Comprehensive Psychiatry 115 (2022) 152301

Contents lists available at ScienceDirect

Comprehensive Psychiatry

journal homepage: www.elsevier.com/locate/comppsych

Therapeutic drug monitoring of sertraline in children and adolescents: A naturalistic study with insights into the clinical response and treatment of obsessive-compulsive disorder

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https://doi.org/10.1016/j.comppsych.2022.152301
Received 2 October 2021; Received in revised form 7 February 2022; Accepted 18 February 2022
Available online 26 February 2022

ARTICLE INFO

Keywords:
TDM
antidepressants
selective serotonin reuptake inhibitors
pharmacovigilance
steady state concentration

ABSTRACT

Background: Sertraline is a selective serotonin reuptake inhibitor with specific indications in child and adolescent psychiatry. Notwithstanding its frequent use and clinical benefits, the relationship between pharmacokinetics, pharmacodynamics, efficacy, and tolerability of sertraline across indications, particularly in non-adult patients, is not fully understood.

Method: This naturalistic therapeutic drug monitoring (TDM) study was conducted in a transdiagnostic sample of children and adolescents treated with sertraline ($n = 78$; mean age, 14.22 ± 2.39; range, 7–18 years) within the prospective multicenter "TDM-VIGIL" project. Associations between dose, serum concentration, and medication-specific therapeutic and side effects based on the Clinical Global Impression scale were examined. Tolerability was measured qualitatively with the 56-item Pediatric Adverse Event Rating Scale.

Results: A strong linear positive dose–serum concentration relationship (with dose explaining 45% of the variance in concentration) and significant effects of weight and co-medication were found. Neither dose nor serum concentration were associated with side effects. An overall mild-to-moderate tolerability profile of sertraline was observed. In contrast with the transdiagnostic analysis that did not indicate an effect of concentration, when split into depression (MDD) and obsessive-compulsive disorder (OCD) diagnoses, the probability of clinical improvement significantly increased as both dose and concentration increased for OCD, but not for MDD.

Conclusions: This TDM–flexible-dose study revealed a significant diagnosis-specific effect between sertraline serum concentration and clinical efficacy for pediatric OCD. While TDM already guides clinical decision-making regarding compliance, dose calibration, and drug–drug interactions, combining TDM with other methods, such as pharmacogenetics, may facilitate a personalized medicine approach in psychiatry.

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) play an important role in treatment strategies across a range of psychiatric indications, including depression and obsessive-compulsive disorder (OCD). Major depression is linked to severe functional impairment and is a remediable risk factor for suicide [1,2]. OCD is another highly debilitating disorder [3,4] manifesting specifically as recurrent and persistent thoughts and compulsions to suppress them through certain behaviors [5,6]. Notably, for about half of diagnosed adult cases, the onset of OCD occurs in childhood or adolescence [7,8]. Sertraline, which is the focus of this work, is considered a first-line medication for children and adolescents with OCD owing to its efficacy profile and good overall tolerability [6,9,10]. Several well-controlled studies have indicated the superiority of this drug over placebo for treating OCD in this age group [9,11,12]. Despite its frequent use, sertraline has been documented to deliver both significant and non-significant effects on improvement in children and adolescents treated for depression [13–15]. This naphthalenamine derivative acts as a highly selective SSRI that weakly inhibits norepinephrine and dopamine receptors [16], and it is generally linked to low concomitant sedation owing to its low affinity to the cholinergic, histaminergic, and alpha-adrenergic receptors [17,18]. Sertraline is also subject to a first-pass metabolism and broken down into *N*-desmethylsertraline, among other metabolites [16,19], with multiple cytochrome P450 (CYP) isoforms involved in this biotransformation [20,21].

Notwithstanding the high level of success and precision in identifying the biological mechanisms behind the action of sertraline both in vitro and in vivo [22–24], the few relevant studies conducted so far in therapeutic settings have failed to find a clear concentration–clinical effect relationship [25–27]. Indeed, the observed variability of responses to drugs from the SSRI family in pediatric clinical trials is substantial, especially for depressive and anxiety disorders [28,29]. Symptom improvement may also require higher doses for OCD compared to major depressive disorder (MDD) [30]. This may be associated with differing symptom responsiveness and neurobiology underlying these disorders [17], including possible differential mechanisms of serotonin neurotransmission, such as short-term availability and long-term postsynaptic receptor changes [31]. Another age-related aspect is that the recommendations regarding sertraline dosage for children and adolescents (25–200 mg, once daily) [9,32] is mostly derived from extrapolating findings from adults, which largely ignores often-observed differences in drug pharmacokinetics and pharmacodynamics in young individuals [33–35]. Accordingly, the application of adult guidelines may result in under- or over-dosage; the former possibility may lead to ineffective treatment, while the latter presents a risk of toxicity. Notably, no reference levels for sertraline concentration are available in children and adolescents. Pharmacokinetics and pharmacodynamics of psychoactive drugs change across the developmental trajectory owing to multiple mechanisms [36]. CYP activity varies with age [37], confering different rates of clearance with a possibly substantial impact on the maximum concentration (C_{max}), half life ($t_{1/2}$), and area under the curve (AUC) [38]. Obvious organic changes during development relate to total body weight, as well as hormonal and pubertal processes. Factors found to influence the fate of a drug in children and adolescents relative to adults include typically higher gastrointestinal resorption, lower binding capacity of lipophilic drugs with plasma proteins and fat tissues, higher glomerular filtration rate, proportionally (to body size) larger liver size, which may contribute to a higher biotransformation rate, and different volumes of distribution [36]. Children and adolescents may thus metabolize drugs differently and have a distinct related dose–response curves, and they also possess a dynamically developing receptor and neurotransmitter system [39,40]. Young persons also seem to be more sensitive to gastrointestinal complaints, such as abdominal pain and vomiting, as well as to be at risk of activating side effects, agitation, and suicidal thoughts [41–45]. Collectively, these aspects typify the unique side effect profile that may emerge in the pediatric population. Therefore, in the treatment of children, titration must be conducted very carefully. Especially in routine clinical practice, the aspects of inter-individual variability in pharmacokinetic response, polypharmacy, and adherence to the prescribed medication regime merit special attention [46].

An objective method to effectively monitor pharmacotherapy is therapeutic drug monitoring (TDM) [47,48], a branch of clinical pharmacology and related bio-sampling and analytic tools [49] for quantifying drug concentrations or their breakdown products in the serum [50,51]. In practice, this approach involves measuring the steady-state drug concentration (i.e., an achieved equilibrium between dose rate and elimination rate) and adjusting the dose in order to reach a concentration known to be efficacious. As such, TDM may be an important component of personalized medicine [52]. Moreover, the field of developmentally informed pharmacotherapy [53] and the relevance of drug safety and pharmacovigilance of psychotropic medication, especially in pediatric populations [54], have been recognized by a growing number of clinicians and researchers. Therefore, there is a need for more studies meeting the highest safety standards while addressing the age- and development-related effects of common and novel psychotropic

medications. So far, TDM has delivered numerous insights into childhood and adolescent psychopharmacology [30,55–58].

The aim of this naturalistic multicentric study was to investigate the associations between dosage, steady state serum concentration, clinical effects, and adverse reactions in a sample of children and adolescents treated with sertraline. First, we tested the linear relationship between dose and concentration. Age, time interval between initiation of therapy with sertraline and blood collection, gender, and weight [15], but also smoking status and concomitant medication were included in the statistical model, as there is evidence that nicotine and polypharmacy may influence the metabolism of antidepressants [47,48]. Subsequent to the initial transdiagnostic approach of the study, in consideration of the disorder-specific rationale, we further tested the hypothesis that the dose and serum concentration are associated with clinical efficacy (measured on an ordered scale) in dependency of diagnosis. We hypothesized that this effect would be statistically significant for OCD patients, but not for MDD patients, given the relatively larger effect size of SSRIs in the treatment of youth with OCD compared to MDD [59].

2. Materials and methods

2.1. Study population and design

The present study is part of the larger prospective multicenter "TDM-VIGIL" (www.tdm-kjp.de) project investigating psychiatric prescription medication in children and adolescents [60,61]. The project was authorized by the ethics committee of the lead study center (University Hospital Wuerzburg; 301/13) and the local ethics committees of the participating centers, is registered in the European Clinical Trials Database (EudraCT: 2013–004881-33), and was conducted according to the Declaration of Helsinki. Data were collected in Germany, Austria, and Switzerland within the competence network TDM in child and adolescent psychiatry. Treatment, response assessment, blood collection, and laboratory drug concentration measurements were conducted within a routine healthcare setting via three different modalities, i.e., inpatient, outpatient, and day-treatment units. The treatment course was monitored by experienced child and adolescent psychiatrists who reported any suggestion of non-compliance. Specifically, compliance was assessed using a pre-defined rating schema ("certain,", "probable,", "uncertain,", "verifiable error in medication intake") and recorded at the timepoint of blood collection/serum concentration measurement, regardless of the setting. Eligible patients were recruited from those starting pharmacotherapy with sertraline or alternatively switching to sertraline, regardless of their diagnosis. Patients attended at least four sessions, and the monitoring period was at least 6 months and varied according to the individual therapy course. For patients for whom more than one TDM measurement was accessible, the chronologically last available and valid data point was used in the analysis. The CGI interview took place on the day of blood sample collection. Additionally, an individual's data were excluded (7.8% of individuals) if a non-compliance issue was noted, intoxication was inferred (intoxication as an indication for TDM did not occur in the analyzed dataset), or the interval between blood collection and laboratory analysis exceeded 72 h.

2.2. Patient assessments

All patients underwent a medical examination by a physician, including assessment of vital signs, electrocardiography, and laboratory blood tests of hepatic and renal function. Clinical diagnoses were made by child and adolescent psychiatrists according to the International Classification of Diseases 10th Revision (ICD-10). Treatment response and potential adverse reactions were quantified on the day of blood collection using the clinician-administered Clinical Global Impression (CGI) scale [62] rated on the basis of drug effects only. The corresponding clinical outcome categories (CGI Therapeutic Effects) were as follows: 1, unchanged or worse; 2, minimal (slight improvement); 3, moderate (decided improvement); 4, marked (vast improvement). The medication-related adverse reactions (CGI Side Effects) were rated as follows: 1, none; 2, does not significantly interfere with patient functioning; 3, significantly interferes with patient functioning; 4, outweighs therapeutic effect. We used these two CGI scales, because unlike the CGI Improvement and CGI Severity indices, they were answered specifically in relation to sertraline and not with respect to "overall therapy" effects. In addition, a detailed and more descriptive assessment of adverse responses to sertraline was conducted using the Pediatric Adverse Event Rating Scale (PAERS) [63]. This clinician-administered instrument was specifically designed to quantify the severity of 56 signs describing adverse events occurring in pediatric patients under treatment with a psychotropic drug. The items were assessed on a five-point Likert scale ("none," "slight," "moderate," "severe," "extremely severe") and also according to whether they were related to the medication. Only the effects related to sertraline, and not to concurrent psychiatric or somatic medication, were of relevance in this work. PAERS assessments have been applied and validated in previous pharmacotherapy studies [64–66]. Indications for the TDM measurement, detailed information on co-medication, nicotine use, weight, and height were also documented.

2.3. Serum concentration analysis

TDM was conducted according to the consensus guidelines of the Working Group on Neuropsychopharmacology and Pharmacopsychiatry (AGNP) [67]. Blood samples were collected at a steady-state trough level from cubital veins into 7.5-mL monovettes without anticoagulants or additives. The samples were centrifuged at 1800 $\times g$ for 10 min and analyzed immediately (samples from Wuerzburg, Germany) or after postage to the TDM laboratory in Wuerzburg, Germany. The concentrations of sertraline were determined using an isocratic reversed-phase high-performance liquid chromatography (RP-HPLC) method (Agilent 1200 series, Agilent Technologies Inc., Santa Clara, CA, USA) with UV-absorbance detection as described previously in detail [30]. Internal quality control samples were integrated into each analytical series, and external control samples were analyzed quarterly. The responsible laboratory is certified by a quality control program (https://www.instand-ev.de). Analytical grade chemicals and solvents were acquired from Sigma-Aldrich Chemie GmbH (Taufkirchen, Germany).

2.4. Statistical data analysis

Out of 88 patients medicated with sertraline, 81 met the quality control criteria for blood analysis, while another three individuals were excluded owing to missing CGI data, resulting in the inclusion of a total of 78 individuals in the analysis. First, linear regression was used to evaluate the relationship between the daily dose of sertraline (in mg) and drug serum concentration (in ng/mL). Models with and without covariates were compared based upon model fit. The covariates included body weight, age, sex, smoking status, co-medication status, and time interval between initiation of therapy with sertraline and blood collection. Spearman's rank correlations between serum concentration, dose, and weight-adjusted dose were additionally calculated for comparison with previous studies. Second, ordinal logistic regressions (proportional odds models) were used to examine the dosage and serum concentration as predictors of clinical efficacy and adverse responses. The parallel regression assumption was checked using the Brant test [68]. Third, to identify an optimal cutoff value for dosage or serum concentration separating good ($n = 50$) and poor responders ($n = 28$) to sertraline (constructed by combining the "marked" and "moderate" categories and the "unchanged" and "minimal" categories, respectively), a receiver operating curve (ROC) analysis was performed using a binary logistic regression model. The optimal threshold between good and poor responders was calculated by simultaneously maximizing the sensitivity and specificity. This analysis was also repeated for the two

largest diagnostic groups in our sample, i.e., OCD (14 responders, 7 non-responders) and depression (22 responders, 11 non-responders). Furthermore, an ordinal regression model was used to test the hypothesized interaction between dosage (and serum concentration) and clinical response in these two groups, OCD ($n = 21$) and depression ($n = 36$). Other diagnoses were less common, and they were numbered as follows: anorexia nervosa ($n = 7$), PTSD ($n = 3$), other anxiety disorders ($n = 2$; panic disorder, mixed anxiety and depressive disorder), autistic spectrum disorder ($n = 2$), and other single diagnoses ($n = 8$). Finally, for an observed significant concentration effect, we calculated, for good responders (defined by pooling both "marked" and "moderate" outcome categories), the 25th–75th interquartile range and the SD interval to the mean, which can be considered a tentative therapeutic reference range [69]. The statistical analyses were performed using R version 4.0.5 (R Foundation for Statistical Computing). The significance threshold was defined as an alpha value of 0.05. The PAERS results are presented descriptively as the percentage of adverse events and most frequently reported items (occurring three times or more) of "slight" and "moderate" severity.

3. Results

Descriptive statistics of main sociodemographic and clinical data, expressed as means with standard deviations or counts with corresponding percentages, for the whole sample and separately for OCD and depression subgroups, are provided in Table 1. In the total sample, the mean daily sertraline dosage was 108.65 ± 49.81 mg (range: 25–250), and the related mean steady-state serum concentration was 42.37 ± 26.43 ng/mL (range: 7–139). Nearly two thirds of the patients responded to sertraline with marked or moderate improvement (11.5% and 52.6%, respectively), while almost one third of the patients responded minimally (32.1%); no improvement or worsening responses were relatively uncommon (3.8%) in this open label study. Additionally, 51 of 78 patients in our dataset were medicated with sertraline for the first time.

There was a strong positive relationship between dosage and serum concentration of sertraline ($\beta = 0.68$, $p < 0.001$). The daily sertraline dose explained 45.5% of the variance in serum concentration (adjusted $R^2_{M1} = 0.455$, $F_{1,76} = 65.39$, $p < 0.001$). Fig. 1 shows the best-fit line and related variability of the effect. Spearman's rank correlation coefficient between dosage and serum concentration was significant ($\rho = 0.722$, $p < 0.001$). When evaluating the body weight-adjusted doses instead (mg · kg^{-1} · day^{-1}), this correlation was even higher ($\rho = 0.782$, $p < 0.001$). The model with covariates explained 56.1% of the variance in serum concentration. The three statistically significant predictors of concentration in the multiple regression equation (adjusted $R^2_{M1} = 0.561$, $F_{7,70} = 15.07$, $p < 0.001$) were dose ($\beta = 0.768$, $p < 0.001$), body weight ($\beta = -0.346$, $p = 0.002$), and co-medication ($\beta = 0.191$, $p = 0.017$). The model with covariate predictors explained significantly more variance than the model without covariate predictors (adjusted $R^2_{M2\text{-}M1} = 0.106$, $SS = 7455.7$, $F_{6,70} = 4.05$, $p = 0.002$). In order to explore the possible impact of the weights of patients with an eating disorder, this analysis was conducted again without the inclusion of seven anorexia nervosa patients, revealing a very similar effect of body weight ($\beta = -0.375$, $p = 0.001$). The exclusion of three patients weighing over 100 kg also gave a comparable result of body weight ($\beta = -0.270$, $p = 0.008$) and had only a minimal impact on other effects.

The ordered logistic analysis revealed statistically significant dosage and clinical efficacy effects ($\beta = 0.013$, $SE\ \beta = 0.005$, $OR = 1.013$ [95% CI 1.004–1.023], $p = 0.005$). There was no significant effect observed in this analysis of serum drug concentration on clinical and adverse recations or of dosage on adverse reactions. In a similar analysis repeated with the covariates, the effect of dose remained significant, and there were no further significant effects observed, including for the covariates. While there was no evidence linking side effects with dosage or concentration, overall slight and moderate levels of adverse responses (in

Table 1
Study population characteristics.

Characteristic	All ($n = 78$)	OCD ($n = 21$)	Depression ($n = 36$)
Sex			
Female	49 (62.8%)	10 (47.6%)	27 (75.0%)
Male	29 (37.2%)	11 (52.4%)	9 (25.0%)
Age (years)			
Mean (SD)	14.218 (2.389)	13.952 (2.578)	14.556 (1.949)
Range	7–18	8–17	10–17
Age group			
Child age range	11 (14.1%)	5 (23.8%)	2 (5.6%)
Juvenile age range	67 (85.9%)	16 (76.2%)	34 (94.4%)
Daily dosage (mg)			
Mean (SD)	108.654 (49.809)	129.762 (56.800)	99.306 (44.516)[d]
Range	25–250	50–250	25–200
Serum concentration (ng/mL)			
Mean (SD)	42.367 (26.434)	49.743 (23.643)	36.639 (23.265)[d]
Range	7–139	7–80	7–101
Body weight (kg)			
Mean (SD)	55.994 (17.059)	58.724 (22.713)	56.833 (10.436)
Range	20.30–111.70	25.50–102.70	42.70–82.70
Body mass index (kg/m^2)			
Mean (SD)	20.565 (4.368)	21.320 (5.702)	20.801 (3.423)
Range	13.87–35.54	14.630–35.54	16.760–31.730
Smoking			
No	71 (91.0%)	20 (95.2%)	31 (86.1%)
Yes	7 (9.0%)	1 (4.8%)	5 (13.9%)
Co-medication			
No	48 (61.5%)	16 (76.2%)	21 (58.3%)
Yes	30 (38.5%)	5 (23.8%)	15 (41.7%)
Co-medication (drug)			
Antipsychotics[a]	21 (26.9%)	4 (19.0%)	6 (16.7%)
Antidepressants[b]	11 (14.1%)	0 (0.0%)	3 (8.3%)
Valproic acid	1 (1.3%)	0 (0.0%)	0 (0.0%)
Treatment modality			
Inpatient	56 (71.8%)	14 (66.7%)	29 (80.6%)
Outpatient	13 (16.7%)	5 (23.8%)	5 (13.9%)
Day-clinic	9 (11.5%)	2 (9.5%)	2 (5.6%)
CGI Therapeutic Effects			
Unchanged or worse	3 (3.8%)	1 (4.8%)	1 (2.8%)
Minimal	25 (32.1%)	6 (28.6%)	13 (36.1%)
Moderate	41 (52.6%)	12 (57.1%)	19 (52.8%)
Marked	9 (11.5%)	2 (9.5%)	3 (8.3%)
CGI Side Effects			
None	47 (60.3%)	12 (57.1%)	22 (61.1%)
Not severe	28 (35.9%)	7 (33.3%)	13 (36.1%)
Severe	3 (3.8%)	2 (9.5%)	1 (2.8%)
Interval (days)[c]			
Mean (SD)	60.25 (66.16)	76.14 (75.27)	50.97 (59.38)[d]
Range	11–350	17–350	11–307
ICD diagnosis			
F20	1 (1.3%)		
F32	35 (44.9%)		35 (97.2%)
F34	1 (1.3%)		1 (2.8%)
F40	1 (1.3%)		
F41	2 (2.6%)		
F42	21 (26.9%)	21 (100%)	
F43	3 (3.8%)		
F50	7 (9.0%)		
F63	1 (1.3%)		
F84	2 (2.6%)		
F92	1 (1.3%)		
F93	1 (1.3%)		
F94	1 (1.3%)		
F95	1 (1.3%)		

[a] Aripiprazole, melperone, olanzapine, risperidone, olanzapine, quetiapine, sulpiride.
[b] Escitalopram, fluoxetine, fluvoxamine, mirtazapine.
[c] Time interval between initiation of therapy with sertraline and blood collection.

[d] $p < 0.05$ (chi-square test for categorical data, with a continuity correction for two-by-two tables; independent samples *t*-test or Mann–Whitney *U* test for continuous data, according to conventional statistical assumptions).

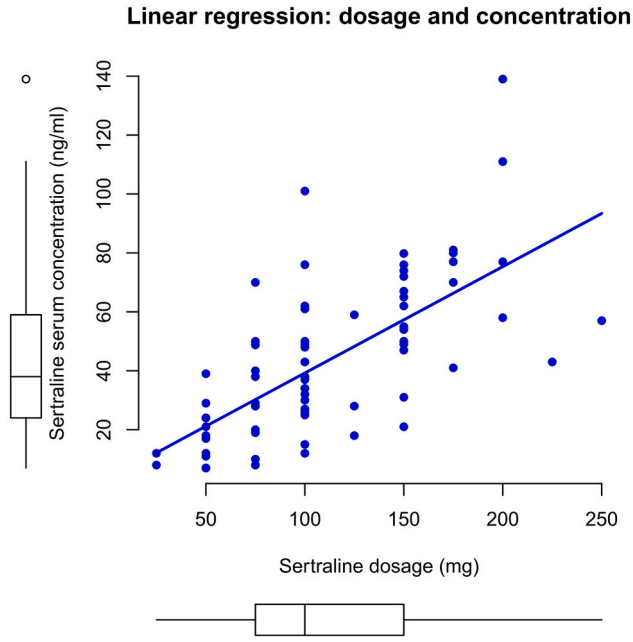

Fig. 1. The significant linear relationship between the daily dose and the steady-state serum concentration of sertraline ($p < 0.001$) in the study sample ($n = 78$). The blue diagonal line is the best-fit line. The boxplots for dose and concentration are situated along the *x*- and *y*-axes, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

17% and 23% of participants, respectively) were reported. The most frequent undesirable effects were headaches, reduced appetite, and sweating, which were recorded seven, six, and five times, respectively (Fig. 2).

Binary logistic regression indicated a significant association between dosage and responder status (weak versus good) ($\beta = 0.020$, $SE\ \beta = 0.006$, OR = 1.020 [95% CI 1.007–1.033], $p = 0.002$), but not serum concentration ($p = 0.194$). The ROC analysis yielded a cut-off value of 100 mg as an optimal value to predict a good clinical response, with a sensitivity of 0.76 (Se) and specificity of 0.57 (Sp). The area under the ROC curve (AUC) was 0.725 (95% CI 0.611–0.839, $p = 0.002$; Fig. 3). We repeated this analysis separately for the two subgroups and found a

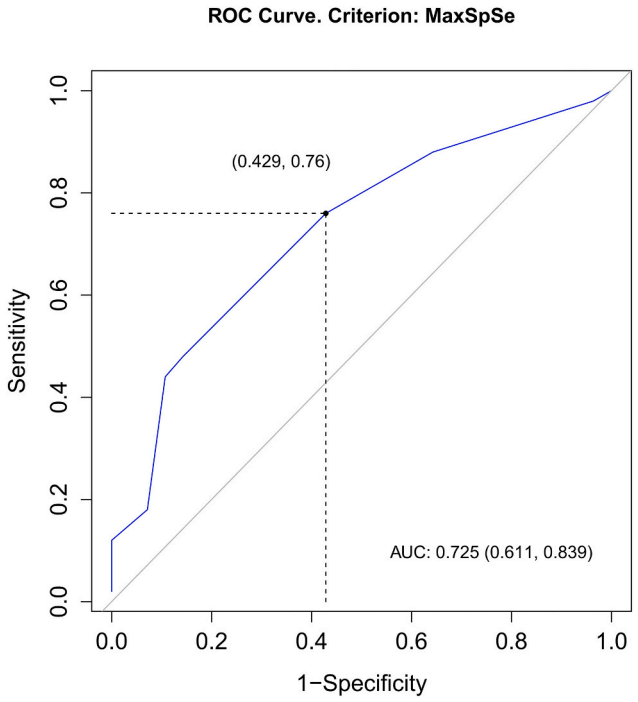

Fig. 3. The receiver operating characteristic (ROC) curve analysis of the sertraline dosage with regard to responder status (weak versus good). AUC, area under the curve. The optimal threshold was identified by simultaneously maximizing test sensitivity and specificity.

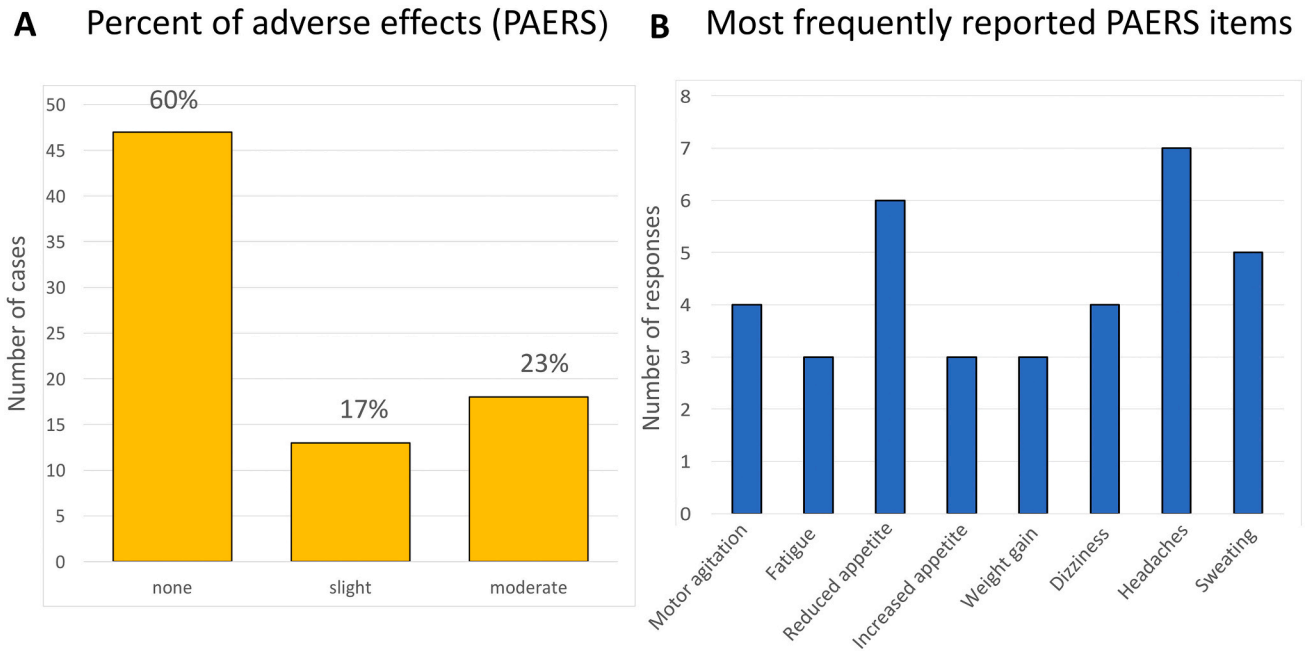

Fig. 2. The frequency of adverse effects from sertraline in the study population, as measured by the Pediatric Adverse Event Rating Scale (PAERS).

strong effect of dose for OCD (logistic regression: $\beta = 0.059$, $SE\ \beta = 0.025$, OR = 1.061 [95% CI 1.011–1.113], $p = 0.017$; ROC: optimal cut-off = 125 mg, Se = 0.857, Sp = 0.857, AUC = 0.944 [95% CI, 0.857–1.031], $p = 0.001$) and a trend towards significance for concentration (logistic regression: $\beta = 0.047$, $SE\ \beta = 0.024$, OR = 1.049 [95% CI, 0.999–1.100], $p = 0.050$; ROC: optimal cut-off = 49 ng/mL, Se = 0.714, Sp = 0.714, AUC = 0.786 [95% CI, 0.586–0.985], $p = 0.072$). There was no significant effect in the depression group.

Finally and importantly, the ordinal regression analyses with efficacy (i.e., CGI Therapeutic Effect) as the outcome variable for the OCD and depression patients revealed the following results: for the model with dosage, a significant effect of group ($\beta = -2.869$, $SE\ \beta = 1.416$, $OR = 0.057$ [95% CI 0.003–0.864], $p = 0.043$) and a significant group by dosage interaction ($\beta = 0.023$, $SE\ \beta = 0.011$, $OR = 1.024$ [95% CI 1.002–1.047], $p = 0.035$); for the model with concentration, a significant effect of group ($\beta = -2.840$, $SE\ \beta = 1.313$, $OR = 0.058$ [95% CI 0.004–0.725], $p = 0.030$) and a significant group by concentration interaction ($\beta = 0.064$, $SE\ \beta = 0.025$, $OR = 1.066$, [95% CI 1.016–1.122], $p = 0.012$). Specifically, these findings were driven by the effect in the OCD group ($\beta = 0.027$, $SE\ \beta = 0.010$, $OR = 1.027$ [95% CI 1.009–1.051], $p = 0.009$ [dose]; $\beta = 0.047$, $SE\ \beta = 0.022$, $OR = 1.048$, [95% CI 1.006–1.101], $p = 0.036$ [concentration]); in contrast, p-values for MDD were not significant [i.e., $p = 0.932$ [dose] and $p = 0.195$ [concentration]). Fig. 4 shows the probabilities of an increase in therapeutic outcome together with daily sertraline dose (4A) and concentration (4B) for the two groups. In the parallel analyses repeated with the covariates, the model with dose showed no significant results, while the model with concentration showed significant results (group: $\beta = -3.081$, $SE\ \beta = 1.341$, $OR = 0.046$ [95% CI, 0.003–0.610], $p = 0.022$; interaction term: $\beta = 0.068$, $SE\ \beta = 0.026$, $OR = 1.071$ [95% CI, 1.018–1.129], $p = 0.010$), with no significant effects of covariates. The tentative dose and concentration reference levels in good responders in the OCD group ($n = 14$) were 66–76 ng/mL (25th–75th interquartile) and 35–79 ng/mL (mean ± SD), respectively.

4. Discussion

4.1. Dose–serum concentration relationship

As hypothesized, this naturalistic multicentric study of children and adolescents medicated with sertraline revealed a positive relationship between dose and serum concentration, with dose explaining nearly half of the variance in concentration. This result is consistent with the pharmacokinetics of sertraline and previously described associations between daily dose and plasma concentration in adults [70,71]. A recent meta-analysis investigating healthy individuals with time-course parameters of sertraline doses between 5 and 400 mg confirmed that reduced bioavailability may cause non-linear pharmacokinetics for doses below 50 mg (corresponding to only two data points in our sample), with dose-proportional pharmacokinetics observed at doses above 50 mg [23]. Nevertheless, in adults, while the inter-individual drug concentration variability was overall found to be high, at least partially as a consequence of genetic variation in 450 CYP metabolizing enzymes, especially gene variants in CYP2C19 [72], intra-individual variability

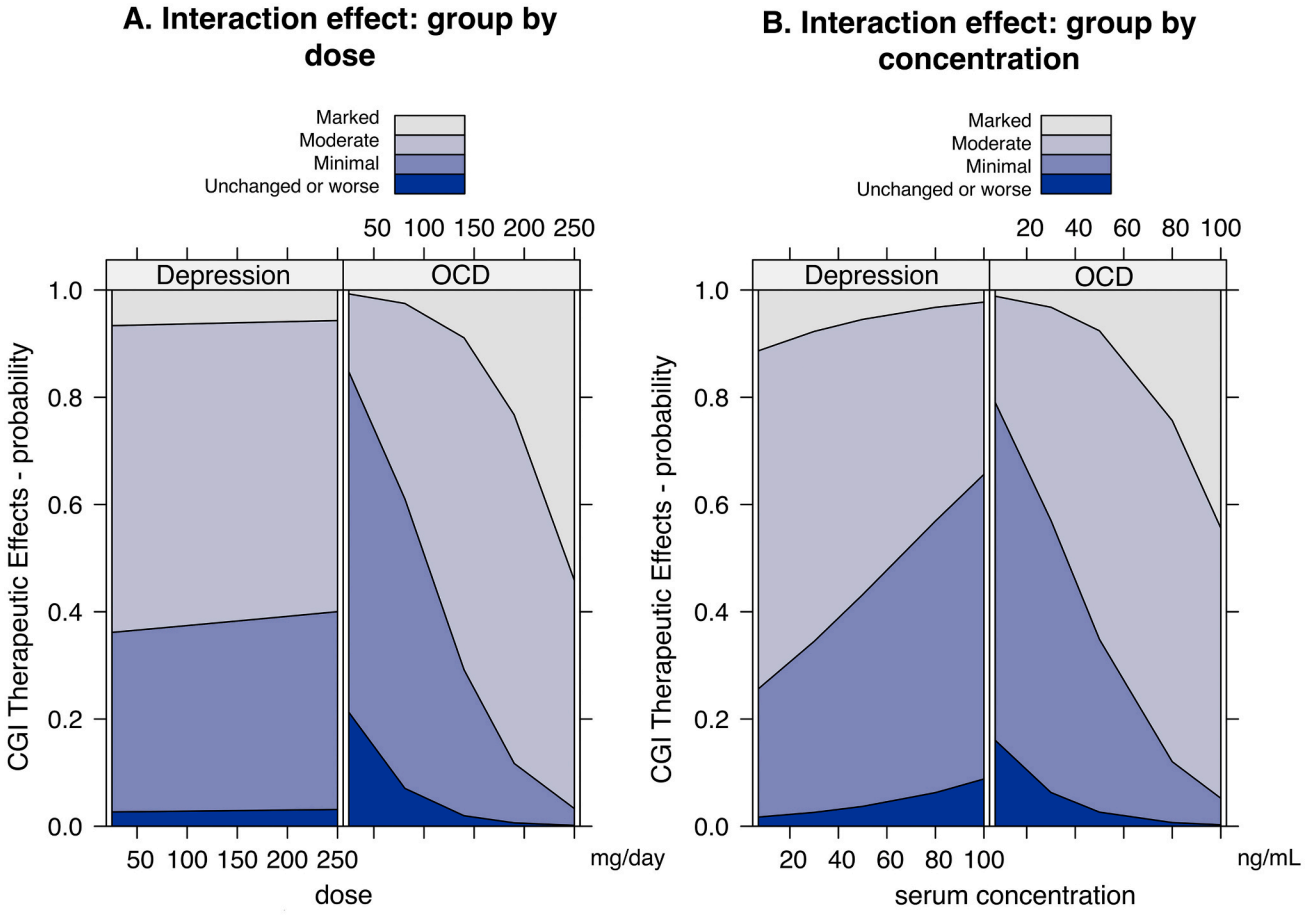

Fig. 4. Plots depicting the probability of clinical improvement (as measured by CGI Therapeutic Effect) as functions of sertraline dosage (A) and serum concentration (B), for each of the two largest diagnostic groups (obsessive-compulsive disorder [OCD] versus depressive disorder). The color-coding indicates four types of clinical output; the y-axes indicate the probability of improvement, while the x-axes indicate the dose or serum concentration. Overall, for the OCD group, in contrast with the depression group, the probability of clinical improvement increased significantly as doses and concentrations increased ($p < 0.05$).

was found to be low [71]. This further substantiates the value of TDM in providing information on compliance or in predicting concentrations after dose adjustment. Notably, the magnitude of our observed dose–concentration effect in young patients was stronger than those in most other investigations and may potentially be explained by differences in metabolic mechanisms. At the same time, age was not significantly related to this finding, despite the known changes in drug metabolism resulting from organ maturation (i.e., kidney and liver function changes), body composition changes, and altered enzyme activity [73]. Moreover, among other covariates, no effect of nicotine use or gender was evident, consistent with earlier results [30,32,71]. It should be noted though, that only 10% of the participants were smokers in our group. Instead, clear associations with weight (higher weight being a negative predictor of concentration) and co-medication (co-medication status being a positive predictor of concentration) were observed in our data. Furthermore, exclusion of patients diagnosed with anorexia nervosa did not alter our result regarding the effect of body weight. In addition, the relationship between polypharmacy and an increased dose–concentration effect suggests the existence of some drug–drug interactions. Possible mechanisms explaining this observation include modulation by CYP2C19, CYP2B6, CYP2C9, CYP2D6, CYP3A4, and CYP2D6 [74] or the multidrug resistance transporter P-glycoprotein [75]. While some TDM studies have found that certain drugs may alter the metabolism of sertraline or vice versa [76,77], other studies have failed to find significant associations [78,79]. Still, our findings suggest such a generic effect of co-medication versus mono-therapy. Given the moderate size of our sample, we did not examine the impact of individual co-medications, an issue that awaits a detailed investigation given the specific characteristics, different inhibitor/inductor status, and narrow clinical windows of these compounds in the human body [80]. In previous studies, the side effects of psychotropic medications in children and adolescents have been shown to be more frequent and more severe as the number of concurrent drugs taken is increased [81]. Therefore, clinicians should carefully consider and monitor the co-administration of sertraline with other pharmaceuticals (including herbal formulations [82]) in pediatric populations [83].

4.2. Associations with clinical efficacy and adverse reactions across diagnoses

Another key finding from this work is the significant effect between therapeutic improvement and daily sertraline dose, as measured transdiagnostically. Our observation aligns with the previously observed dose–response relationship for orally administered sertraline, revealed by meta-analyses in adults with both depression [84] and OCD [85]. The optimal dosage strategy is indeed the mainstay of clinical psychopharmacology. Two important conclusions derived from the existing evidence in adults may also apply to younger patients. First, the burden of side effects may be elevated for higher doses, and second, there may be no significant potentiation of efficacy beyond some threshold dose levels, making high dosing strategies possibly inadequate or counterproductive. The lack of support for serum concentration predicting clinical improvement transdiagnostically may be explained by several factors. The same observation was also documented by two other TDM studies with sertraline in 319 patients aged 15–96 [71] and in 90 patients aged 8–18 [30]. Like the present work, these two studies also used data from routine TDM settings. While the samples derived from such datasets reflect real-life treatment scenarios and naturalistic patient flow, detecting a significant effect of biogenic amine antidepressants may be largely hindered by a low signal-to-noise ratio under such conditions. As proposed by Preskorn [86] and Hiemke [69], especially for experimental designs with flexible doses, the heterogeneity of patients and diagnoses, as well as the mixture of verum responders, non-responders, and placebo responders, complicate examination of the concentration–response relationship. Additional possible confounders are related to uncontrolled conditions, such as treatment duration, non-standardized timing of blood collection, and use of a broad transdiagnostic instrument to measure improvement, as opposed to more specific instruments such as the Children's Yale–Brown Obsessive-Compulsive Scale [87] or Children's Depression Inventory [88]. We hypothesize that the effect of dose and clinical efficacy, without a simultaneous effect of concentration, may be partially explained by the heterogeneity of patients among developmental stages, across the broad diagnosis spectrum, different genetics amd metabolism, as well as in relation to the signal-to-noise ratio. The plausability of this hypothesis is supported by our findings, as when the analysis was narrowed down to the OCD group, effects on clinical outcome were observed for both the dose and serum concentration. In addition, no association with adverse effects was observed for dose or concentration in our study. The above listed explanations of missing associations with efficacy may also apply to this finding. Alternatively, this may be owing to a relatively high safety profile of sertraline within the recommended dose range in children and adolescents [89–91]. An exhaustive and more quantitative assessment using the PAERS showed that 60% of our patients were free of adverse effects, while reactions of slight (17%) and moderate (23%) severity included headaches, reduced appetite, sweating, motor agitation, dizziness, altered appetite, and fatigue. These reactions are similar to those observed in adults [92]. Although rather infrequent, severe adverse reactions from sertraline are still possible [93,94], and clinicians, through the application of TDM, should minimize the risk of undesirable effects. A special warning applies to possible suicidal thoughts and behaviors in young patients treated with antidepressants. Although the FDA Black Box warning on increased suicidality being linked to antidepressant use has elicited criticism and pointed to negative consequences [95], while also provoking support of the caution as possibly legitimate [96], it is of critical importance that this risk potential guides decision-making and pharmacotherapy, especially its initial phase.

While no specific cut-off value separating good from poor responders to sertraline across diagnoses was found for concentration, the dose of 100 mg was determined in this binary classifier analysis as an outcome predictor transdiagnostically. The most common primary diagnoses in our study were depressive disorder and OCD, followed by anorexia nervosa, post-traumatic stress disorder, and autistic disorder. Previous studies conducted in children and adolescents with specific indications have suggested that lower doses of 50 mg for depression or anxiety disorder are sufficiently effective or probably most suitable, based on the recommended dosage for adults [32,97,98]. At the same time, other studies on pediatric depression involving a 10-week treatment period adjusted for efficacy reached an endpoint mean dosage of 131 mg [99] or 110 mg per day [100]. Based on the above findings, 100 mg appears to approximately reflect the actual efficacy profile of sertraline in children and adolescents in a routine multi-diagnostic clinical setting. Nevertheless, this finding should be considered as preliminary, and we caution against using this result for current dosing recommendations. Clinicians typically endorse starting pediatric patients with a low initial dose of 25 mg per day, titrated at 25 or 50 mg increments up to a maximum of 200 mg (for OCD), if necessary, with a focus on administration of the lowest therapeutically effective drug dose. We speculate that a higher dose may in certain cases be more adequate than excessive polypharmacy; however, this tentative suggestion needs more research.

4.3. OCD-specific effects

Effective treatment of OCD must consider the behavioral rigidity of compulsive symptoms, which may be particularly resistant to modification in severe cases. Indeed, useful insights related to dosage, concentration, and clinical effects were revealed by our analysis comparing the two largest groups in our study, individuals with OCD and MDD. We found an interaction effect showing specifically that, in comparison with MDD, the probability of clinical improvement in OCD significantly increased with both higher doses and higher resulting concentrations. Accumulated evidence corroborates both shared and differential

characteristics of OCD relative to other anxiety disorders and depression on clinical, neurobiological, and genetic levels [101,102]. Notably, acute tryptophan depletion in patients who were responders to sertraline has been shown to not affect OCD symptoms, despite exacerbating depression symptoms [31]. This suggests that SSRI-related improvements in OCD may not be dependent on the short-term availability of serotonin, but instead on long-term postsynaptic receptor changes. Other researchers have proposed that SSRIs may rather induce compensatory mechanisms modulating the hyperactive fronto-cortical circuits driving OCD symptomology [103], as exemplified by a finding that post-treatment serotonin synthesis capacity in the brain was unchanged, but still co-varied with clinical outcome [104]. Furthermore, a therapeutic effect of medication typically manifests later in OCD than in depression [105] (up to 12 weeks versus up to 4–6 weeks). For OCD, there is also a tendency for reduced placebo and antidepressant responses compared to other anxiety disorders [106]. Our finding points to different underlying etiological mechanisms, as already suggested by the clearly distinct phenomenologies of OCD and depression. Notably, while both SSRIs (e.g., sertraline) and tricyclic antidepressants (e.g., desipramine) have similar efficacies in treating major depression in adults [107,108], SSRIs seem much more effective than noradrenergic antidepressants in treating concurrent OCD and major depression [109,110]. The above mechanisms may account for our notable findings on dosage, concentration, and improvement in OCD, while response to depression may plateau at a certain dosage level. Finally, the tentative effective serum concentration levels identified in our study were 66–76 ng/mL (25th–75th interquartile) and 35–79 ng/mL (mean ± SD), respectively, well within the range established for treatment of depression in adults, i.e., 10–150 ng/mL [67]. However, given the very broad range for adults and small size of our sample, future research should further confirm and extend this finding.

4.4. Limitations, role of TDM in clinical practice, and perspectives for future studies

There are several limitations to the present study, including its naturalistic design, which prioritizes the clinical objectives and leaves some factors—such as compliance, precise timing of data collection, center effects, sex ratio, or other therapeutic procedures besides sertraline—less controllable in this mixture of inpatient, day-clinic, and outpatient settings. Ideally, future studies should use a fixed-dose design and larger samples to draw more robust conclusions. Another limiting factor is the outcome assessment based on the CGI, which, despite being an informative, practical, and transdiagnostic clinician-rated measure, is not sufficiently detailed to characterize all the facets of a patient's mental health status. In addition, for the purpose of this study, the CGI was specifically rated in relation to the effects of sertraline and not the overall treatment. This study was primarily a pharmacovigilance study and not an efficacy study, and no information on concurrent psychological treatment was actively collected or assessed. However, all the centers were responsible for implementing the most recent diagnostic and treatment guidelines for the corresponding disorders, with cognitive-behavioral therapy as first-line treatment (see for example [110] for OCD; Associations of the Scientific Medical Societies in Germany). The lack of a placebo condition, which may be a considerable issue in psychopharmacology of pediatric populations [59], further constrains interpretations of our results. Given the overall scarcity of developmentally oriented studies on OCD, more research is needed to elucidate the underlying biological basis and mechanisms causing symptom reduction. There are several reasons TDM may become a very useful tool in clinical care, especially with respect to monitoring, problem prevention, and addressing individual-level questions. Exposing patients, especially young ones, to drug concentrations that are either too high or low may subject them to unnecessary health risks, negatively influence the efficacy or treatment time, and globally affect the treatment costs well beyond TDM costs. Routine monitoring is very important, particularly for medications with narrow reference levels and high adverse effect potential, such as clozapine or lithium. Controlling for drug adherence is another essential factor. Therapeutic references for psychotropic medications (if available) are population-based, but this does not always translate into individual-level concentrations. TDM may also greatly clarify insufficient responses, adverse effects reported for common doses, unexpected changes in symptoms, and issues related to polypharmacy. Furthermore, determination of therapeutically optimal serum concentrations, possibly at multiple time points, enables setting uniform reference levels for patients returning with relapses, symptom aggreviation, or other changing conditions [111]. Finally, a very promising way to leverage information from TDM for pharmacological treatment is combining TDM with pharmacogenetics [46]. This may open unprecedented possibilities to determine poor or ultrarapid drug metabolism and thus the subtyping of patients for their anticipated risk of adverse reactions, therapy success, and recommended dose level. Recent pharmacokinetic modelling approaches [112] and analyses from medical record data in pediatric patients [113] suggest that pharmacogenetics partially accounts for variability in clinical responses and tolerability of sertraline in the treatment of depressive and anxiety disorders. In particular, allelic variants of CYP2D6 and CYP2C19 are important candidates for consideration of these issues, though the effects of these gene variants await validation in younger patients [114] and proper cost-effectiveness estimation in a clinical setting.

4.5. Conclusions

This flexible dose investigation is the first TDM study emphasizing pediatric OCD treated with sertraline and following modern research standards. It revealed differential associations between daily dose, serum concentration, efficacy, tolerability profiles, and diagnoses. Future studies should address the existing knowledge gaps related to sources of variability in the pharmacodynamics and pharmacokinetics of sertraline and other frequently used antidepressants in relation to specific disorders and from a developmental perspective.

Declaration of competing interest

KE, RT, MR, MG and PP received grant research support from BfArM. MR currently receives a research grant from Kids-Safe, Innovation Committee of the German Federal Joint Committee (G-BA grant number 01NVF16021). PP receives grant research support from the German Federal Ministry of Education and Research (BMBF) and was involved in clinical trials from Servier and Lundbeck; he received an advisor honorarium from Boehringer Ingelheim and speaker's honoraria from Shire, Infectopharm and Gerot Lannach. CC has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Damitsa, Gedeon Richter, Hikma, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, SK Life Science, Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of LB Pharma. TB received personal fees from Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Takeda, Infectopharm, and Eli Lilly; serving as an advisor or consultant to Bristol Myers Squibb, Desitin Arzneimittel, Eli Lilly, Medice, Novartis, Pfizer, Shire, UCB, and Vifor Pharma; receiving conference attendance support, conference support, or speaking fees from Eli Lilly, Janssen McNeil, Medice, Novartis, Shire, and UCB; being involved in clinical trials conducted by Eli Lilly, Novartis, and Shire; and receiving royalties from Hogrefe, Kohlhammer, CIP-Medien, and Oxford University Press. SW has received in the last 5 years royalties from Thieme, Hogrefe, Kohlhammer,

Springer, Beltz. Her work was supported in the last 5 years by the Swiss National Science Foundation, diff. EU FP7s programs, Hochspezialisierte Medizin of the Kanton Zurich, Switzerland, BfArM, ZInEP, Hartmann Müller Stiftung, Olga Mayenfisch, Gertrud Thalmann, Vontobel, Unicentia, Erika Schwarz Fonds, Gesundheitsförderung Schweiz. The other authors (ET, LS, CW, AK, KR, UM, SU, MS, HR, GA, WB, CF, TH, HI, MKae, MKö, TR, SR, CR, GS, FT, and SF declare no conflict of interest.

Acknowledgments

The pharmacovigilance project 'TDM-VIGIL' was funded by a grant research from the German Federal Institute for Drugs and Medical Devices (BfArM, reference number: V-15322/68605/2013-2018). The patient registry of the 'Competence Network on Therapeutic Drug Monitoring in Child and Adolescent Psychiatry' was additionally supported by the German Federal Ministry of Education and Research (BMBF-FKZ: 001EZ0937) and the 'Verein zur Durchführung Neurowissenschaftlicher Tagungen e.V.', Paulsborner-Strasse 44, 14193 Berlin.

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