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RESEARCH ARTICLE

Therapeutic drug monitoring in adolescents with anorexia nervosa for safe treatment with adjunct olanzapine

Andreas Karwautz[1] | **Michael Zeiler**[1] | **Julia Schwarzenberg**[1] | **Dunja Mairhofer**[1] | **Michaela Mitterer**[1] | **Stefanie Truttmann**[1] | **Julia Philipp**[1] | **Doris Koubek**[1] | **Maria Glüder**[1] | **Gudrun Wagner**[1] | **Anouk Malcher**[1] | **Gabriele Schöfbeck**[1] | **Clarissa Laczkovics**[1] | **Hans W. Rock**[2] | **Annika Zanko**[3] | **Hartmut Imgart**[3] | **Tobias Banaschewski**[4] | **Christian Fleischhaker**[5] | **Christoph U. Correll**[6] | **Christoph Wewetzer**[7] | **Susanne Walitza**[8] | **Regina Taurines**[9] | **Stefanie Fekete**[9] | **Marcel Romanos**[9] | **Karin Egberts**[9] | **Manfred Gerlach**[9]

[1]Eating Disorders Care and Research Unit, Department of Child and Adolescent Psychiatry, Medical University of Vienna, Wien, Austria

[2]CIO Marburg GmbH, Fronhausen, Germany

[3]Parklandklinik, Bad Wildungen, Germany

[4]Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Mannheim, Germany

[5]Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Center Freiburg, Freiburg, Germany

[6]Berlin Department of Child and Adolescent Psychiatry, Psychosomatic Medicine and Psychotherapy, Charité University Medical Center, Berlin, Germany

[7]Kliniken der Stadt Köln GmbH, Clinic for Child and Adolescent Psychiatry Holweide, Children's Hospital Amsterdamer Straße, Cologne, Germany

[8]Department of Child and Adolescent Psychiatry and Psychotherapy, University Hospital of Psychiatry Zurich, Zürich, Switzerland

[9]Department of Child and Adolescent Psychiatry, University of Würzburg, Würzburg, Germany

Correspondence
Andreas Karwautz, Eating Disorders Care and Research Unit, Department of Child and Adolescent Psychiatry, Medical University Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.
Email: andreas.karwautz@meduniwien.ac.at

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Abstract

Objective: Medication is commonly used in anorexia nervosa (AN) despite largely missing high grade evidence. Olanzapine (OLZ) is the best-evidenced substance used off-label in this group, with conflicting outcome regarding BMI, clinical and safety parameters. Therefore, it is important to strictly assure quality of treatment with OLZ in AN by using 'Therapeutic Drug

Karin Egberts and Manfred Gerlach shared last authorship.

Monitoring' according to AGNP-guidelines, including serum levels and adverse drug reactions (ADRs) to support safety for adolescents with AN and attempt to generate an initial age- and disorder-specific therapeutic reference range.

Method: Sixty-five adolescents with AN (aged 10–18) treated with OLZ (98% female; 97.5% AN-restricting-type) were prospectively observed, ADRs reported, and correlations between dosage and serum levels measured at trough level were calculated, a preliminary therapeutic range defined.

Results: Mean dosage of OLZ was 8.15 (SD: 2.91) mg and 0.19 (SD: 0.07) mg/kg respectively, average concentration was 26.57 (SD: 13.46) ng/mL. Correlation between daily dosage/dosage per kg and serum level was 0.72 (**$p < 0.001$)/0.65 (**$p < 0.001$), respectively. ADRs with impairment were rare (6.3%). 75% improved clinically (CGI). BMI increased significantly by 1.5 kg/m^2 ($t = 10.6$, $p < 0.001$). A preliminary therapeutic reference range is 11.9 and 39.9 ng/mL.

Conclusions: OLZ in the hands of specialists is a well-tolerated and safe treatment adjunct for adolescents with AN.

KEYWORDS
adolescents, adverse drug reactions, anorexia nervosa, olanzapine, TDM

Highlights

- Olanzapine in adolescents with anorexia nervosa is a safe and well-tolerated adjunct to a multidisciplinary inpatient treatment approach using therapeutic drug monitoring.
- Correlations of dosage and serum levels are high.
- A preliminary disorder- and age-specific reference range was successfully defined for the first time.

1 | INTRODUCTION

Therapeutic Drug Monitoring (TDM) has been used and implemented in child and adolescent psychopharmacology as a comprehensive surveillance system of drug use in off-label situations. TDM is strongly recommended for the use of drugs in children and adolescents, in particular when a drug has no marketing authorisation for use in specific disorders or for a certain age group (Egberts et al., 2015; Gerlach et al., 2016; Hiemke et al., 2018), to minimise legal and safety problems for physicians and patients. TDM can ideally be offered in natural treatment settings (Egberts et al., 2022; Karwautz et al., 2013; Mitterer-Asadi et al., 2014) as described and set into scene within the 'Network of TDM in child and adolescent psychiatry e.V.' (TDM-KJP; Egberts et al., 2021, 2015; Egberts et al., 2022).

1.1 | TDM in eating disorders

TDM, and as part of this the measurement of serum concentrations of drugs in particular, was rarely used in adolescent populations with eating disorders so far. In fact, only three studies have been published, all reporting on the use of olanzapine (OLZ). Fekete et al. (2017) included 39 adolescent patients with eating disorders (35 with typical anorexia nervosa [AN], 2 with atypical AN and 2 with bulimia nervosa) recruited from five German centres. This is the only study so far reporting data on daily dosing (mean: 9.23 [SD: 4.18] mg/day), serum levels (mean: 32.8 [SD: 23.7] ng/mL), and correlations between dosage and serum level (r_s: 0.62). Bachmann et al. (2008) reported a large variability of OLZ concentrations in adolescent patients but included 5 AN patients only. Theisen et al. (2006) included 13 AN patients using a

mean dose of 7.5 mg (range: 5–15) of OLZ resulting in serum levels of high variability ranging from 1.0 to 62.6 ng/mL (mean: 18.7 ng/mL). Dose-corrected serum concentrations were found to be similar compared with 80 schizophrenia patients.

In the largest study to date—however, in adults only–by Attia et al. (2019) plasma levels are reported. The mean OLZ dose in adults was 7.77 mg/day. Serum levels of OLZ were measured at 8 and 16 weeks of outpatient treatment and averaged 21 ng/mL (SD 12.8) after 8 and 22 ng/mL (SD 18.2) after 16 weeks.

OLZ is approved for the treatment of schizophrenia and of manic or mixed episodes associated with bipolar 1 disorder in adolescents aged 13–17 years by the U.S. Food and Drug Administration (FDA), but not by the European Medicines Agency. Its use for the core-symptoms of AN is discussed since many years with cognitive ruminations and excessive fear of gaining weight being candidates for targeted treatment with antipsychotics, in particular (Fekete et al., 2017; Mehler-Wex et al., 2008). The use of OLZ in AN has strong evidence; however, this evidence is limited to improvements in weight gain (Himmerich et al., 2023). OLZ is well tolerated in the largest study to date in adults (Attia et al., 2019) with no short-term influence on serum parameters. For OLZ, therapeutic reference ranges of blood concentrations are reported in patients with schizophrenia only and only one study commented on a possible therapeutic reference range in minors; however, not specified for diagnoses and eating disorders in particular (Fekete et al., 2017).

2 | AIMS

We aimed to investigate in a naturalistic setting (1) the correlations of OLZ-doses with the OLZ-serum levels, (2) the short-term safety of OLZ in an adolescent cohort with AN by measuring potential adverse drug reactions (ADRs) of this agent during the study period using standardized measures and serum markers, (3) whether OLZ influences clinical outcome measured by changes in Global Clinical Impression (GCI) Scale, and (4) to derive preliminary therapeutic reference ranges for OLZ in adolescent AN.

We hypothesised that during the application of a multidimensional treatment programme for adolescent with AN including adjunctive treatment with OLZ (1) the doses given and the serum levels measured will correlate highly-independently of co-medication, (2) OLZ is safe in the short-term with rare ADRs and if present, rarely severe, and (3) GCI scores will improve and (4) it will be possible to estimate first data on a preliminary therapeutic range for this drug in this very vulnerable population. Overall, applying TDM as a safety tool should lead to enhanced coping with the disease and its treatment and more guidance on safety.

This study is the TDM-study with the largest number of adolescent patients with AN so far setting in scene the most rigorous system of surveillance for safety.

3 | METHODS

3.1 | Study design and procedure

Data was prospectively collected from 2009 to 2018 at inpatient departments specialised in the treatment of eating disorders (child and adolescent psychiatry or psychosomatics) using multidimensional and multidisciplinary treatment approaches (Mairhofer et al., 2021) in Germany, Switzerland and Austria using an Internet-based patient registry for structured data documentation. All study centres are members of the competence network for TDM in child and adolescent psychiatry (www.tdm-kjp.com; for details see Mehler-Wex et al. (2009)). Twenty-one patients were recruited as part of the TDM-KJP network study, and 44 patients as part of the TDM-VIGIL pharmacovigilance study' (EudraCT 2013-004881-33) funded by the German Federal Institute for Drugs and Medical Devices (BfArM-code: V-15322/68605/2013–2018). For an overview on the study design as well as primary and other secondary outcome measures see Egberts et al. (2022). The study was carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The independent ethics committees of all participating centres approved the study.

Those patients who were clinically judged by the responsible consultant child and adolescent psychiatrist to eventually profit from psychopharmacologic support were—together with their parents- asked to participate in this open-observational and documentation within the TDM-patient registry system. Written informed consent was obtained from both patients and parents. Participation did not influence the clinical decision if or which drug has to be offered. The responsible consultant was completely free to decide if and which dosage of the medication and co-medications are used in each single case. Any kind of co-medications were allowed.

Outcome assessments (details see below) took place at several time points during the study period. However, in the present work, two time points (at baseline prior to the onset of OLZ-administration and at discharge reflecting the last TDM-registry entry) were included in the analysis.

3.2 | Inclusion criteria

Patients were eligible for inclusion when they (a) were below the age of 18 at admission, (b) had typical or atypical AN according to ICD-10 classification of both subtypes (restricting or binge-purging), (c) took OLZ to address the core symptomatology of AN as prescribed by the treating consultant child and adolescent psychiatrist, (d) were treated within an inpatient setting of a specialised department taking part in the Competence Network for TDM in child and adolescent psychiatry (www.tdm-kjp.com; Mehler-Wex et al., 2008), and (e) provided personal written informed consent (in addition to their parents) for being included in the study and for having documented their data in the TDM-registry.

3.3 | Exclusion criteria

Patients were excluded from the study when (a) they were not able to understand the procedure due to cognitive impairments, (b) did not consent to all parts of the study protocol (e.g. taking blood samples, undertaking clinical interviews, completing outcome questionnaires), or (c) did not consent to take OLZ for AN core symptomatology. All other patients were eligible for inclusion into this naturalistic observational study.

3.4 | Measures and instruments

3.4.1 | TDM procedure

TDM was performed adhering to the guidelines of the AGNP (Hiemke et al., 2018). OLZ serum levels were measured in the special laboratory for TDM of the Centre of Mental Health of the University Hospital Würzburg. Blood was taken from cubital veins at steady-state conditions into 7.5 mL monovettes without anti-coagulation factors or additives. Steady state is normally reached in OLZ after 5 half-life periods (approx. 35 h → 175 h). Serum levels only were included if they have been taken after more than 7 days on steady-state conditions (280 h). Blood was taken at trough level between 12 and 24 h after the last OLZ dose and before the first daily dose was administered. Blood was centrifuged at 1800 g for 10 min and then analysed immediately or within 3 days after postage to the TDM-laboratory. Serum concentrations of OLZ were analysed by an automated column-switching method coupled to an isocratic high-performance liquid chromatography system and a variable ultraviolet detector as described in detail elsewhere (Fekete et al., 2017).

3.4.2 | Baseline (T0) and outcome (T1) parameters

The following parameters were assessed at baseline (T0, prior to the onset of OLZ intake) and/or at discharge reflecting the last TDM entry (T1):

Body height and weight were measured at T0 and T1. The body-mass-index (BMI) as well as sex- and age-adjusted BMI percentiles and BMI standard deviation scores (SDS) according to available normative data (Kromeyer-Hauschild et al., 2001) were calculated.

The diagnosis of AN was made using ICD-10 criteria for AN typical (F50.0) and AN atypical (F50.1) and AN restricting type (F50.00) and AN binge-purging type (F50.01), respectively (World Health Organization, 1993).

Clinical severity was measured by the Clinical Global Impressions Scale (Guy, 1976) using the subscale 'severity (CGI-S)' assessed by clinician's judgement. Scores on the CGI-S ranged from 1 = not ill at all to 7 = most extremely ill (T0, T1). Clinical improvement was measured using the CGI subscale 'global improvement (CGI-I)' (T1) which was also based on the clinician's judgement. The CGI-I ranged from −3 (very much worse) to +3 (very much better) with a value of 0 indicating no change in the clinical impression. For the purpose of this study, this score was also dichotomised by categorising patients with any improvement (from +1 = moderately better to +3 = very much better) into one group (subsequently names as 'responders') and patients with no change (0) and any deteriorations (−1 to −3) into another group (subsequently named as 'non-responders'). Suicidality was obtained through clinical judgement and along with the PAERS assessment (see below).

Global functioning was measured by Global Assessment of Functioning (GAF, American Psychiatric Association, 2000) ranging from 1 (persistent danger for oneself or other) to 100 (maximum level of functioning, no symptoms) (T0, T1).

3.4.3 | Adverse drug reactions (ADRs)

Several measures were included to assess ADRs: First, the 'Clinical Global Impression—Side Effects Scale' (CGI-SE, Guy, 1976) which is a brief 4-point rating scale assessing ADRs based on the clinician's judgement (1 = no ADRs, 2 = ADRs not significantly interfering with the patient's functioning, 3 = ADRs significantly interfering with patient's functioning, 4 = ADRs stronger than efficacy) was obtained at T1.

Second, the 'Paediatric Adverse Event Rating Scale' (PAERS, Wehmeier et al., 2008)- designed to measure symptoms and ADRs–was obtained at T0 and T1. This

instruments consists of 56 physical and psychological symptoms that may occur in the context of drug administration and which are assessed during a clinical interview for their presence (yes vs. no), suspected association with the drug administration, severity and functional impairment. However, it must be noted that some items are reflecting ED related symptoms, which we expect to improve but not worsen during ED treatment (weight gain, increase in appetite). Thus, weight gain and increase in appetite was not considered as ADRs in the present study. A symptom was considered as an ADR if it was supposed to be associated with the intake of the primary psychiatric medication or a psychiatric comedication at T1 based on the clinician's judgement. In addition, the presence of any PAERS symptoms (irrespective of their suspected association with the drug) was obtained at T0 and T1 and we also considered change in PAERS symptoms from T0 to T1.

Third, we also documented (severe) ADRs in a special form that were recorded to the study coordinator and/or to the sponsoring medical agency (BfArM).

Forth, in order to see whether OLZ has a negative effect on serum markers during this short-term evaluation, we explored changes in several serum markers (e.g. prolactin, haemoglobin, creatinine) between T0 and T1.

3.5 | Data analysis

The statistical analysis was performed using IBM SPSS Statistics 27.0. Statistical significance was set to $p < 0.05$ if not described otherwise. Apart from descriptive statistics (mean, SD, percentages), we calculated Pearson correlation coefficients to analyse the association between OLZ dosage and OLZ serum concentrations for the total sample and patient subgroups. Differences in daily OLZ dosage and serum levels between patient subgroups were explored using *t*-tests. Following the approach by Hiemke et al. (2018) we determined a preliminary therapeutic range for OLZ in adolescents with AN by calculating the arithmetic mean of the OLZ serum concentration of patients who responded to the treatment. The mean +/− 1SD then results in the preliminary therapeutic range. Alternatively, the preliminary therapeutic range is defined by the interquartile range (IQR) of the OLZ serum concentration of responders (Hiemke et al., 2018). Response was defined twofold: (1) At least moderately improvement in the CGI-I; (2) at least 0.8 kg weight gain per week.

The change in clinical symptoms including weight, BMI, BMI percentile and GAF from T0 to T1 was analysed using independent *t*-tests. Associations between clinical outcomes (CGI-I response status average weekly weight change, response status based on average weekly weight gain: ≥0.8 kg/week vs. < 0.8 kg/week) and the OLZ serum concentration were analysed using *t*-tests and Pearson correlation.

Descriptive statistics were primarily used to explore potential ADRs. However, we also calculated the Pearson correlation coefficient to describe the association between the OLZ serum concentration and the number of reported ADRs (PAERS items) at T1. Moreover, we performed McNemar tests to analyse the change in the occurrence of PAERS symptoms from T0 to T1.

In order to explore potentially adverse T0-T1 changes in serum markers, we performed *t*-tests for matched samples considering a total of 35 serum markers assessed in the clinical routine (due to missing data, the sample size was different for each serum marker, see results). To account for multiple testing, a Bonferroni-adjusted significance level of 0.001 was used for these analyses.

We also performed a post-hoc power analysis to calculate the achieved power of this study to detect pre-post changes (*t*-test for matched samples) in the most relevant outcome variables (weight, BMI, GAF) given the achieved sample size, effect size and a significance level of 0.05. The post-hoc calculated power was >99% for the change in weight and BMI as well as 98% for the change in GAF scores.

4 | RESULTS

4.1 | Study participants

The study population consisted of 65 adolescents treated at child and adolescent psychiatric/psychosomatic wards specialised in the treatment of juvenile eating disorders between 2009 and 2018. Information on diagnoses, subtype of AN and origin are given in Table 1. Treatment teams were not biased towards their clinical decisions of whether they used OLZ or not or also whether they used a different drug by the status of the patient being included in the TDM-study or not. The responsible clinician got feedback on the serum levels along with a recommendation on how to respond properly in case of noticeable low or high serum levels, for example, reducing or enhancing the dosage, checking compliance or influential factors.

4.1.1 | Clinical baseline characteristics (T0)

Clinical baseline characteristics, global functioning, severity and suicidality are given in Table 1. The mean global level of functioning of the patients according to

Variable	N	%	Variable	Mean (SD)	Range
Gender			Age	15.11 (1.78)	10–18
Female	64	98.5	Clinical characteristics		
Male	1	1.5	Body weight in kg	38.95 (6.3)	21.4–58.0
Diagnosis			Body height in m	1.62 (0.09)	1.3–1.8
Typical AN (F50.0)	63	97.0	BMI (kg/m^2)	14.68 (1.6)	10.8–19.3
Atypical AN (F50.1)	2	3.0	BMI percentile	2.25 (5.2)	<0.1–30.2
Restrictive subtype	41	87.0	BMI SDS	−2.97 (1.2)	−6.4–0.5
Binge-purging subtype	6	13.0	Functioning		
Subtype unknown	18		Global functioning (GAF)	47.6 (1.2)	24–70
Origin					
Vienna, AT	47	72.3			
Würzburg, D	7	10.8			
Bad Wildungen, D	6	9.2			
Berlin, D	1	1.5			
Freiburg, D	1	1.5			
Köln, D	1	1.5			
Mannheim, D	1	1.5			
Zürich, CH	1	1.5			
Severity of illness (CGI-S)					
Moderately ill	2	3.2			
Markedly ill	28	45.2			
Severely ill	25	40.3			
Extremely ill	7	11.3			
Not known	3	4.8			
DSM-5 severity					
Mild	16	24.6			
Moderate	12	18.5			
Severe	16	24.6			
Extreme	20	30.8			
Unknown	1	1.5			
Suicidality					
Present	1	1.5			
Absent	48	73.8			
Unknown	16	24.7			

TABLE 1 Study participants, diagnoses, origin, clinical characteristics, functioning, severity and suicidality measured at baseline (n = 65 patients with AN).

GAF-score was 47.6 (serious symptoms and serious impairment) (SD: 1.2) ranging between 24 (severe inability to function in almost all areas) and 70 (some mild symptoms and some difficulty in functioning). The investigated cohort showed moderate to extreme illness severity with the majority suffering from marked and severe illness (n = 53; 85.5%). Suicidality was absent in nearly three quarters of the cases.

4.2 | Intervention

OLZ treatment started after the baseline visit and lasted 54.5 days in average (SD: 63; median: 33 days; range: 7–371 days; IQR: 21–61) until the last observed visit which included the measure of the OLZ serum level under steady-state conditions. Thus, the period between baseline (T0) and last available measurement (T1) was 7.78 (SD: 9.3) weeks in average with a median of 4 weeks (range: 1–53; IQR: 3–8).

4.2.1 | OLZ monotherapy versus OLZ with co-medication

OLZ was administered as monotherapy in 30 (46.2%) and together with psycho-pharmacological co-medication in 35 (53.8%) of the cases. As co-medication antidepressants (mostly mirtazapine, fluoxetine or sertraline) were used (reported if used at any time point irrespective of duration and dosage) in 34 (52.3%) of the cases, antipsychotics were used in 6 (9.2%) and benzodiazepines (in particular lorazepam) in 8 (12.3%) of the cases.

4.3 | OLZ serum concentration in relation to OLZ dosage

In the total sample of 65 patients the mean daily dose of OLZ used was 8.15 (SD: 2.91) mg and 0.19 (SD: 0.07) mg per kg taking their body weight into account. The mean con-centration of OLZ was 26.57 (SD: 13.46) ng/mL. The correlations of daily dose and OLZ se-rum concentration was 0.72 ($p < 0.001$), that of daily dose per kg and serum concentration was 0.65 ($p < 0.001$) (see Figure 1).

Daily dosage, OLZ serum concentrations and dosage-serum concentration correlations separately for different subgroups of patients are shown in Table 2. There were no statistically significant differences regarding daily dosage, daily dosage per body weight and OLZ serum concentrations between younger versus older adolescents, very lean patients (<third BMI percentile) and those above the third BMI percentile and between patients receiving OLZ monotherapy and those receiving psychiatric co-medication (all t-test not significant with p-values >0.190). In all these sub-groups the correlations between daily dosage or daily dosage per kg were high and statistically significant (all correlations $p < 0.01$).

4.4 | Adverse drug reactions (ADRs)

Measured by means of the CGI-S, no ADRs were reported in 9 (14.3%) patients, ADRs not significantly interfering with the patient's functioning in 50 (79.4%) cases, and ADRs significantly interfering with the patient's functioning in 4 (6.3%) cases. There was no case for whom ADRs were rated as being stronger than the drug's clinical efficacy. Summarising, 93.7% experienced no significant interference with their functioning by OLZ treatment.

ADRs were also measured in detail by PAERS-ratings at T1 in all 65 cases. Any ADRs (=PAERS symptom supposed to be associated with the medication regardless of severity) were observed in 73.8% of patients (mean number of ADRs: 4.28, SD: 5.28, median: 3.0, IQR: 0–5.5). The most frequent reported ADRs are shown in Figure 2.

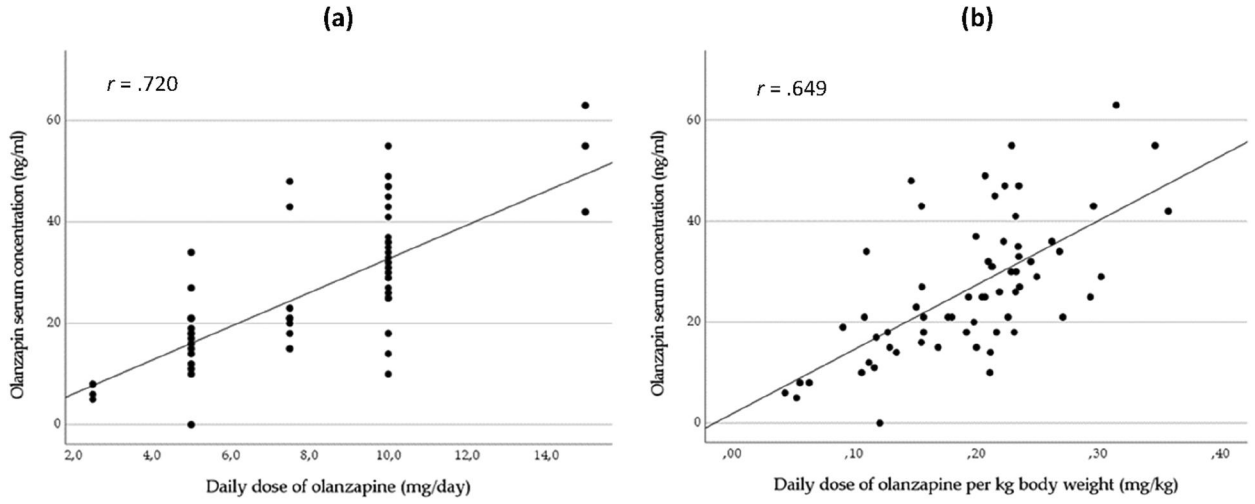

FIGURE 1 Scatter plot showing the association between the (a) daily dose of OLZ; (b) daily dose OLZ per kg body weight with the OLZ serum concentration at steady state conditions in 65 patients with anorexia nervosa.

TABLE 2 OLZ serum concentrations and dosage-serum concentration correlations.

Sample	OLZ daily dose (mg) Mean (SD)	OLZ daily dose per kg (mg/kg) Mean (SD)	OLZ serum concentration (ng/mL) Mean (SD)	Correlation (mg × ng/mL)	Correlation (mg/kg × ng/mL)
Total (n = 65)	8.15 (2.91)	0.19 (0.07)	26.57 (13.46)	0.720**	0.649**
Age ≤14 years (n = 26)	7.98 (2.74)	0.20 (0.06)	26.19 (13.42)	0.783**	0.710**
Age >14 years (n = 39)	8.27 (3.04)	0.19 (0.07)	26.82 (13.66)	0.684**	0.632**
BMI <3rd percentile (n = 33)	8.33 (3.04)	0.20 (0.07)	25.58 (13.88)	0.738**	0.728**
BMI ≥3rd percentile (n = 32)	7.97 (2.80)	0.18 (0.06)	27.59 (13.16)	0.717**	0.605**
OLZ monotherapy (n = 30)	7.83 (2.69)	0.19 (0.06)	25.07 (13.56)	0.619**	0.595*
OLZ & co-medication (n = 35)	8.43 (3.10)	0.20 (0.07)	27.86 (13.43)	0.793**	0.689**

Abbreviations: BMI body-mass-index; OLZ olanzapine.

*p < 0.01, **p < 0.001.

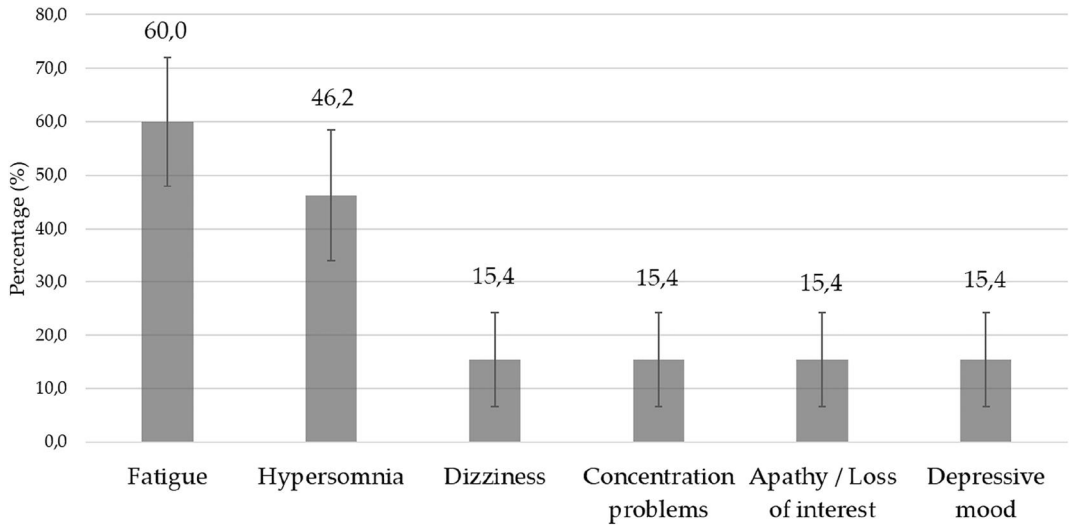

FIGURE 2 Percentage of patients with ADRs (PAERS items with suspected association with the medication) at T1 (only ADRs occurring in at least 10 patients are shown). Error bars represent 95% confidence intervals.

A complete list of the prevalence of adverse events is provided in Table S1.

It is also important to clarify whether the ADRs are related to OLZ serum concentrations. Indeed, there was a medium-sized significant association between the OLZ serum concentration and the number of ADRs at T1 (r = 0.284, t = 2.349, p = 0.022, see also Figure 3).

Additionally, we have looked at any PAERS symptoms reported at baseline (T0) and at the time of last TDM entry (T1) irrespective of their association to the medication. At T0, a mean number of 12.00 (SD: 6.44) symptoms (regardless of their severity) was reported (median: 11, range: 0–30, IQR: 8–16). At T1, a mean number of 10.49 (SD: 5.39) was reported (median: 10; range 1–23, IQR: 6–14.5) while the most prevalent symptoms were depressive mood (80.0%), fatigue (73.8%), irritated or bad mood (61.5%), hypersomnia (49.2%), hair loss or abnormal hair growth (49.2%), concentration problems (44.6%) and agitation (43.1%) of which the majority of symptoms were of mild or moderate severity.

PAERS symptoms newly emerging at T1 although not yet present at baseline assessment may be regarded

as candidates for ADRs. At T1, 38.5% of patients showed fatigue and hypersomnia although not yet present at T0 which represents a statistically significant deterioration (McNemar-tests: $p < 0.001$). This is also in line with the prevalence of ADRs shown in Figure 3.

A detailed table on the prevalence of PAERS symptoms at T0 and T1 including their severity and functional impairment as well as changes between T0 and T1 are provided in the Table S1.

4.4.1 | Changes in routine/safety/laboratory serum values/markers

Laboratory serum values that showed a statistically significant change from T0 to T1 (on a significance level of $\alpha = 0.001$ adjusted according to Bonferroni) are shown in Table 3. A significant increase in serum levels was observed for leucocytes, free T3, prolactin, anorganic phosphate and IFG-1, while a significant decrease was

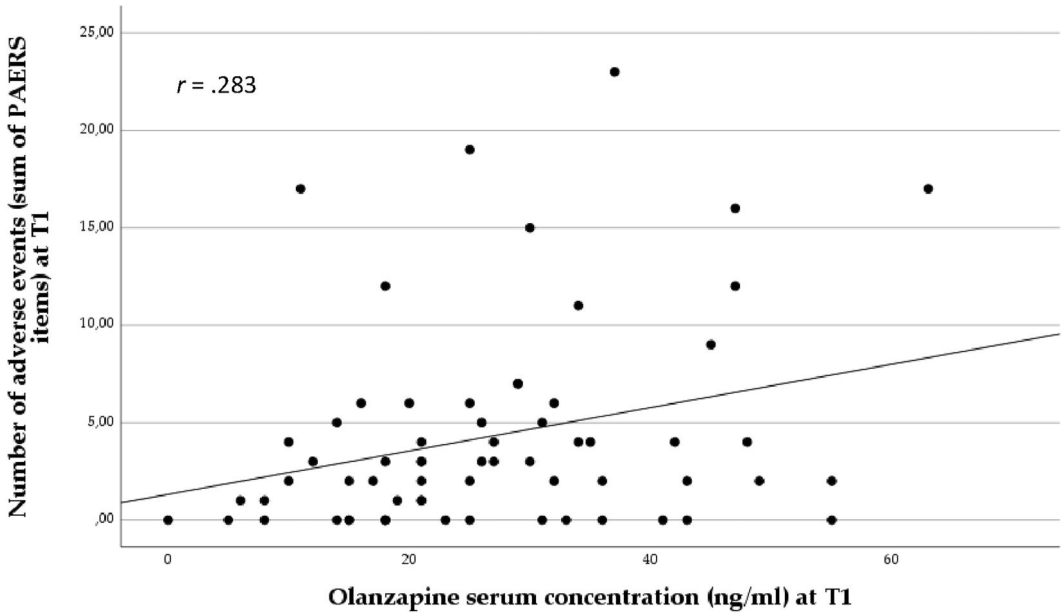

FIGURE 3 Scatter plot showing the association between the OLZ serum concentration and the number of ADRs at T1 ($n = 64$).

TABLE 3 T0-T1 changes in serum markers (serum markers that showed a statistically significant change $p \leq 0.001$ presented only).

Serum marker (n)	T0 Mean (SD)	T1 Mean (SD)	Difference t(df), p-value	Individual serum level at T1 compared to the reference range[a]		
				Below	Within range	Above
Haemoglobin g/dL ($n = 54$)	13.24 (1.09)	12.81 (0.94)	−2.719 (53), 0.009	16.7%	81.5%	1.9%
Leucocytes G/L ($n = 54$)	4.72 (1.12)	5.28 (1.10)	3.746 (53), <0.001	24.1%	75.9%	0.0%
Free T3 pg/mL ($n = 32$)	2.04 (0.75)	2.65 (0.65)	3.784 (31), 0.001	27.3%	72.7%	0.0%
Prolactin ng/mL ($n = 31$)	**23.13 (22.97)**	**42.95 (24.03)**	**4.402 (30), <0.001**	**3.1%**	**15.6%**	**81.3%**
Magnesium mmol/L ($n = 46$)	0.89 (0.08)	0.84 (0.06)	−4.444 (45), <0.001	0.0%	81.5%	8.5%
Inorganic phosphate mmol/L ($n = 49$)	1.24 (0.15)	1.36 (0.15)	4.306 (48), <0.001	0.0%	100%	0.0%
Creatinine mg/dL ($n = 54$)	0.77 (0.14)	0.67 (0.13)	−5.077 (53), <0.001	20.4%	72.2%	7.4%
Total bilirubin mg/dL ($n = 47$)	0.68 (0.58)	0.43 (0.24)	−3.691 (46), 0.001	n.a.	83.0%	17.0%
SHBG nmol/L ($n = 27$)	143.19 (69.94)	74.59 (26.90)	−5.774 (26), <0.001	[b]	[b]	[b]
IGF-1 ng/mL ($n = 26$)	156.46 (86.77)	248.04 (60.62)	5.398 (25), <0.001	3.4%	96.6%	0.0%

Note: Bold values indicate that this parameter is significantly different in T0 versus T1.

[a]The following reference ranges were used: Haemoglobin [12.0–15.0], Leucocytes [4.5–12.0], Free T3 [2.28–5.01], Prolactin [4.8–23.3], Magnesium [0.70–0.91], Inorganic phosphate [1.00–1.70], Creatinine [0.57–0.87], Total bilirubin [0.0–0.6], IGF-1 [101.0–576.3].

[b]No reference range available.

observed in magnesium, creatinine, total bilirubin and SHBG. Serum levels for most of the serum markers were within the recommended reference range at T1 in most cases indicating that the T0-T1 changes may not be clinically relevant (and some as free T3 increase with recovery of AN) except for prolactin. At T1, the prolactin serum level was above the reference range in 81.3% of patients. Furthermore, the OLZ serum concentration was moderately to strongly associated with the prolactin level at T1 ($r = 0.441$, $p = 0.012$).

4.4.2 | ADRs reported to the study coordinator/medical agency

In seven cases we had to report ADRs to the study coordinator. In two patients the ADRs were severe (suicide attempt while previous suicide attempts were known from the patient's history), in five patients the ADRs were rated as non-severe. We reported 10 different ADRs, 7 of them occurred once (fatigue, vertigo, high spirits, apathy, incontinence, concentration difficulties, emotional variability) and 3 of them twice (hypersomnia, in-crease of prolactin, suicide attempt).

4.5 | Change in clinical symptoms and associations with OLZ serum concentration

From the baseline (T0) to the discharge (T1) assessment, AN patients significantly improved in weight (meanΔ 3.9 kg, $t(61) = 10.891$, $p < 0.001$), BMI (meanΔ 1.5 kg/m^2, $t(61) = 10.599$, $p < 0.001$) and BMI percentile (meanΔ 5.7, $t(61) = 5.694$, $p < 0.001$). Moreover, GAF scores significantly improved from 47.82 to 54.00 on average ($t(61) = 4.076$, $p < 0.001$). With regard to the CGI-I, 48 patients (75.0%) responded to the treatment (at least moderate improvement based on the clinician's judgement), while 9 patients (14.1%) showed no change and 7 patients (11.0%) showed a deterioration.

CGI-I responders (mean: 27.25, SD: 11.36) did not significantly differ from non-responders (mean: 25.90, SD: 13.97) with regard to the OLZ serum concentration ($t(62) = 0.350$, $p = 0.727$). Furthermore, only a small statistically non-significant association between the OLZ serum concentration and average weekly weight change was observed ($r = 0.192$, $p = 0.134$, see Figure S1). Moreover, patients showing a response to the treatment defined as an average weekly weight gain of a minimum of 0.8 kg did not statistically differ between patients who did not show a response with regard to the OLZ serum concentration ($t(\text{df}) = 1.188$, $p = 0.240$, $d = 0.30$, see Figure S2).

4.6 | Preliminary therapeutic range for OLZ in AN derived from the present data

Patients who showed a response to the treatment (at least moderate improvement in the CGI-I scale) had a mean OLZ serum concentration of 25.90 ng/mL (SD: 13.97). Thus, the preliminary therapeutic range (mean +/− 1 SD) for AN in adolescents is calculated to be between 11.9 and 39.9 ng/mL when using 5, 7.5 or 10 mg OLZ with a mean dosage of 8.1 mg (SD: 2.21). Using the IQR, the preliminary therapeutic range was calculated to be between 15.0 and 33.5 ng/mL. Alternatively, response in AN can be defined as a weekly average weight gain of a minimum of 0.8 kg. Patients having managed to reach this goal in weight gain, showed an average OLZ serum concentration of 27.79 ng/mL (SD: 14.76) which resulted in a slightly different preliminary therapeutic reference range of 13.0–42.6 ng/mL when using 5, 7.5, 10 or 15 mg OLZ with a mean dosage of 8.4 mg (SD: 3.37). Using the IQR, the preliminary therapeutic range was between 16.5 and 39.0 ng/mL.

The highest serum level measured in a patient was 63 ng/mL at a dose of 15 mg per day, thus no patient reached a serum concentration exceeding the recommended therapeutic reference range defined by Fekete et al. (2017) for adolescents (20–80 ng/mL).

5 | DISCUSSION

Our study is the first using elaborate TDM-measures in a larger sample of adolescent inpatients suffering from AN treated with the antipsychotic drug OLZ as part of a multidimensional therapeutic approach. Our 65 adolescent inpatients treated in 8 centres suffered from moderate to extreme AN in the majority of the cases (85.5%) and with a moderate to extreme DSM-5 severity rating according to BMI in the majority of the cases (75.4%). The inpatient setting enables good surveillance of medication intake by the nursing team securing compliance.

First, we found a high correlation of daily dosage of OLZ and OLZ serum concentration (0.72) and a somewhat lower correlation of daily dosage per kg and serum concentration (0.65). This is true for patients below the age of 14 and those above, patients with a BMI below the third percentile or those above, and patients treated with OLZ with or without psychiatric co-medication.

Bachmann et al. (2008) and Theisen et al. (2006) both found high intra- and inter-individual variability of serum levels; however, in a sample of adolescents with various psychiatric disorders with the majority having psychotic disorders treated in in- and outpatient settings and including low numbers of AN patients only ($n = 5$ or

13, resp.). Inter-individual variability was lowest in AN compared to schizophrenia (Theisen et al., 2006) with correlation between dosage and serum concentration of 0.8 in AN versus 0.5 in schizophrenia. This correlation is comparable with our data.

Compared with Fekete et al. (2017) including 39 adolescent patients with eating disorders (mainly AN) our patients were treated with similar average daily doses (9.23 [SD: 4.18] mg/day versus our data: 8.15 [SD: 2.9]), had similar average serum levels measured at the same TDM-laboratory (32.8 [SD: 23.7] ng/mL versus our data: 26.6 [SD: 13.5]) with similar correlations between daily doses and serum levels (r: 0.62 vs. our data: r: 0.72). This is important as the same TDM-laboratory method was used. In addition we looked specifically at weight-adjusted measures for this thin population with a similar correlation between serum concentration and daily dosage per kg body weight of 0.65.

Overall, high correlation between dosage and serum concentration found in AN patients of this age group is good news for practitioners as it suggests that using daily standard dosages of OLZ between 5 and 15 mg do not result in over- or under-treatment and neither potentially ineffective or even toxic serum concentrations in this vulnerable population. The result of a significant correlation of OLZ dosage and serum concentration also with hindsight of age, leanness, and co-medication is good news for safety of treatment with OLZ in adolescent AN. Thus, using dosages between 2.5 and 15 mg of this medication in patients with this diagnosis without serum concentration outliers does allow to check serum concentrations in adolescents treated with OLZ at steady-state only. Patients without treatment response (no weight gain, no change in eating disorder specific symptomatology) should be checked for OLZ-serum concentrations.

Second, we found high short-term safety by measuring ADRs and serum markers. Six percent only (n = 4 patients) experienced ADRs with relevant impairment. The number of ADRs was positively associated with OLZ serum concentrations. Fatigue and hypersomnia were the two most common ADRs not present at inclusion. Indeed, AN patients receiving OLZ seem to show a higher number of ADRs compared to the entire sample of patients included in the TDM-VIGIL study (73.8% vs. 57.7%). However, the percentage of severe adverse events was similar (6.3% vs. 5.3%). Thus, psychopharmacological treatment of AN patients need careful monitoring of ADRs. Those with adverse events during treatment should be checked for OLZ-serum concentrations.

The good tolerability (in 94%) of OLZ found was similar to the study by Pruccoli et al. (2022) (86%), Fekete et al. (2017) (92.5%), and Spettigue et al. (2018) (100%). The number of ADRs was significantly associated with OLZ serum levels, contrary to Fekete et al. (2017) who found no association. However, the association we found was medium–sized only after controlling for co-medication, and Fekete et al. (2017) did not distinguish in detail AN-patients from psychotic patients on the ADRs measures.

Serum prolactin was the only serum marker with a clinically relevant increase and positively associated with OLZ serum concentration. Regarding serum markers, the marginal changes with no impact during the first 4 weeks found by us are in line with the most detailed study on serum measures by Swenne and Rosling (2011) who found an increase in prolactin and in part TSH as the only changes of relevance during this time period related to medication. An increase in prolactin levels in 32% of OLZ patients observed in another study (Spettigue et al., 2018) was higher than in our study, while the prolactin increase occurred within the first few weeks in most cases; however, the overall number of patients with prolactin increase was small (n = 7). Nevertheless, hyperprolactinemia has influence on reproductivity with amenorrhoea and sexual dysfunction being of clinical importance. We thus conclude that OLZ should be administered as short as possible (no longer than about 10 weeks) and, if needed, carefully monitored in the longer term (e.g. serum checks every month). Moreover, dosage higher than 10 mg should lead to higher vigilance regarding prolactin status.

Third, this TDM-pharmacovigilance study was not designed for evaluating efficacy or effectiveness of OLZ in adolescent patients with AN. We investigated, whether in the group of patients receiving a specialised multidimensional inpatient treatment with adjunct OLZ body weight, clinical presentation (by CGI-I), and global functioning (GAF) would improve.

These results are by large comparable with the results by Fekete et al. (2017), Norris et al. (2011), and Pruccoli et al. (2022) but contrary to Kafantaris et al. (2011) and partly in line with Attia et al. (2019) in adults. The numbers of minor patients treated is low in Kafantaris et al. (2011) (n = 10) and Spettigue et al. (2018) (n = 10), and medium in Norris et al. (2011) (n = 43). As there is no control group in observational TDM-studies we are unable to give firm information on potential efficacy of OLZ in adolescent AN.

Forth, to define a preliminary therapeutic range for this vulnerable population is important. Kloosterboer et al. (2020) report on the sparse evidence on concentrations-effect correlations of psychotropic medication in minors in general and on therapeutic reference ranges being not evaluated or reported. Fekete et al. (2017)

($n = 115$) authored the only paper to date suggesting a reference range (20–80 ng/mL) for OLZ treatment of adolescents with mixed disorders (psychotic disorders and AN) similar to that in adults and in schizophrenia.

Depending on the specific method and definition of response, we calculated a preliminary therapeutic range for OLZ in adolescent AN to be between 11.9 and 39.9 ng/mL which is narrower compared with that suggested by Fekete et al. (2017).

5.1 | Strengths

Our report refers to a relatively large number of patients with strictly diagnosed AN mainly of high severity within a small age range, resulting in a quite homogenous sample. Rigorous quality measures (serum concentrations, ADRs) were used by a state-of-the-art TDM system designed precisely for this age group under psychopharmacological treatments. Our TDM-study is the only study to date complying with all quality criteria reported by Kloosterboer et al. (2020). Patients are derived from multiple eating disorder specialised treatment sites using the same methodology. ADRs were measured taking into account that some symptoms assessed are present before treatment and this has been controlled for. Further, it is an open study without controls mirroring naturalistic situations in clinical practice (a strength and a limitation). We are able to suggest a preliminary therapeutic range of OLZ for adolescents with AN and conclude that adjunct OLZ treatment is a safe intervention for adolescent AN in the short term.

5.2 | Limitations

Our report is limited to a short period of time averaging about 7.8 weeks. Thus, all results and recommendations need to refer to this limited time perspective. It is an open study without controls mirroring naturalistic situations in clinical practice. As there is no control group within this prospective observational TDM-study conclusions on potential efficacy/effectiveness cannot be drawn. We did not systematically assess insulin and fasting glucose (Kafantaris et al. (2011)) due to practical reasons and restraints. We did not control for CYP-genotypes, smoking, concurrent disease, food-drug interactions, brain maturation, and drug-drug interactions. As in some patients the dosage had to be adapted (reduced or enhanced) as a result of serum concentration reports to the clinicians this could have led to under-detection of ADRs at T1.

5.3 | Conclusions

OLZ in the hands of child and adolescent psychiatrists and/or AN-specialists is a well-tolerated and safe psychopharmacological treatment option. As part of a multidimensional inpatient treatment setting for adolescents with AN, the use of adjunct OLZ resulted in positive effects on weight-gain and therapeutic outcome.

AUTHOR CONTRIBUTIONS

Conceptualisation, Manfred Gerlach, Karin Egberts, Andreas Karwautz; methodology, Manfred Gerlach, Karin Egberts, Andreas Karwautz; software, Hans W. Rock; formal analysis, Michael Zeiler; investigation, Julia Schwarzenberg, Dunja Mairhofer, Michaela Mitterer, Julia Philipp, Doris Koubek, Maria Glüder, Gudrun Wagner, Anouk Malcher, Gabriele Schöfbeck, Clarissa Laczkovics, Annika Zanko, Tobias Banaschewski, Hans W. Rock, Christoph U. Correll, Christoph Wewetzer, Susanne Walitza, Regina Taurines, Stefanie Fekete, Marcel Romanos; data curation, Hans W. Rock, Michael Zeiler; writing – original draft preparation, Andreas Karwautz; writing – review and editing, Michael Zeiler, Manfred Gerlach, Karin Egberts, Andreas Karwautz; visualisation, Andreas Karwautz, Michael Zeiler; supervision, Andreas Karwautz, Hartmut Imgart, Karin Egberts; project administration, Karin Egberts, Andreas Karwautz, Hartmut Imgart; funding acquisition, Manfred Gerlach, Karin Egberts. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, A.K., upon reasonable request.

ETHICAL STATEMENTS

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2008, and approved by the Ethics Committee of the Medical University of Vienna (protocol code: 223/2008, date of approval: 01.07.2008 and protocol code: 2186/2013, date of approval: 19.11.2014).

PATIENT CONSENT STATEMENT

Informed consent was obtained from all subjects (and legal representatives if subjects aged <18) involved in the study.

ORCID

Andreas Karwautz https://orcid.org/0000-0001-9053-998X
Michael Zeiler https://orcid.org/0000-0002-7087-6134
Clarissa Laczkovics https://orcid.org/0000-0002-0492-2286
Karin Egberts https://orcid.org/0000-0002-0270-0954

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