Schizophrenia Research 210 (2019) 143–148

Contents lists available at ScienceDirect

Schizophrenia Research

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

Effect of fluvoxamine augmentation and smoking on clozapine serum concentrations

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ARTICLE INFO

Article history:
Received 30 January 2019
Received in revised form 18 May 2019
Accepted 26 May 2019
Available online 8 June 2019

Keywords:
Therapeutic drug monitoring
Clozapine
Fluvoxamine
Smoking
Cytochrome P450
Interaction
CYP1A2
Pharmacokinetics

ABSTRACT

Background: Clozapine (CLZ) is metabolized via cytochrome P450 CYP1A2 to *N*-desmethylclozapine (NCLZ). Smoking induces CYP1A2 thereby increasing clozapine metabolism whereas fluvoxamine inhibits CYP1A2. Studies suggest that the beneficial effect of fluvoxamine augmentation in raising serum clozapine concentrations also occurs when serum concentrations are low due to smoking. Yet, little is known about the influence of fluvoxamine augmentation on clozapine serum concentrations in smoking versus non-smoking patients.
Methods: A TDM database was analyzed. Serum concentrations of CLZ, NCLZ, dose-adjusted serum concentrations (C/D) and metabolite-to-parent ratios (MPR) were compared using non-parametrical tests in four groups: clozapine-monotherapy in non-smokers (V_{NS}, $n = 28$) and smokers (V_S, $n = 43$); combined treatment with clozapine and fluvoxamine in non-smokers (V_{NS+F}, $n = 11$) and smokers (V_{S+F}, $n = 43$).
Results: The CLZ monotherapy smoking group showed lower values of C/D CLZ of −38.6% ($p < 0.001$), C/D NCLZ −35.6% ($p < 0.001$) and a higher MPR ($p = 0.021$) than in the non-smoking group. The combination of CLZ and fluvoxamine in non-smoking patients led to higher C/D values: C/D CLZ +117.9% ($p < 0.001$), C/D NCLZ +60.8% ($p = 0.029$) while the MPR did not differ between groups ($p = 0.089$). Changes were comparable to fluvoxamine augmentation in the smoking group with increased C/D CLZ of +120.1% ($p < 0.001$), C/D NCLZ of +85.8% ($p < 0.001$) and lower MPR ($p = 0.006$).
Conclusions: Smoking in clozapine monotherapy reduced median dose-adjusted serum concentrations more than a third. Combined treatment with fluvoxamine and clozapine led to higher median C/D values in both, smokers and non-smokers. The opposing effects of CYP1A2 induction by smoking and inhibition by fluvoxamine on clozapine serum concentrations balanced out.

1. Introduction

Tobacco smoking is more prevalent in patients with severe mental illnesses than in the general population and in particular in patients with schizophrenia with a smoking prevalence of 62% (de Leon and Diaz, 2012). Clinicians have to consider that smoking is a relevant factor in dosing strategies due to an enhanced clearance of several hepatically metabolized drugs (Augustin et al., 2018; Kroon, 2007). This consideration is necessary because smoking is known to induce distinct CYP isoenzymes with a clinically relevant impact on drug pharmacokinetics. Especially polycyclic aromatic hydrocarbons, generated by tobacco smoking, seem to be responsible for the induction of isoenzymes CYP1A1, CYP1A2 and CYP2E1 (Schrenk et al., 1998; Zevin and Benowitz, 1999). The induction or inhibition of CYP isoenzymes can have substantial effects on drug metabolism and the serum concentration of a drug and its metabolites (Pelkonen et al., 1998). For clinical efficacy and patients' safety, the drug concentration plays a crucial role and especially for clozapine, a therapeutic reference range is well defined and established to enhance the proportion of patients that show response or remission (Hiemke et al., 2018). Clozapine's metabolism is known to be influenced by smoking, however, data in a naturalistic

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https://doi.org/10.1016/j.schres.2019.05.033
0920-9964/

setting is scarce. A recent meta-analysis included only four high quality studies with a total number of 196 patients that studied the impact of smoking on pharmacokinetics of clozapine (Tsuda et al., 2014).

Data suggest that a combined treatment of clozapine and fluvoxamine, a potent CYP1A2 inhibitor, may have beneficial effects on metabolic parameters and psychopathology (Kishi et al., 2013; Polcwiartek and Nielsen, 2016). Concomitant treatment with fluvoxamine has been linked to attenuated weight gain and reduced metabolic side effects compared to clozapine monotherapy (Lu et al., 2004) and it has been hypothesized that a combined treatment increases efficacy and tolerability of clozapine even in patients with treatment resistant schizophrenia (Legare et al., 2013).

Fluvoxamine significantly prolongs the elimination half-life of clozapine and reduces the so called metabolite-to-parent ratio (MPR, ratio of *N*-desmethylclozapine, NCLZ/clozapine, CLZ, (Wang et al., 2004)). NCLZ has been linked to metabolic side effects such as increased weight gain and hyperlipidemia due to its antagonism at 5-HT_{2c} receptors (Procyshyn et al., 2007; Reynolds et al., 2005). While there is only one study suggesting that high MPRs, i.e. relatively high NCLZ concentrations, are favorable in terms of working memory performance (Rajji et al., 2015), the addition of fluvoxamine to an ongoing clozapine treatment appears to be linked to a favorable clinical response and less side effects driven by higher CLZ serum concentrations following fluvoxamine's inhibition of CYP1A2.

To elucidate both, the impact of fluvoxamine and smoking on clozapine's pharmacokinetics, we analyzed a therapeutic drug monitoring (TDM) database consisting of CLZ and NCLZ serum concentrations in smoking and non-smoking patients with schizophrenia. Patients were treated with clozapine monotherapy or received a co-medication with fluvoxamine. By analyzing TDM databases, clinically important issues such as drug-drug interactions (Paulzen et al., 2018; Schoretsanitis et al., 2016), the effect of smoking on drug concentrations (Augustin et al., 2018; Paulzen et al., 2016a), adverse drug reactions (Schoretsanitis et al., 2016), or treatment response in relation to pharmacokinetic patterns of drug concentrations (Paulzen et al., 2016a; Paulzen et al., 2016b; Spina et al., 2016) can be addressed.

Clozapine is a tricyclic atypical antipsychotic of the dibenzodiazepine class indicated for treatment-resistant schizophrenia. It is mainly metabolized by CYP1A2 with moderate influence of CYP2C19 and CYP3A4 (Jaquenoud Sirot et al., 2009). Protein binding of clozapine is high and mean elimination half-life under steady state conditions is approximately 12 h. Clozapine is extensively metabolized and the major metabolite *N*-desmethylclozapine is pharmacologically active (Lameh et al., 2007; Mendoza and Lindenmayer, 2009). A therapeutic reference range of 350 to 600 ng/mL is proposed (Hiemke et al., 2018). TDM of clozapine is of high clinical relevance to avoid side effects such as sedation and concentration-dependent proconvulsive properties of clozapine (Mauri et al., 2014).

Fluvoxamine is a selective serotonin reuptake inhibitor and σ_1-receptor agonist. In the US, it is only indicated for the treatment of obsessive-compulsive disorder, although in other countries (e.g. Germany) it is approved for the treatment of major depressive disorder. Fluvoxamine has a mean elimination half-life of around 16 h and is mainly metabolized by CYP2D6 and CYP1A2 (Miura and Ohkubo, 2007). Fluvoxamine shows nonlinear pharmacokinetics, most likely in dosages above 50 mg (Hiemke and Hartter, 2000). In vitro studies have shown that fluvoxamine inhibits cytochrome P450 isoenzymes CYP1A2, 2C19, 2C9, 2D6 and 3A4 linked to the demethylation of CLZ and formation of NCLZ (Olesen and Linnet, 2000).

Although the influence of fluvoxamine on clozapine serum concentrations is known for more than two decades, little is known about combined interactions of fluvoxamine and smoking on clozapine pharmacokinetics. Accordingly, aim of this study was to clarify the interaction of fluvoxamine and smoking on clozapine's pharmacokinetics to better predict the influence of a combined treatment in smoking and non-smoking patients with schizophrenia.

2. Materials and methods

The study was conducted at the Department of Psychiatry, Psychotherapy and Psychosomatics of RWTH Aachen University Hospital and the Alexianer Hospital Aachen, Germany. A TDM database consists of serum concentrations of clozapine (CLZ) and *N*-desmethylclozapine (NCLZ) from inpatients with schizophrenia that were treated in both institutions between 01/2013 and 11/2018. In both hospitals patients were allowed to smoke in special areas, therefore there was no institutional restriction of smoking behavior. Data collection was performed as part of the clinical routine at steady-state conditions (>5 half-life times, trough level blood sampling). In cases of multiple available serum concentrations for one single patient, only the most recent value was included in the analysis. Retrospective analysis of clinical data for this study was in accordance with the local regulatory authority.

We considered four study groups; two groups of patients receiving clozapine monotherapy consisting of non-smokers ($V_{NS,}$ $n = 28$) and smokers ($V_{S,}$ $n = 43$) and two groups receiving clozapine with fluvoxamine augmentation consisting of non-smokers ($V_{NS+F,}$ $n = 11$) and smokers ($V_{S+F,}$ n = 43). No matching processes for age, sex, diagnoses, severity, length or onset of illness were undertaken. All groups consisted of patients without a co-medication with so far known or previously described CYP2D6 inhibitory or CYP1A2, CYP3A4, CYP2C9 or CYP2C19 inhibitory or inducing properties according to established databases for cytochrome P450 influencing drugs (FDA, 2014; Hiemke et al., 2018).

2.1. Quantification of clozapine

Blood samples were drawn just before drug administration (trough levels) at steady state conditions (> 5 elimination half-lives under the same drug dose). Serum concentrations of both, CLZ and NCLZ were quantified using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) as described elsewhere (Couchman et al., 2013; Rao et al., 2009).

2.2. Statistical analysis

Serum concentrations of CLZ and NCLZ were compared between the four groups; two groups on clozapine monotherapy consisting of non-smokers (V_{NS}) and smokers (V_S) and two groups treated with clozapine and fluvoxamine consisting of non-smokers (V_{NS+F}) and smokers (V_{S+F}). Dose-adjusted plasma concentrations (ratio of the drug concentration C and the applied daily dose D, C/D, in [ng/mL]/[mg/day]) for clozapine, *N*-desmethylclozapine as well as the metabolite-to-parent ratio (MPR; NCLZ/CLZ) were calculated. Histograms yielded evidence of a non-normal distribution of the analyzed serum concentrations. Therefore, we performed a non-parametrical Kruskal-Wallis test with a significance level of 0.05 to compare the distributions of serum concentrations of CLZ and NCLZ between the groups. To conduct pairwise comparison of the serum concentrations between the groups, a Mann Whitney *U* test (M-W *U*) with the same significance level was applied. Statistical analysis was carried out using IBM SPSS Statistics version 24.0 (SPSS Inc. Chicago, USA).

3. Results

125 of 139 patients from the TDM database were eligible for analysis (14 patients had confounding co-medication according to the FDA classification of in vivo inhibitors or inducers of CYP enzymes (FDA, 2017)) and were excluded from analysis. Drug concentrations of 125 patients were assigned to the four groups, V_{NS} ($n = 28$), V_S ($n = 43$), V_{NS+F} ($n = 11$) and V_{S+F} (n = 43). The demographic data is summarized in Table 1.

Table 1
Patients' demographic characteristics.

Group	Number of patients	Median age (years)	Sex		Clozapine (mg/day)	Fluvoxamine (mg/day)
			% female	% male	Median (range)	Median (range)
V_{NS}	28	47 (19–69)	60.7	39.3	262.5 (125–650)	–
V_{NS+F}	11	55 (28–73)	45.5	54.5	200 (50–275)	50 (12,5–100)
V_S	43	38 (19–69)	37.2	62.8	350 (100–750)	–
V_{S+F}	43	40 (19–61)	30.2	69.8	250 (50–600)	50 (12,5–100)

V_{NS} = non-smokers without comedication with fluvoxamine; V_{NS+F} = non-smokers co-medicated with fluvoxamine; V_S = smokers without comedication with fluvoxamine; V_{S+F} = smokers co-medicated with fluvoxamine.

The median serum concentrations (ng/mL), median dose-adjusted serum concentrations of clozapine, *N*-desmethylclozapine, and metabolite-to-parent ratio (NCLZ/CLZ) are displayed in Table 2.

The Kruskal-Wallis test detected no differences regarding sex distribution or age between the four groups ($p = 0.077$ and $p = 0.051$). However, the groups differed significantly in terms of daily dose of clozapine ($p = 0.002$) but not fluvoxamine ($p = 0.451$). The comparison of the distribution of the serum concentrations yielded significant differences between the groups for CLZ ($p < 0.001$) and NCLZ ($p = 0.003$). Significant differences were also detected for dose-adjusted serum concentrations; groups differed significantly for both, C/D CLZ ($p < 0.001$) and C/D NCLZ ($p < 0.001$). Significant differences were also found for MPRs ($p = 0.002$).

To further disentangle the differences between the groups, we conducted pairwise comparisons between pairs of groups using a M-W *U* test. We first analyzed the effect of smoking on clozapine metabolism without fluvoxamine augmentation. The comparison of V_{NS} vs. V_S revealed significant distribution differences for CLZ and NCLZ ($p = 0.002$, $p = 0.025$). For CLZ, smokers showed significantly lower median serum concentrations (−30.2%, 122,5 ng/mL lower) compared to non-smokers. For NCLZ, median serum concentrations were − 23.7% or 56 ng/mL lower. Smokers showed a significantly higher metabolite-to-parent ratio ($p = 0.021$; 0.647 compared to 0.514). The comparisons of dose-adjusted serum concentrations between the groups revealed similar results; C/D CLZ ($p < 0.001$) and C/D NCLZ ($p < 0.001$) were −38.6% and −35.6% lower in smokers than in non-smokers. Important to note, the two groups did not differ in terms of sex narrowly missing the *p*-value of 0.05 ($p = 0.054$). There were no significant differences regarding age and daily dose of clozapine between the two groups ($p = 0.104$, $p = 0.119$).

We then focused on the effect of fluvoxamine in non-smoking and smoking patients. In non-smokers, the comparison of V_{NS} vs. V_{NS+F} did not reveal significant distribution differences for CLZ and NCLZ ($p = 0.914$, $p = 0.158$). Comparisons of the MPR did not reach significance ($p = 0.089$). The comparison of the dose-adjusted serum concentrations showed significant differences between C/D CLZ ($p < 0.001$) and C/D NCLZ ($p = 0.029$) with +117.9% and + 60.8% higher values in the fluvoxamine group. The groups differed significantly in terms of the daily dose of clozapine ($p = 0.004$) with lower doses in the fluvoxamine group, but not in terms of age or sex ($p = 0.301$, $p = 0.469$).

Analyzing the effect of fluvoxamine in smoking patients, the comparison of V_S vs. V_{S+F} showed significant differences for CLZ ($p < 0.001$) and NCLZ ($p = 0.001$), as the group of smokers concomitantly treated with fluvoxamine showed significantly higher serum values of both, CLZ (+63.6%, 180 ng/mL higher) and NCLZ (+42.2%, 76 ng/mL higher). The metabolic ratio was −21.8% lower in the fluvoxamine group ($p = 0.006$). Dose-adjusted comparisons revealed +120.1% higher values in the fluvoxamine group for C/D CLZ ($p < 0.001$) and +85.8% higher values for C/D NCLZ ($p < 0.001$). Both groups did not differ in terms of age, sex or daily clozapine dose ($p = 0.928$, $p = 0.496$, $p = 0.073$).

By addressing the effect of smoking in patients that were under combined treatment with clozapine and fluvoxamine, V_{NS+F} vs. V_{S+F}, we found significant differences only for NCLZ ($p = 0.032$) but not for CLZ ($p = 0.361$). Concentrations of NCLZ were +49.7% or 85 ng/mL higher in the group of active smokers compared to non-smokers. Metabolic ratios did not differ between groups ($p = 0.1$). There were significant differences in dose adjusted comparisons for C/D CLZ ($p = 0.034$, −38% lower in smokers compared to non-smokers) but not for C/D NCLZ ($p = 0.356$). Groups differed significantly in terms of age ($p = 0.024$) and daily dose of clozapine ($p = 0.007$) as smokers were younger and received a higher median daily dose of clozapine. There were no differences concerning sex distribution between the groups ($p = 0.344$).

Finally, we investigated the combined effect of fluvoxamine augmentation in non-smokers compared to smokers on clozapine monotherapy. Analysis of V_{NS} vs. V_{S+F} did not yield significant differences for serum concentrations of CLZ or NCLZ ($p = 0.196$, $p = 0.244$). The MPR did not differ between groups ($p = 0.605$). Regarding dose-adjusted-comparisons, there were no significant differences for C/D CLZ ($p = 0.151$) and C/D NCLZ ($p = 0.077$). The groups differed significantly in terms of sex ($p = 0.012$) but not age ($p = 0.075$) as the proportion of males was higher in the V_{S+F} group while the daily clozapine dose did not differ between groups ($p = 0.868$).

Figs. 1 and 2 show box-plots of median dose-adjusted serum concentrations of CLZ and NCLZ between the four groups: patients receiving clozapine monotherapy being non-smokers ($V_{NS,}$ $n = 28$) or smokers ($V_{S,}$ $n = 43$) and patients receiving clozapine with fluvoxamine augmentation being non-smokers ($V_{NS+F,}$ $n = 11$) or smokers ($V_{S+F,}$ n = 43).

4. Discussion

Clinical evidence concerning the impact of smoking or concomitantly administered fluvoxamine medication on the metabolism of clozapine has been known for a long time. Clinicians know that both factors affect the metabolism of clozapine. However, data regarding changes of clozapine and *N*-desmethylclozapine serum concentrations due to the influence of smoking and/or fluvoxamine, thereby quantifying the extent of the impact of both factors, is lacking and has not been published so far.

Table 2
Median serum concentrations (range), dose-adjusted serum concentrations (C/D) of clozapine, *N*-desmethylclozapine (NCLZ) and metabolite-to-parent ratios in the study groups.

Group	CLZ	NCLZ	NCLZ/CLZ	C/D CLZ	C/D NCLZ
V_{NS}	405.5 (113–882)	236 (78–464)	0.514 (0.3–1.1)	1.434 (0.8–5.1)	0.807 (0.4–1.9)
V_{NS+F}	427 (192–909)	171 (106–357)	0.416 (0.2–0.6)	3.125 (2.0–4.8)	1.298 (0.5–2.3)
V_S	283 (51–747)	180 (33–504)	0.647 (0.3–1.1)	0.88 (0.3–3.7)	0.52 (0.2–1.5)
V_{S+F}	463 (146–1590)	256 (39–557)	0.506 (0.3–1.1)	1.937 (0.6–5.9)	0.966 (0.3–3.4)

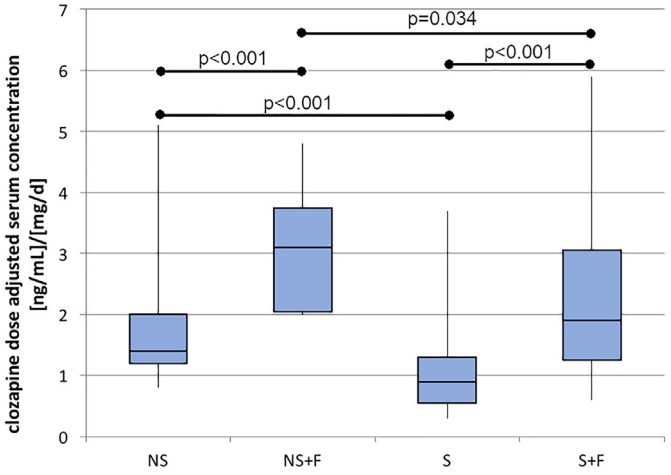

Fig. 1. Box-plot of median dose-adjusted serum concentrations of clozapine. Note the significantly higher C/D values in the non-smoking compared with the smoking-group and the significant effect of fluvoxamine on the dose adjusted serum concentrations in both groups.

Aim of the study was to assess the impact of both influencing factors on clozapine serum concentrations and the concentration of its main metabolite, *N*-desmethylclozapine, in a naturalistic setting by analyzing a therapeutic drug monitoring database. Data was collected from inpatients in the professional clinical setting of a university hospital and a regional community hospital. The data quality is considered to be high as all samples were collected at trough levels at steady-state conditions in the morning, extensive information on concomitant medication was available on electronic medical records, medication adherence was ensured and assessment of smoking status in the inpatient hospital setting (yes/no; no extent of consumption) was performed.

We compared four groups that differed in terms of smoking status and co-medication with fluvoxamine. Findings on the effect of smoking in clozapine monotherapy are in-line with previous research in the field. Tobacco smoking patients showed a reduction of −38% in dose-adjusted clozapine concentrations and a reduction of −36% in the dose-adjusted concentrations of *N*-desmethylclozapine. Decreases in drug concentrations in our analysis were slightly lower than the proposed 50% reduction in daily doses of clozapine in non-smokers compared to smokers as suggested by Tsuda et al. (Tsuda et al., 2014). However, in contrast to the meta-analysis by Tsuda and colleagues, we were better able to ensure adherence because only inpatients were included, electronic medical records registered whether medication was taken by the patient or not and we excluded samples with concomitant

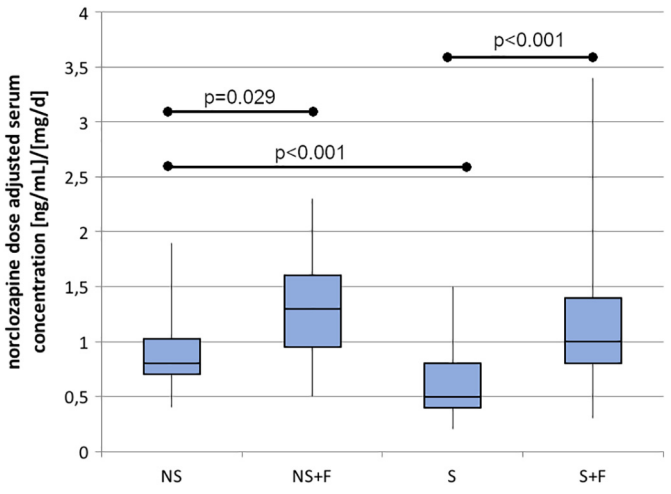

Fig. 2. Box-plot of median dose-adjusted serum concentrations of *N*-desmethylclozapine.

medication known to influence CYP metabolism. Our data share the limitation that the amount of cigarette consumption per day was not assessed. This may be relevant as it has been reported that the extent of smoking on CYP1A2 activity depends on the number of cigarettes (Plowchalk and Rowland Yeo, 2012).

The impact of fluvoxamine augmentation on clozapine metabolism was comparable between smokers and non-smokers. The increases in comparative C/D ratios showed a beneficial effect of fluvoxamine addition. Non-smokers receiving fluvoxamine augmentation showed a +117.9% and +60.8% increase in median dose-adjusted drug concentrations of CLZ and NCLZ compared to non-smoking patients without fluvoxamine. However, the non-smoking group receiving fluvoxamine was small ($n = 11$). The impact of fluvoxamine augmentation in smokers was comparable to that in non-smokers, as smokers showed +120.1% higher median dose-adjusted clozapine- and + 85.8% higher dose-adjusted *N*-desmethylclozapine concentrations. This profound effect of a fluvoxamine augmentation on clozapine metabolism in smokers is in-line with previous studies (Lu et al., 2000; Wetzel et al., 1998). However, these studies were significantly smaller with a total of thirty and eighteen patients in comparison to our data of 125 patients. As our study did not assess side effects, the clinical impact of fluvoxamine augmentation can only be evaluated in terms of the serum concentrations but not if the addition was beneficial in terms of side effects or treatment efficacy.

It is notable that although fluvoxamine changed the C/D ratio of both, CLZ and NCLZ, in the groups of smokers and non-smokers, we found significant changes in the MPR only by comparing the groups of smokers with or without fluvoxamine. Median MPR was the lowest in non-smokers with fluvoxamine augmentation (V_{NS+F}) and the highest in smokers without fluvoxamine (V_S) as expected according to CYP1A2 induction by smoking and inhibition by fluvoxamine. Yet, these differences did not reach significance in the analysis of the groups of non-smokers with clozapine monotherapy (V_{NS}) compared to non-smokers with fluvoxamine augmentation (V_{NS+F}). We suppose that the non-smoking group with fluvoxamine augmentation with 11 patients was too small for the effect to be detectable.

Interestingly, the analysis of non-smokers without fluvoxamine augmentation compared to smokers with fluvoxamine augmentation showed neither significant differences in serum concentrations of CLZ and NCLZ nor for dose-adjusted serum concentrations of CLZ and NCLZ. In our sample the inhibition of CYP1A2 by fluvoxamine counterbalanced the induction of CYP1A2 by smoking. The inhibition of fluvoxamine was not stronger than the impact of smoking on clozapine metabolism at a moderate median daily dose of 50 mg fluvoxamine.

In patients treated with clozapine and fluvoxamine, we strongly advise therapeutic drug monitoring. Therapeutic drug monitoring assists the clinician to ensure adequate serum concentrations, treatment safety and efficacy. A 'level 1 recommendation' for therapeutic drug monitoring of clozapine is also supported by the update 2017 of the 'Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology' by Hiemke et al. (Hiemke et al., 2018). A level 1 recommendation means that clinical trials have shown beneficial effects of therapeutic drug monitoring and drug concentrations within the so called therapeutic reference range suggest the highest probability of response or remission. Subtherapeutic drug concentrations may lead to relapse or response at the level of placebo. Furthermore, supratherapeutic drug concentrations hold an increased risk of adverse drug reactions, seizures or toxicity.

Our study elucidates both, the single effect of smoking and fluvoxamine augmentation alone and the combined impact of both cytochrome CYP1A2 influencing factors on clozapine metabolism. In case of fluvoxamine augmentation, the patients' smoking status should be actively assessed. In our sample the induction of CYP1A2 by smoking is offset by the inhibition of CYP1A2 by fluvoxamine or vice versa. Further research on fluvoxamine augmentation should always include

data on the patients' smoking status, preferably assessing the amount of cigarettes consumed per day.

4.1. Limitations

The TDM database consists of a naturalistic sample and relies on retrospective data which can be considered less reliable than data from a prospective clinical study and more prone to bias. Important parameters such as onset and duration of illness, clinical rating scales, and knowledge about adverse effects, comorbidities and duration of prior clozapine or fluvoxamine use were not available making further analyses for confounding effects impossible. There was no quantification of smoking status (e.g. number of cigarettes per day) and, therefore, an analysis based on the amount of cigarettes smoked per day was not possible. The lack of clinical data limits the interpretation of the evidence. Individual variations in sampling time were not assessed, yet, minor variations are likely considering the clinical setting. The fact that genetic polymorphisms were not assessed poses a considerable limitation to the data. To minimize the patient bias, only the most recent value was included in the analysis in the case of multiple available serum concentrations for one single patient.

Role of the funding source

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

Contributors

MA, MP, GS, GG, PP participated in the research design of the study.
MA, CL, MP collected TDM samples.
MA, MP, GS performed initial statistical analysis.
MA, MP wrote the first article draft.
All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

Gerhard Gründer has served as a consultant for Allergan (Dublin, Ireland), Boehringer Ingelheim (Ingelheim, Germany), Eli Lilly (Indianapolis, Ind, USA), Janssen-Cilag (Neuss, Germany), Lundbeck (Copenhagen, Denmark), Ono Pharmaceuticals (Osaka, Japan), Otsuka (Chiyoda, Japan), Recordati (Milan, Italy), Roche (Basel, Switzerland), Servier (Paris, France), and Takeda (Osaka, Japan). He has served on the speakers' bureau of Eli Lilly, Janssen Cilag, Neuraxpharm (Langenfeld, Germany), Lundbeck, Otsuka, Recordati, Roche, Servier, and Trommsdorf (Aachen, Germany). He has received grant support from Boehringer Ingelheim and Roche. He is co-founder of Mind and Brain Institute GmbH (Zornheim, Germany), Brainfoods GmbH (Zornheim, Germany) and InMediCon GmbH (Pentling, Germany). He reports no conflict of interest with this publication. Georgios Schoretsanitis received a grant from the bequest "in memory of Maria Zaoussi", State Scholarships Foundation, Greece for clinical research in Psychiatry for the academic year 2015–2016. Michael Paulzen is co-founder of InMediCon GmbH (Pentling, Germany). He reports no conflict of interest with this publication. All other authors declare no conflicts of interest as well. The research study did not receive funds or support from any source.

Acknowledgements

We thank the laboratory team which provided the therapeutic drug monitoring results.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.033.

References

Augustin, M., Schoretsanitis, G., Hiemke, C., Gründer, G., Haen, E., Paulzen, M., 2018. Differences in duloxetine dosing strategies in smoking and nonsmoking patients: therapeutic drug monitoring uncovers the impact on drug metabolism. J Clin Psychiatry 79 (5).

Couchman, L., Belsey, S.L., Handley, S.A., Flanagan, R.J., 2013. A novel approach to quantitative LC-MS/MS: therapeutic drug monitoring of clozapine and norclozapine using isotopic internal calibration. Anal. Bioanal. Chem. 405 (29), 9455–9466.

Food and Drug Administration, 2017. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-1.

Hiemke, C., Hartter, S., 2000. Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacol. Ther. 85 (1), 11–28.

Hiemke, C., Bergemann, N., Clement, H.W., Conca, A., Deckert, J., Domschke, K., Eckermann, G., Egberts, K., Gerlach, M., Greiner, C., Gründer, G., Haen, E., Havemann-Reinecke, U., Hefner, G., Helmer, R., Janssen, G., Jaquenoud, E., Laux, G., Messer, T., Mossner, R., Muller, M.J., Paulzen, M., Pfuhlmann, B., Riederer, P., Saria, A., Schoppek, B., Schoretsanitis, G., Schwarz, M., Gracia, M.S., Stegmann, B., Steimer, W., Stingl, J.C., Uhr, M., Ulrich, S., Unterecker, S., Waschgler, R., Zernig, G., Zurek, G., Baumann, P., 2018. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 51 (1−02), 9–62.

Jaquenoud Sirot, E., Knezevic, B., Morena, G.P., Harenberg, S., Oneda, B., Crettol, S., Ansermot, N., Baumann, P., Eap, C.B., 2009. ABCB1 and cytochrome P450 polymorphisms: clinical pharmacogenetics of clozapine. J. Clin. Psychopharmacol. 29 (4), 319–326.

Kishi, T., Hirota, T., Iwata, N., 2013. Add-on fluvoxamine treatment for schizophrenia: an updated meta-analysis of randomized controlled trials. Eur. Arch. Psychiatry Clin. Neurosci. 263 (8), 633–641.

Kroon, L.A., 2007. Drug interactions with smoking. Am. J. Health Syst. Pharm. 64 (18), 1917–1921.

Lameh, J., Burstein, E.S., Taylor, E., Weiner, D.M., Vanover, K.E., Bonhaus, D.W., 2007. Pharmacology of N-desmethylclozapine. Pharmacol. Ther. 115 (2), 223–231.

Legare, N., Gregoire, C.A., De Benedictis, L., Dumais, A., 2013. Increasing the clozapine: norclozapine ratio with co-administration of fluvoxamine to enhance efficacy and minimize side effects of clozapine therapy. Med. Hypotheses 80 (6), 689–691.

de Leon, J., Diaz, F.J., 2012. Genetics of schizophrenia and smoking: an approach to studying their comorbidity based on epidemiological findings. Hum. Genet. 131 (6), 877–901.

Lu, M.L., Lane, H.Y., Chen, K.P., Jann, M.W., Su, M.H., Chang, W.H., 2000. Fluvoxamine reduces the clozapine dosage needed in refractory schizophrenic patients. J Clin Psychiatry 61 (8), 594–599.

Lu, M.L., Lane, H.Y., Lin, S.K., Chen, K.P., Chang, W.H., 2004. Adjunctive fluvoxamine inhibits clozapine-related weight gain and metabolic disturbances. J Clin Psychiatry 65 (6), 766–771.

Mauri, M.C., Paletta, S., Maffini, M., Colasanti, A., Dragogna, F., Di Pace, C., Altamura, A.C., 2014. Clinical pharmacology of atypical antipsychotics: an update. EXCLI J. 13, 1163–1191.

Mendoza, M.C., Lindenmayer, J.P., 2009. N-desmethylclozapine: is there evidence for its antipsychotic potential? Clin. Neuropharmacol. 32 (3), 154–157.

Miura, M., Ohkubo, T., 2007. Identification of human cytochrome P450 enzymes involved in the major metabolic pathway of fluvoxamine. Xenobiotica 37 (2), 169–179.

Olesen, O.V., Linnet, K., 2000. Fluvoxamine-clozapine drug interaction: inhibition in vitro of five cytochrome P450 isoforms involved in clozapine metabolism. J. Clin. Psychopharmacol. 20 (1), 35–42.

Paulzen, M., Haen, E., Stegmann, B., Hiemke, C., Gründer, G., Lammertz, S.E., Schoretsanitis, G., 2016a. Body mass index (BMI) but not body weight is associated with changes in the metabolism of risperidone; a pharmacokinetics-based hypothesis. Psychoneuroendocrinology 73, 9–15.

Paulzen, M., Haen, E., Stegmann, B., Unterecker, S., Hiemke, C., Gründer, G., Schoretsanitis, G., 2016b. Clinical response in a risperidone-medicated naturalistic sample: patients' characteristics and dose-dependent pharmacokinetic patterns. Eur. Arch. Psychiatry Clin. Neurosci.

Paulzen, M., Schoretsanitis, G., Hiemke, C., Grunder, G., Haen, E., Augustin, M., 2018. Reduced clearance of venlafaxine in a combined treatment with quetiapine. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 85, 116–121.

Pelkonen, O., Maenpaa, J., Taavitsainen, P., Rautio, A., Raunio, H., 1998. Inhibition and induction of human cytochrome P450 (CYP) enzymes. Xenobiotica 28 (12), 1203–1253.

Plowchalk, D.R., Rowland Yeo, K., 2012. Prediction of drug clearance in a smoking population: modeling the impact of variable cigarette consumption on the induction of CYP1A2. Eur. J. Clin. Pharmacol. 68 (6), 951–960.

Polcwiartek, C., Nielsen, J., 2016. The clinical potentials of adjunctive fluvoxamine to clozapine treatment: a systematic review. Psychopharmacology 233 (5), 741–750.

Procyshyn, R.M., Wasan, K.M., Thornton, A.E., Barr, A.M., Chen, E.Y., Pomarol-Clotet, E., Stip, E., Williams, R., Macewan, G.W., Birmingham, C.L., Honer, W.G., Clozapine, Risperidone Enhancement Study, G, 2007. Changes in serum lipids, independent of weight, are associated with changes in symptoms during long-term clozapine treatment. J. Psychiatry Neurosci. 32 (5), 331–338.

Rajji, T.K., Mulsant, B.H., Davies, S., Kalache, S.M., Tsoutsoulas, C., Pollock, B.G., Remington, G., 2015. Prediction of working memory performance in schizophrenia by plasma ratio of clozapine to N-desmethylclozapine. Am. J. Psychiatry 172 (6), 579–585.

Rao, L.V., Snyder, M.L., Vallaro, G.M., 2009. Rapid liquid chromatography/tandem mass spectrometer (LCMS) method for clozapine and its metabolite N-desmethyl clozapine (norclozapine) in human serum. J. Clin. Lab. Anal. 23 (6), 394–398.

Reynolds, G.P., Templeman, L.A., Zhang, Z.J., 2005. The role of 5-HT2C receptor polymorphisms in the pharmacogenetics of antipsychotic drug treatment. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 29 (6), 1021–1028.

Schoretsanitis, G., Stegmann, B., Hiemke, C., Gründer, G., Schruers, K.R., Walther, S., Lammertz, S.E., Haen, E., Paulzen, M., 2016. Pharmacokinetic patterns of risperidone-associated adverse drug reactions. Eur. J. Clin. Pharmacol. 72 (9), 1091–1098.

Schrenk, D., Brockmeier, D., Morike, K., Bock, K.W., Eichelbaum, M., 1998. A distribution study of CYP1A2 phenotypes among smokers and non-smokers in a cohort of healthy Caucasian volunteers. Eur. J. Clin. Pharmacol. 53 (5), 361–367.

Spina, E., Hiemke, C., de Leon, J., 2016. Assessing drug-drug interactions through therapeutic drug monitoring when administering oral second-generation antipsychotics. Expert Opin. Drug Metab. Toxicol. 12 (4), 407–422.

Tsuda, Y., Saruwatari, J., Yasui-Furukori, N., 2014. Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine. BMJ Open 4 (3), e004216.

Wang, C.Y., Zhang, Z.J., Li, W.B., Zhai, Y.M., Cai, Z.J., Weng, Y.Z., Zhu, R.H., Zhao, J.P., Zhou, H.H., 2004. The differential effects of steady-state fluvoxamine on the pharmacokinetics of olanzapine and clozapine in healthy volunteers. J. Clin. Pharmacol. 44 (7), 785–792.

Wetzel, H., Anghelescu, I., Szegedi, A., Wiesner, J., Weigmann, H., Harter, S., Hiemke, C., 1998. Pharmacokinetic interactions of clozapine with selective serotonin reuptake inhibitors: differential effects of fluvoxamine and paroxetine in a prospective study. J. Clin. Psychopharmacol. 18 (1), 2–9.

Zevin, S., Benowitz, N.L., 1999. Drug interactions with tobacco smoking. An update. Clin Pharmacokinet 36 (6), 425–438.