Low Escitalopram Concentrations in Patients with Depression predict Treatment Failure: A Naturalistic Retrospective Study

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Key words
SSRI, escitalopram, depressive disorder, clinical effects, depression, pharmacokinetics

received 13.12.2022
revised 15.01.2023
accepted 17.01.2023

Bibliography
Pharmacopsychiatry 2023; 56: 73–80
DOI 10.1055/a-2039-2829
ISSN 0176-3679

Georg Thieme Verlag KG, Rüdigerstraße 14,
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Supplementary Material is available under https://doi.org/10.1055/a-2039-2829

ABSTRACT

Introduction Cross sectional therapeutic drug monitoring (TDM) data mining introduces new opportunities for the investigation of medication treatment effects to find optimal therapeutic windows. Medication discontinuation has been proven useful as an objective surrogate marker to assess treatment failure. This study aimed to investigate the treatment effects of escitalopram and pharmacokinetic influences on blood levels using retrospectively assessed data from a TDM database.

Methods Data was collected from 134 patients longitudinally treated with escitalopram for whom TDM was requested to guide drug therapy. Escitalopram metabolism was estimated by the log-transformed dose-corrected concentrations and compared within subpopulations differing in age, gender, renal function, smoking status, body mass index, and comedication.

Results Patients with a depressive episode who were treated with escitalopram and discontinued the treatment within the hospital stay showed lower serum concentrations compared to patients who continued escitalopram treatment with a concentration of 15 ng/mL separating both groups. Variability was high between individuals and factors influencing blood levels, including dose, sex, and age. Comedication that inhibits cytochrome P450 (CYP) 2C19 isoenzymes were further found to influence escitalopram pharmacokinetics independent of dose, age or sex.

Discussion Medication switch is a valuable objective surrogate marker to assess treatment effects under real-world conditions. Of note, treatment discontinuation is not always a cause of insufficient response but may also be related to other factors such as medication side effects. TDM might not only be useful in addressing these issues but titrating drug concentrations into the currently recommended reference range for escitalopram will also increase response in non-responders and avoid treatment failure in underdosed patients.

Background

Escitalopram, a selective serotonin reuptake inhibitor (SSRI), is approved in the EU for the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD) and obsessive-compulsive disorder (OCD). Its antidepressant effect and good tolerability profile have been convincingly shown for a dose range between 10 to 20 mg per day. Escitalopram is primarily metabolised by the isoenzymes cytochrome P450 (CYP) 2C19 (36 %), CYP 2D6 (30 %), and CYP 3A4 (34 %) [1]. On this account, several frequently co-prescribed psychiatric and somatic medications such as risperidone, amitriptyline, melperone, promethazine, metamizole, simvastatin and verapamil may interfere with escitalopram metabolism. Surprisingly, there is little information about the influence of prescribed comedication [2]. In addition, age, sex, and hepatic function have been described as factors influencing escitalopram drug exposure [1–7]. However, findings are inconsistent [2, 8].

For escitalopram dose titration, monitoring of blood levels is strongly indicated [9], meaning that higher escitalopram concentrations will result in a higher probability of response in those patients. Limited data is available describing the relationship between the antidepressant efficacy of escitalopram and drug exposure. Dose-response meta-analyses report conflicting results, but, in general, do not support high dose ranges for SSRIs [10, 11]. Meta-analyses that consider drug exposure, i. e., blood concentration, were not able to find a clear drug exposure – response relationship for SSRIs yet [12]. For escitalopram, only one prospective cohort study investigating such a relationship has been reported. The sample comprised 70 patients with MDD. Treatment effects were assessed after one and three months of continuous treatment under flexible doses [13]. However, a clear cut-off that indicates the onset of treatment response was not reported. A second study, a large Scandinavian study, assessed escitalopram drug exposure retrospectively. The authors found the CYP 2C19 genotype being a substantial factor in escitalopram exposure and therapeutic failure assessed by medication switch [6]. Information on diagnoses, comorbidities, or comedication was, however, not available in this sample. Despite scarce and, to some extent conflicting evidence for a concentration/efficacy-relationship for escitalopram, current guidelines recommend dose titration for escitalopram within a reference range between 15 to 80 ng/mL [9]. The present study adds evidence on concentration/efficacy assumptions for the SSRI escitalopram. It comprises a sample of patients that were treated under real-world conditions. Following the example of Jukic et al. [6], treatment effects were assessed in retrospect by the use of medication switch as a surrogate marker. In our study, detailed information is available on demographic data, diagnoses, comorbidities, comedication, and laboratory parameters that allowed us to test whether the assumptions also hold true for patients being treated under various circumstances such as psychiatric comedication and concomitant diagnoses other than depression. We furthermore investigated a cut-off that is able to distinguish responders from non-responders. As a result, the major goal of our study was to investigate the treatment effects of escitalopram drug exposure. The second aim of our study was to identify influences on drug exposure that account for escitalopram's high interindividual pharmacokinetic variability such as age, sex, BMI, smoking status, renal and hepatic function, and comedication [2, 4, 5, 8].

Material and Methods

Study design and patients

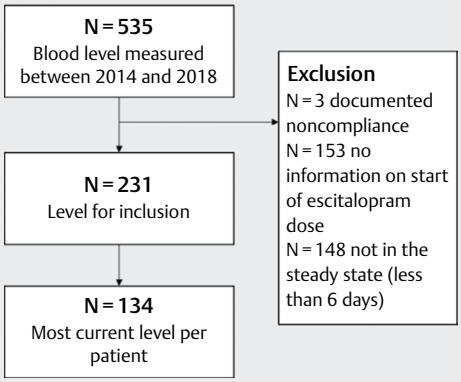
We retrospectively obtained patient data from routine therapeutic drug monitoring at the Central Institute of Mental Health in Mannheim within the period between January 21, 2014 and December 18, 2018 (▶ **Fig. 1**). Patients treated with an oral dose of escitalopram for a psychiatric indication were included. Patients were excluded if the escitalopram blood level was not at a steady state, treatment compliance was not achieved, or death occurred during ongoing treatment. Data from medical records such as patients' demographics, diagnoses according to ICD-10 criteria, factors potentially influencing pharmacokinetics (laboratory measures, smoking status, body mass index, comedication), and medication profile at the date of discharge were collected from patients for whom TDM was requested to guide the antidepressant drug therapy. QTc intervals during treatment were extracted from patient files when present. The majority of patients were inpatients (65.7 %) and day-care patients (33.6 %). Minimal drug concentrations (trough levels not confirmed) were measured under steady-state conditions (confirmed from medical records). Only one level per patient, the last sample was selected, for which the daily dose was given. Drugs interacting with *CYP 2D6, CYP 2C19*, and *CYP 3A4* (according to the medication interaction tool PSIAC© (Springer-Verlag GmbH, assessed on April 12 2022), were identified from the medication list. The use of anonymised patients' data for the purpose of this study was approved by the ethics committee of the Medical Faculty Mannheim, University of Heidelberg. Written informed consent was not required for this study. This study was conducted in accordance with the World Medical Association Declaration of Helsinki.

Definition of treatment success and failure

Escitalopram treatment failure was estimated by the switch to another antidepressant or by observing that escitalopram had been discontinued at discharge. We hypothesized that a switch to or the initiation of another antidepressant within the same residence most likely represented a treatment failure within the current episode of depression. Treatment success was suggested in patients being discharged with escitalopram. In outpatients, in semi-in-, and in inpatients, "discharge date" was defined as the end of the current case. Secondly, information on adverse effects was extracted from medical records. The effects of escitalopram medication were investigated (i) in a sample of patients with depressive disorder, and (ii) in the total sample. In the next step, we selected only patients whose dose had not been increased or decreased within sampling time and date of discharge, i. e., remained stable, to control for potential bias by the inclusion of non-responders (a common reason for dose increase) and/or patients potentially experiencing side-effects (a common reason for dose reduction). We also tested whether concomitant antidepressant or antipsychotic medication or frequently reported comorbidities could have influenced the results.

Escitalopram concentration assays

The analytical assays were validated and certified for routine therapeutic drug monitoring [14]. Briefly, escitalopram was determined



▶ **Fig. 1** Study flow chart.

in serum by liquid chromatography – mass spectrometry (LC–MS/MS). Initial sample purification was done by protein precipitation; the supernatant was injected into an ultra-high-performance liquid chromatograph with tandem mass spectrometric detection. Calibration curves were linear ($r^2 > 0 \cdot 99$) in validated ranges: 0–800 ng/mL. The lower limit of detection was 10 ng/mL. Imprecision and inaccuracy parameters of the assays were lower than 5 %. For calculations, results reported as < 10 ng/ml (N = 27) were set to 5 ng/mL.

Statistical analysis

For primary analyses, logistic regression analyses were applied to test for an association between treatment failures and drug exposure (assessed as serum concentration of escitalopram) including the covariates age, sex, and comedication with antidepressants or antipsychotics in the total sample and in the sample of patients with depression. Analysis was repeated in patients whose doses remained stable from the time of blood sampling to discharge, or the end of the current case. In addition, a Kruskal–Wallis test was applied to compare concentrations in different patient groups (patient with/without treatment failure; patients with/without antidepressant comedication; patients with different comorbidities). Receiver operating characteristic (ROC) analysis was used to define a threshold in concentration in order to predict treatment failure. For the analysis of therapeutic thresholds, only patients with stable doses, as described above, were included. For all analyses, $p \leq 0.05$ was defined as statistically significant. All statistical analyses were performed with IBM SPSS Statistics for Windows, version 26.0 (IBM, Armonk, N.Y).

The pharmacokinetic variability of escitalopram was expressed as the range in dose-adjusted serum concentrations (C/D ratios in (ng/mL)/(mg/day)). Hence, C/D ratios serve as a measure of relative drug exposure in patients, which enable the investigation of factors influencing escitalopram pharmacokinetics. Prior to the statistical analysis, C/D ratios were natural log transformed into a more normalized dataset as described before [6]. A stepwise multivariate linear regression analysis (MLRA) was used to evaluate the effect of age, gender, renal function (glomerular filtration rate (GFR) computed by CKD-EPI Creatinine Equation [15]), liver function (increased aspartate transaminase (AST) or alanine transaminase (ALT) plus increased AST/ALT ratio), BMI, smoking status and CYP comedication–defined groups on C/D ratios. Further regression analyses were performed for each CYP-interfering medication group. The control group comprised patients without other potentially CYP-interfering comedication (inhibiting or inducing). Patients with more than one potentially interfering inductor/inhibitors were excluded prior to analysis.

Results

Sample characteristics

The sample comprised 134 patients aged from 14 to 89 years (47.1 ± 18.5 years; 41.8 % males). Most patients were diagnosed with depression (F32.X or F33.X, N = 103) with 5, 42, and 56 patients, respectively, experiencing a minor (ICD F32.1 or F33.1), moderate (ICD F32.2 or F33.2), or severe depressive episode (ICD F32.3 or F33.3) at the time of drug monitoring. The remaining 31 patients experienced the following diagnosis: (i) psychotic disorder (ICD F20-F29, N = 9), (ii) personality disorder (ICD F60.X, N = 5), (iii) anxiety disorder (ICD F40 or F41, N = 5), (iv) alcohol use disorder (ICD F10.X, N = 2), or (v) bipolar disorder (ICD F31.X, N = 2). For eight patients, no diagnosis was reported. For 49 patients, more than one psychiatric diagnosis was noted with up to four additional comorbid psychiatric conditions. Somatic conditions were also frequent (N = 49). The most frequent other psychiatric disorders were personality disorders (ICD F60.X, N = 24), anxiety disorders (ICD F40.X or F41.X, N = 23), alcohol use disorder (ICD F10.X, N = 19), psychotic disorders (ICD F20-F29, N = 9), cannabinoid use disorders (ICD F12.X, N = 9), and bipolar disorder (ICD F31.X, N = 7). Concomitant medication was frequent; it was reported in 88.1 % of patients (N = 118) with up to 17 additional drugs and 3.3 ± 3.0 concomitant drugs on average (for the full list see **Supplementary Table 1**). Another antidepressant drug was given in 55 (41.1 %) of all patients and the most preferred was mirtazapine (N = 27). An antipsychotic acting drug was applied in 41 patients (30.6 %). Thirty-six patients were not treated with another drug that was classified as a "Central nervous system (CNS)-relevant drug" (see **Supplementary Table 1**). Additional interventions with antidepressant effects were noted in six patients, with five of them receiving periodic electroconvulsive therapy and one patient being treated with transcranial magnetic stimulation therapy. The most common doses were 20 mg (43.3 %), 10 mg (28.4 %), and 15 mg (22.4 %) daily. One patient received a lower dose of 5 mg, and seven patients were treated with doses above 20 mg per day. The mean escitalopram blood level was 24 ± 17 ng/mL (range 5–76 ng/mL, IQR 11–34 ng/mL).

Concentration-dependent treatment effects

While six patients were excluded because of additional antidepressant interventions, the efficacy sample comprised 128 patients. Of those, 97 patients were treated for depressive disorders (ICD 10 F32.X or F33.X) and 85 of these had stable doses from blood sampling to the date of discharge or were not discharged with escitalopram**.** The majority received additional CNS-relevant medications (N = 95 of 128). Detailed information on the patient sample

▶ **Table 1** Patients demographics

	Efficacy sample	Treatment success (discharged with ESC)	Treatment failure (not discharged with ESC)
Number of patients	**N = 128**	**N = 95**	**N = 33**
age (years) median (range)/ IQR	47 (17–89)/ 30–59	47 (18–86)/ 29–58	48 (17–89)/ 32–61
Sex (%males)	42.2	43.2	39.4
Setting (Inpatient/ Outpatient/ Semi-In)	88/1/45	59/0/36	23/1/9
Diagnosis of depression (% of patients)	76.9	72.6	84.8
Without another antidepressant (% of patients)	60.2	62.1	51.5
Escitalopram concentration (ng/mL) median (range)/ IQR	19.6 (5–76)/ 11–35	21.3 (5–76)/ 14–35	10.6 (5–68)/ 5–29
Escitalopram dose (mg/day) median (range)/ IQR	15 (10–30)/ 10–20	20 (10–30)/ 10–20	15 (10–20)/ 10–20
C/D ratio median (range)/ IQR	1.24 (0.25–7.47)/ 0.63–2.04	1.35 (0.33–7.47)/ 0.78–1.94	0.63 (0.25–4.84)/ 0.33–2.24

ESC, escitalopram; IQR, interquartile range

can be found in ▶ **Table 1**. For the majority of patients with depression (62 %), escitalopram serum levels were within the therapeutic reference range of 15–80 ng/mL, while for 38 % of patients, levels were below this range. The logistic regression model on the effects of escitalopram concentration, age, sex, comedication antidepressant and comedication antipsychotics on the likelihood that participants had escitalopram as discharge medication was statistically significant ($p < 0.001$, $R^2 = 0.056$). Only escitalopram concentrations remained a significant variable ($p = 0.012$). Overall, higher blood levels (21 vs. 11 ng/mL, $p = 0.006$) and higher dose-corrected concentrations (1.4 vs. 0.63 (ng/mL)/(mg/day), $p = 0.03$) were found in patients that were discharged with escitalopram (N = 95) compared to patients not discharged with escitalopram (N = 33), whereas doses did not differ between both groups. This also holds true when selecting patients experiencing a depressive episode (ICD 10 F32.X or F33.X) at this time point (blood level: $p = 0.011$; C/D ratio: $p = 0.046$, N = 97; ▶ **Fig. 2**) and when excluding patients whose dose had been increased or decreased within sampling time and discharge (blood level: $p = 0.002$; C/D ratio: $p = 0.041$; dose: $p = 0.017$). The logistic regression analyses in these subsamples confirmed these findings [(i) subsample depressive patients: $p < 0.001$, $R^2 = 0.099$, (ii) subsample constant doses: $p < 0.001$, $R^2 = 0.153$)]. Lower escitalopram concentrations were found in patients with depression that were discontinued on escitalopram ($p = 0.02$) and also in those who additionally had stable dose regimens ($p = 0.008$). ROC analyses were performed after the exclusion of patients with increased or decreased doses after blood sampling. The ROC curve identified a cut-off point that discriminates treatment success from failure at 18.5 ng/mL (AUC = 0.686 [CI 0.566; 0.807], $p = 0.002$, N = 111) in the total sample and of 15 ng/mL (AUC = 0.695 [CI 0.562; 0.827], $p = 0.003$, N = 85; ▶ **Fig. 3**) in the patients with depression.

In general, the majority (81 %) of patients with a depression that were discharged with escitalopram ("treatment success") had a drug level above 15 ng/mL. The treatment success rate below this threshold was 51.3 %. The interquartile concentration of patients discharged with escitalopram treatment was 16–36 ng/mL (N = 57). Of patients with treatment failure, more than half (54 %) had concentrations below the recommended therapeutic threshold. Most of these patients (89 %) were switched to another antidepressant drug within this time span. Of patients who continued escitalopram treatment, only 29 % had concentrations below 15 ng/mL. Among these, after escitalopram Drug Monitoring, the treating clinician decided (i) to retain the administered dose in 20 patients (ii) to increase the dose in eight patients, and (iii) to decrease the dose in one patient. In the remaining 70 patients with blood levels within the therapeutic reference range, the dose was retained in 87.1 % of patients.

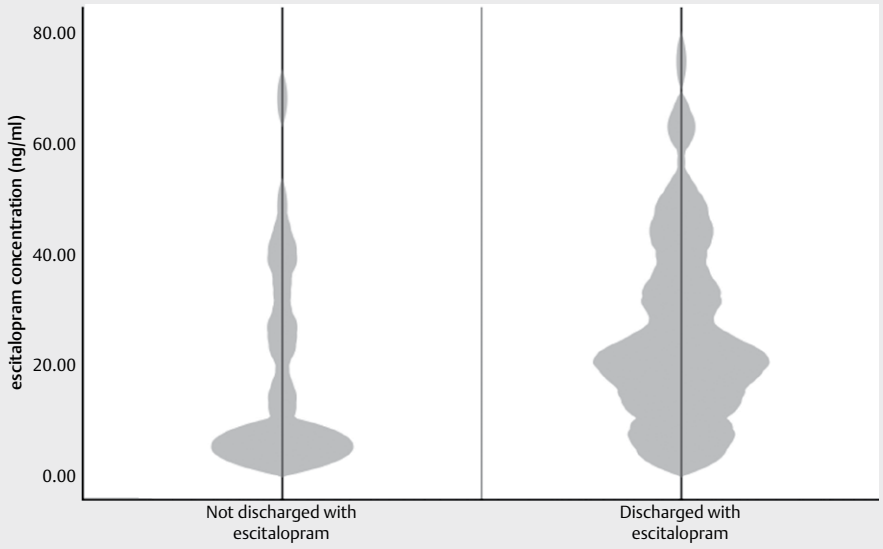
Patients' blood levels and doses did not differ between patients treated with or without another antidepressant or antipsychotic drug at the time of inclusion (see **Supplementary Table 1** for the list of comedication). Escitalopram levels did neither differ between patients with or without a depressive episode, nor between the severity of current depressive episodes. When comparing escitalopram blood levels in patients with and without the most frequently reported comorbidities, no differences were observed for (i) personality disorders (ICD F60.X, N = 24), (ii) anxiety disorders (ICD F40.X or F41.X, N = 23), (iii) alcohol use disorders (ICD F10.X, N = 19), (iv) psychotic disorders (ICD F20-F29, N = 9), (v) cannabinoid use disorders (ICD F12.X, N = 9), or (vi) bipolar disorders (ICD F31.X, N = 7).

Side effects were reported in 9 % (12 of 134) of patients, with one case of nausea, two cases of increased transpiration, one case of dry mouth, one case of increased liver values, one case of hair loss/extended monthly bleeding, two cases of libido problems, and four cases with unknown side effects. No association was found between drug exposure and QTc interval (data not shown, N = 43).

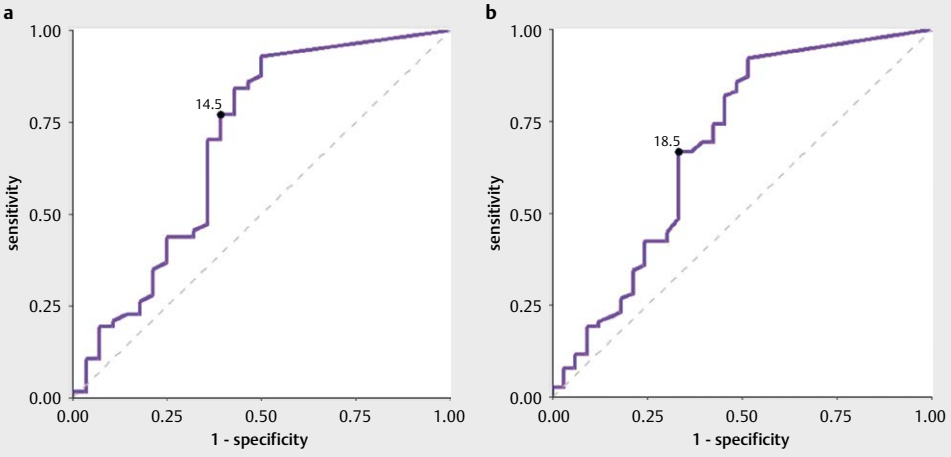
Factors influencing escitalopram concentrations

Effect of demographic parameters

The total sample showed a good correlation between blood levels and applied escitalopram doses ($r = 0.3$; $p < 0.001$, N = 134) with a high interindividual variation in drug exposure among all dosage levels. The mean C/D ratio of the total sample was 1.52 ± 1.15 (ng/mL)/(mg/day). Liver function was identified as abnormal only in two patients and hence this variable was not included in the analysis. Linear regression analyses revealed age, sex and CYP 3A4 inhibiting comedication as factors moderating dose-corrected escitalopram levels ($r = 0.56$, $p < 0.001$, N = 134, MLRA), see ▶ **Fig. 4** for effects of age). No effect was found for weight/BMI or GFR. Women showed 47.2 % higher median C/D ratios compared to men (C/D: 1.56 vs. 1.06, $p = 0.004$, N = 78/56). As a consequence, women, in general had higher mean escitalopram concentrations compared to men (23.5 vs. 15.6 ng/mL, $p = 0.006$) while being treated with comparable dosages. C/D ratio ($r = 0.306$, $p < 0.001$, N = 134) and concentrations ($r = 0.214$, $p = 0.013$, N = 134) negatively correlated



▶ **Fig. 2** Escitalopram as discharge medication in patients with a depressive episode (N = 97, p = 0.01, median blood level 7.8 ng/mL (N = 28) vs. 21.5 ng/mL (N = 69)).

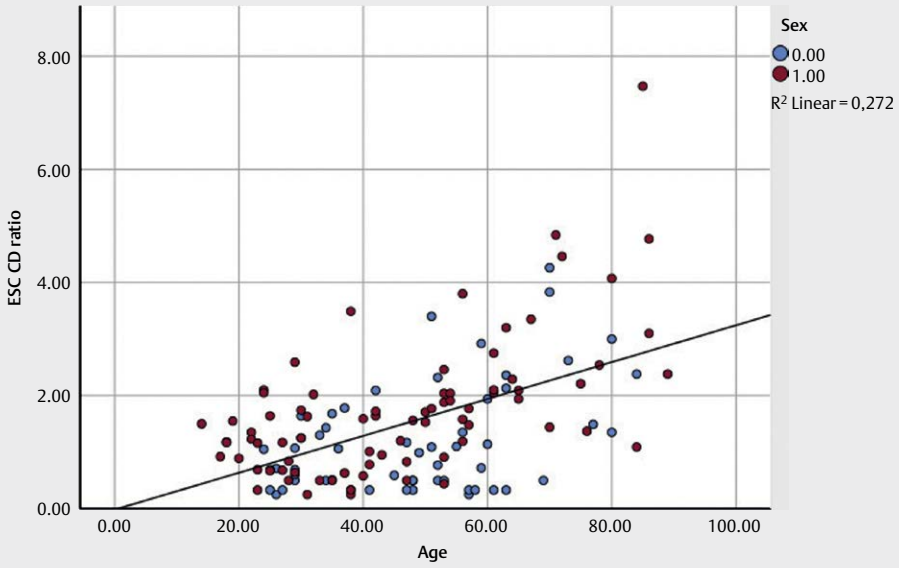


▶ **Fig. 3** Receiver operating characteristic (ROC) curve for patients with stable dose from sampling time point to discharge in a. patients with depression (AUC = 0.695 [CI 0.562; 0.827], p 0.003, closest top left 14.5 ng/mL, N = 85) b. complete sample (AUC 0.686 [CI 0.566; 0.807], p 0.002, closest top left 18.5 ng/mL, N = 111).

with the GFR assessed by serum creatinine, but not when corrected for age and sex. The AST/ALT ratio also showed a medium correlation with the C/D ratio (r = 0.209, p = 0.046, N = 92), but not when corrected for age and sex. A similar result was shown for cigarette consumption (smokers vs. non-smokers; p = 0.022). The body mass index was available for 96 subjects. Body weight was revealed as a significant influence on escitalopram exposure (corrected for age and sex, p = 0.027), but not when corrected for dose.

Effect of comedication

The overlapping effects of CYP interfered with comedication; therefore, CYP groups were tested separately in logistic models, each including age and sex as covariates. Effects were observed within the group of "potentially clinically relevant inhibitors" as well as in the group of "known clinically relevant inhibitors" (definitions according to the PSIAC© medication interaction tool, see **Supplementary Tables 2** and **3** for a list of relevant drugs) and both groups were further combined. Patients comedicated with CYP 2C19 inhibitors (p = 0.006) showed higher escitalopram concentrations after correction for age and sex ($R^2 = 0.312$, $p < 0.001$, N = 82). Treatment with CYP 2C19 or CYP 3A4 inducers and CYP 3A4 or CYP 2D6 inhibitors did not show effects on dose-corrected escitalopram concentrations when compared to a control group without CYP-interfering medication. The analysis of individual substances revealed



▶ **Fig. 4** Age-dependant escitalopram concentration 0, male; 1, female.

higher C/D ratios in five patients treated with simvastatin compared to the control group (p = 0.037). Other CYP 2C19, CYP 3A4 or CYP 2D6 inhibiting substances were not found to influence escitalopram blood levels. Small samples of patients per group (< 7), however, did not allow for a clear evaluation.

Discussion

To date, psychiatric rating scales present the gold standard to assess treatment effects. Their use is not only highly prone to errors but also introduces a considerable amount of bias, e. g., by absent interrater reliabilities, short duration of drug treatments before clinical assessments or by artificially distorted treatment conditions [16, 17]. Our study introduces an objective surrogate marker for the assessment of treatment effects in a retrospectively evaluated patient sample, allowing a validation of the currently recommended therapeutic reference range for escitalopram under real-world conditions. The majority of our patients (64 %) had serum concentrations within the currently recommended reference range. Of note, every third patient (36 %) did not reach therapeutically sufficient concentrations (above 15 ng/mL) while being treated with recommended doses of 10–20 mg/day. Under 20 mg daily dose, 21 % of patients still did not have sufficient escitalopram levels above 15 ng/mL. In our sample, patients being discontinued on escitalopram during their hospital stay had lower concentrations compared to patients who were discharged on escitalopram, independent from further clinical decisions on dose titrations. More than half the number of patients with treatment failure had concentrations below the recommended therapeutic threshold. Achieving an adequate escitalopram blood – and consequently – brain concentration is of particular relevance for patient populations with depression since a minimum serotonin transporter (SERT) occupancy of 80 % in the brain has been shown to be essential to achieve antidepressant treatment effects. Neuroimaging studies have consistently shown a necessity for concentrations above 16–18 ng/mL to hit this target threshold [18]. Our findings strongly support the recommended threshold of 15 ng/mL [9] for the antidepressant efficacy of escitalopram and emphasize the need for TDM to support decisions on whether to further modify escitalopram dosing in individuals.

We furthermore present an overview of escitalopram pharmacokinetics, in a sample of older-aged patients and patients being treated with several concomitant medications. The mean serum concentration and C/D ratio in our study were in line with previously reported findings [13, 19–21], although, higher than those indicated in the TDM guidelines [9]. In line with reporting of previous studies, we found increasing C/D ratios with age [2, 21]. In our study, patients at the age 60 years and older have more than twice as high escitalopram concentrations compared to patients aged 30 years and younger (C/D ratios: 2.56 ± 1.47 vs. 1.06 ± 0.55). The study confirms the recommendation of the patient medication information for escitalopram [1] that suggests a maximum dosage of 10 mg/day for patients aged 65 and older. Our findings furthermore suggest the need for further adaptions on escitalopram dosing recommendations in terms of sex differences. A woman will, in general, achieve a 47 % higher escitalopram concentration compared to a man under the same escitalopram dose. These findings suggest that TDM is of particular importance in patients with hepatic or renal functional impairments with higher age contributing to these variables [21]. Further caution is required in patients on CYP-interfering polypharmacy with CYP 2D6, CYP 2C19 or CYP 3A4 inhibiting substances.

Several limitations of this study are worth mentioning. First, medication switch, here introduced as an objective surrogate pa-

rameter for treatment failure, does not, in contrast to common rating scales, exclusively relate to missing antidepressant effects/ nonresponse. The occurrence of side effects is also a common reason for a switch to another medication. Treatment success, indicated by a continued treatment with escitalopram, might be at least partially attributed to several other factors besides the respective drug concentration such as psychological interventions and psychosocial factors (e. g., stress levels and social support). The routine TDM setting did not allow us to control patient adherence to the treatment nor to control for other influences, e. g., psychosocial factors or medication side effects, on therapeutic decisions. The treatment success rate of 71 % in our sample was higher than previously reported response rates in patients with depression [22]. The low occurrence of side effects in only six patients suggests an incomplete registration of side effects in the medical files.

Second, information on relevant CYP 2D6 and CYP 2C19 genetic variability was not available. The activity of both isoenzymes is of major importance in the biotransformation of escitalopram and have been shown to substantially impact escitalopram drug concentrations. A relevant genetic variability may also be introduced in the form of the polymorphic efflux transporter P-glycoprotein (P-GP). P-GP can furthermore be inhibited or induced through several co-administered drugs i. e., carbamazepine or ketoconazole, which can have a clinically relevant influence on the brain concentrations of the P-GP substrate escitalopram [23]. None of the patients in our sample were treated with an inhibitor or inductor drug marked as clinically relevant according to the interaction software PSIAC.

Third, since the nature of the study does not allow for a determination of treatment effects at the time of blood withdrawal, an exact evaluation of treatment failure cannot be determined from this study. Consequently, a hypothesis-oriented clinical study in more controlled settings is needed to validate the methodology used in this work. To sum up, the data presented here strongly support a target concentration of 15 ng/mL to prevent treatment failure in patients with depression. Of all patients with depression, 75 % had blood levels below 34 ng/mL, which strongly questions the current upper limit of the reference range of escitalopram.

Conclusion

Retrospective evaluation of medication profiles constitutes a valid tool to assess treatment failure in patients treated with escitalopram. Our study adds evidence to the results from previous studies indicating that age and sex highly affect drug exposure to escitalopram in a clinically relevant manner that necessitates dose adaption in those patient subpopulations. Our findings confirm the currently recommended lower threshold level of therapeutic reference range of 15 ng/mL of escitalopram and support the level 2 ("recommended") recommendation of the AGNP expert group [9] to monitor escitalopram blood levels.

Funding Sources

The authors declare that the study did not receive any funding.

Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

XH developed the first draft of the manuscript. LE and FA contributed to data collection, interpretation and writing of the manuscript. GG participated in the research design, supervised the entire manuscript writing and contributed to the revision of the manuscript. XH and FA performed the statistical analysis.

Conflict of Interest

GG has served as a consultant for Allergan, Boehringer Ingelheim, Institute for Quality and Efficiency in Health Care (IQWiG), Janssen-Cilag, Lundbeck, Otsuka, Recordati, and ROVI. He has served on the speakers' bureau of Gedeon Richter, Janssen Cilag, Lundbeck, Otsuka, and Recordati. He has received grant support from Boehringer Ingelheim, Lundbeck and Saladax. He is co-founder and/or shareholder of Mind and Brain Institute GmbH, Brainfoods GmbH, OVID Health Systems GmbH and MIND Foundation gGmbH. All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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