) mg, with a minimum of 100 and a maximum of 400 mg. The mean maximum reached dosage was 521.4 (± 204.5) mg (range 200–1000 mg). The most

Table 1 Demographic and clinical characteristics of the patients

	Diagnosis	Como rbidity	Age at admission (years)	Admission BMI	Discharge BMI	Concurrent treatments	VPA at start (mg)	VPA max (mg)	Treatme nt with VPA (days)	Freque ncy	Reason for introduction	Inter rupti on	ADR
Patient 1	ANR		14.9	14.52	15.4	Sertraline (concurrent)	250	500 (C)	17	OD	Compliance	Ineffi cacy	
Patient 2	ANA	OCD, MDD	16.6	15.37	16.93	Fluvoxamine and pimozide (concurrent)	300	300 (C)	242	OD	Compliance		
Patient 3	ANR		15.1	16.36	17.61	Olanzapine (concurrent)	200	500	63	BDS	Compliance		
Patient 4	ANR		15.4	12.5	12.53		250	500	14	BDS	Aggressiveness, compliance		Somn olence
Patient 5	ANR		14.5	12.7	15.84	Risperidone, then quetiapine, then quetiapine + sertraline	250	500	67	BDS	Unstable mood		
Patient 6	ANR		16	14	15.28	Sertraline, then sertraline + olanzapine	250	500	43	BDS	Unstable mood, compliance		
Patient 7	ANR		16.5	15.32	15.95		200	200	14	OD	Unstable mood		
Patient 8	ANB		17.9	12.77	14.83	Venlafaxine	100	600	63	BDS	Aggressiveness		
Patient 9	ANR		13.6	13.02	16.5	Olanzapine, promazine (concurrent)	300	600	12	TDS	Unstable mood, compliance	Ineffi cacy	
Patient 10	ANR		19.5	15.17	15.58	Clotiapine and escitalopram, then risperidone	400	400	48	BDS	Unstable mood	Ineffi cacy	
Patient 11	ANB		16.4	13.41	15.39	Quetiapine (concurrent)	200	800	132	BDS	Mood, compliance		

Table 1 (continued)

	Diagnosis	Como rbid-ity	Age at admission (years)	Admission BMI	Discharge BMI	Concurrent treatments	VPA at start (mg)	VPA max (mg)	Treatme nt with VPA (days)	Freque ncy	Reason for introduction	Inter rupti on	ADR
Patient 12	ANR	BD-II	15.5	14.26	15	Olanzapine, sertraline (concur-rent)		1000 (C)		BDS	Unstable mood		
Patient 13	ANR	BPE	13.7	12.75	13.65	Risperidone, fluoxetine (concur-rent)	200	300	34	OD	Unstable mood, psychotic symptoms		
Patient 14	ANR	MDD	16.3	15.7	17	Aripipra-zole, then aripipra-zole + ser-traline		600 (C)	60	BDS	Unstable mood, aggres-siveness	Ineffi cacy	

ANA Atypical Anorexia Nervosa; *ANB* Anorexia Nervosa, binge/purging; *ANR* Anorexia Nervosa, restrictive; *ADR* Adverse Drug Reactions; *BDS* two times daily; *BD-II* Bipolar Disorder, type II; *BMI* Body-mass Index; *BPE* Brief Psychotic Episode; *C* Chrono formulation; *MDD* Major Depressive Disorder; *OCD* Obsessive–Compulsive Disorder; *OD* once daily; *TDS* three times daily

frequent treatment scheme at maximum dosages was twice daily (nine patients, 64.3%), followed by once daily in the morning (three patients, 21.4%), once daily in the evening (one patient, 7.1%) and three times daily (one patient). Four patients (28.6%) received Chrono formulation (prolonged release) (patients 1, 2, 13, and 15). The mean duration of inpatient treatment with valproate was 62.2 (± 63.1) days. The most frequent reasons for the administration of valproate were unstable mood (57.1%) and insufficient compliance with the psychological and nutritional program (seven patients, 50%), followed by aggressive behaviour (21.4%). Four out of 14 patients (28.6%) interrupted their treatment with valproate due to lack of clinical efficacy in treatment goals. The remaining patients (71.4%) continued valproate intake during the hospitalization and were discharged with the indication to continue treatment with valproate, due to its positive effect on the target symptoms for an initial period pending an outpatient treatment. The mean plasmatic level of VPA, measured at the highest dosage of VPA, was 66.3 (± 25.0) mg/L. Because of secondary amenorrhea and reduced bone density, one patient started HRT with nomegestrol acetate 5 mg, on the last day of hospitalization, but no further assessment of VPA levels was performed. No patient experienced gynaecological symptoms or alterations of the menstrual cycle after beginning treatment with valproate.

Adverse drug reactions

One patient in 14 (7.1%) reported an ADR, namely, somnolence. The main variations in PLT, AST and ALT values after the introduction of valproate are reported in Table 2. The minimum and maximum variations in PLT levels were − 63.0 × 10^3/microL and + 36.0 × 10^3/microL, respectively, with a 124 × 10^3/microL as the lowest reached level. With respect to ALT, the minimum and maximum variations were − 90.0 U/L and + 12.0 U/L, respectively, with a maximum post-VPA level of 37.0 U/L. Concerning the AST, the minimum and maximum variations were − 374.0 and + 23.0, respectively, with a maximum post-VPA level of 56.0 U/L. Prior to the start of valproate treatment, complete abdominal ultrasounds were performed in eight patients, revealing intraperitoneal fluid in five cases. No patient presented alterations in the liver or other abdominal sites. Pelvic ultrasounds performed in two patients revealed, in both cases, minimally visible ovaries, with scantily ovarian follicles. No sign of PCOS was documented. No patient was treated with more than two drugs other that valproate at the same time, and all the treatments were started as monotherapies. As for concurrent treatments, plasma levels of concurrent second-generation antipsychotics (SGA) were obtained in three cases (patient 3, 5 and 11). Patient 3 was assuming olanzapine (5 mg/day), with a pre-valproate plasma level

Table 2 Levels of PLT, AST and ALT before and after introduction of VPA

	Before VPA	After VPA	Difference	Reference
PLT ($\times 10^3$/microL)	208.2 (± 35.3)	199.9 (± 39.4)	− 8.1 (± 31.6)	150–380
AST (U/L)	27.3 (± 26.3)	22.3 (± 6.8)	− 5.5 (± 28.3)	< 32
ALT (U/L)	52.6 (± 105.1)	14.0 (± 8.0)	− 31.3 (± 108.8)	< 31

ALT alanine transaminase; *AST* aspartate transaminase; *PLT* platelets; *VPA* valproate

of 41 mcg/L (reference: 20–80 mcg/L). One month after initial administration of valproate, even though olanzapine was increased to 7.5 mg/day, olanzapine plasma level reached 29 mcg/L. Patient 5 started valproic acid one while on risperidone 1 mg for 1 month. Risperidone levels were assessed only 1 week after the start of valproic acid, reaching 10 mcg/L (reference: 20–60 mcg/L). As for patient 11, quetiapine up to 75 mg/day was started while in treatment with valproate. Quetiapine plasma levels remained non-measurable (< 5 mcg/L; reference: 70–170 mcg/L) whether after one or after 3 months since quetiapine introduction.

Discussion

The use of valproate in the treatment of Anorexia Nervosa and Feeding and Eating Disorders in general in children and adolescents is currently not indicated due to lack of evidence [2]. To date, one small case series and three case reports have documented cases of FED treated with valproate, with a total of six cases presented in literature (three with AN). Our case series reports on the use of valproate as an adjunctive treatment for 14 patients with AN. Thus, it represents the largest and most homogenous sample of patients with FED treated with valproate described in literature so far.

None of our patients received valproate as a primary psychopharmacological intervention to target eating disorder-specific psychopathology. Unstable mood (57.1%), lack of compliance (50%) and aggressive behaviour (21.4%) represented the reasons for valproate introduction. An effect on target symptoms was obtained on 10/14 patients (71.4%). An effect of valproate has been documented for non-FED patients in previous studies for unstable mood and aggressiveness [4]. Thus, these symptoms may represent a potential therapeutic target for valproate in AN.

All of our patients were hospitalized with a primary therapeutic goal of weight restoration. They received a psychological, nutritional psychiatric inpatient treatment, of which valproate should be considered a treatment augmentation. With regard to weight restoration, all of the patients improved their BMI during hospitalization, with a mean modification of was + 1.4 (± 1.0) kg/m^2. In all of the cases the discharge BMI was superior to admission BMI, although one patient gained a non-relevant improvement (+ 0.03). Despite its potential effect on weight increase [4], modifications of weight in our sample seem to result from the complete therapeutic intervention, rather than the sole use of valproate. However, a possible effect of valproate on compliance, aggressiveness and unstable mood could have positively influenced the global therapeutic effect. Since FED may occur in comorbidity with diverse mental disorders, such as bipolar disorder, substance abuse and Autism Spectrum Disorder [9, 10], with potential effects on prognosis, the effect of valproate on behavioural and psychiatric symptoms complicating FED could have an impact on clinical management.

Significantly, only one of our patients (7.1%) experienced a side effect, somnolence, from the administration of valproate. We observed no increase in liver enzymes, either in AST or in ALT levels. When considering effects on platelets levels (possible reduction), we found a limited modification of PLT after introduction of valproate − 8.1 (± 31.6) × 10^3/microL and a maximum reduction of − 63.0 × 10^3/microL. None of our patients experienced cytopenia. Thus, administration of valproate did not cause evident ADR in liver enzymes and PLT levels in our sample. The effect of different plasmatic concentrations of valproate on metabolic parameters should be assessed by clinical studies. Interestingly, for the two patients with documented plasma levels of SGA in our sample, we observed a decreased level of olanzapine after valproate introduction, a failure to reach measurable quetiapine levels, and low risperidone levels. Valproate has been indicated to influence plasma concentrations of other psychiatric treatments, with evidence of different pharmacokinetic interactions with antipsychotics, antidepressants, and AED [4]. Given the frequent polypharmacotherapy of patients with severe AN, and the possible alterations in liver function and fluid concentrations related to this condition, we suggest that the association between valproate and SGA should carefully be weighed and monitored in the treatment of ED.

Teratogenesis, PCOS and interactions with HRT may represent possible gynecological adverse effects of treatment with valproate. Valproate is a major teratogen, and its use in females of childbearing potential is currently avoided [5]. In this study, valproate was administered inpatient females, with the indication to continue this therapy after hospital discharge, for an initial period pending an outpatient treatment. Despite the risk of an unprogrammed pregnancy in patients with acute AN can

be presumed lower than in unaffected peers, a recent meta-analysis has documented that reproductive function can be restored by appropriate AN treatment and weight regain [10]. Clinician and patients should be aware of the risk of valproate therapy, and a special pregnancy prevention program should be implemented. Concerning amenorrhea, this symptom was present in 10/13 females in our sample prior to the administration of valproate. No evident gynecological alteration or sign of PCOS emerged. One patient started HRT during valproate treatment, but no further dosage of VPA levels was performed. Notwithstanding these data, we believe prescribers should carefully weigh the administration of valproate to adolescent females, especially in the case of highly gynecologically impaired patients with AN. Moreover, the possible interaction between HRT and VPA, as demonstrated for other AEDs [6], should also be verified for valproate.

Strengths and limits

The evidence presented in this study suggests a possible role of valproate in the treatment of anorexia nervosa. Although a direct effect of valproate on core symptoms of AN has never been investigated, adjunctive treatments with valproate could be viable in selected cases, specifically when low compliance with treatment programs, aggressive behaviours and unstable mood prevent patients with acute psychopathological symptoms of AN from following a psychological and nutritional treatment.

This study has some limitations. Given its nature as a case series, we cannot propose clinical hypotheses on the basis of the collected data. The limited sample does not allow us to make direct correlational analyses or generalize to broader clinical populations. Nevertheless, this paper describes the largest series to date of patients with FED who have been treated with valproate, increasing the total number of cases described in literature from 6 to 20. Future studies should assess our results in broader populations and with comparison groups.

What is already known on this subject?

The use of valproate in the treatment of Anorexia Nervosa (AN) is not recommended by clinical guidelines due to lack of evidence. Data published in case reports and a small case series suggest that valproate could play a role in the management of aggressive and behavioural symptoms co-occurring with Feeding and Eating Disorders (FED).

What does this study add?

This study retrospectively describes a case series of 14 young patients with AN, who were treated with adjunctive valproate in an inpatient treatment program. Administration of valproate was started to manage compliance and behavioural disturbances. In most of the patients, the introduction of valproate was followed be an improvement of target symptoms, with minor adverse drug reactions. Low concurrent plasma levels of antipsychotics were noticed in two patients. The findings described in this study could have implications for clinical practice even if clinicians and patients should be aware of the risk of valproate therapy, and a special pregnancy prevention program should be implemented.

Author contribution AP and JP reviewed literature data, collected and analysed the data, wrote the manuscript, and revised the manuscript.

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Availability of data and materials The data sets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the Human Research Ethics Committee of the University of Technology Sydney (UTS) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics approval was obtained from the local Ethical Committee prior to conducting this research.

Informed consent Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

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