Differences in Duloxetine Dosing Strategies in Smoking and Nonsmoking Patients:

Therapeutic Drug Monitoring Uncovers the Impact on Drug Metabolism

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ABSTRACT

Background: For certain psychotropic drugs, such as clozapine or olanzapine, the influence of smoking on drug metabolism is well studied. Tobacco smoke increases the metabolism of drugs that are substrates for cytochrome P450 (CYP) 1A2 due to CYP induction. The antidepressant duloxetine, acting as a serotonin-norepinephrine reuptake inhibitor, is mainly metabolized via CYP1A2. To date, little is known about the influence of smoking on serum duloxetine concentrations.

Methods: A therapeutic drug monitoring database consisting of plasma concentrations of duloxetine collected from January 2013 to June 2017 was analyzed. A group of nonsmoking patients undergoing treatment with duloxetine (n = 89) was compared to a group of active smokers also receiving duloxetine (n = 36). Serum concentrations of duloxetine and dose-adjusted serum concentrations were compared using non-parametric tests.

Results: Groups did not differ concerning sex ($P = .063$), but the group of active smokers was younger ($P < .001$) and received higher daily doses of duloxetine ($P = .001$). Smokers showed significantly lower median serum duloxetine concentrations (38.4% lower, $P = .002$) and 53.6% lower dose-adjusted serum concentrations (0.325 [ng/mL]/[mg/d] in smokers vs 0.7 [ng/mL]/[mg/d] in nonsmokers, $P < .001$).

Conclusions: Despite higher daily doses, smokers had considerably lower serum duloxetine concentrations. The induction of CYP1A2 by tobacco smoke is a clinically relevant factor for drugs that are substrates for CYP1A2. Clinicians should actively assess smoking status, inform patients about the effect of smoking on duloxetine metabolism, and anticipate higher serum concentrations in the case of smoking cessation. Therapeutic drug monitoring ensures treatment efficacy by enabling the personalizing of treatment, as smokers need higher duloxetine doses to target serum concentrations within the therapeutic reference range.

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Smoking is more prevalent in patients with mental illness than in the general population and is particularly common in patients with depression.[1,2] Whether a patient smokes is an important factor in prescribing and setting doses of psychotropic drugs. For certain drugs, such as fluvoxamine,[3] mirtazapine,[4] olanzapine and clozapine,[5] the influence of smoking on drug metabolism is extensively studied. The influence of smoking on plasma concentration is high. In nonsmokers, a dose reduction of 30% for olanzapine and 50% for clozapine is recommended.[5]

For antidepressants, the impact of smoking on drug metabolism is increasingly recognized.[6] Smoking is hypothesized to induce cytochrome P450 (CYP) isoenzymes leading to changes in antidepressants' pharmacokinetics. Polycyclic aromatic hydrocarbons, generated by tobacco smoking, seem to be especially responsible for the induction of isoenzymes CYP1A1, CYP1A2, and CYP2E1.[7,8] Induction or inhibition of CYP isoenzymes can have substantial effects on drug metabolism, thereby affecting serum or plasma concentrations of a particular drug and its metabolites.[9] The serum concentration plays a crucial role for clinical efficacy and patients' safety. For the selective serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant duloxetine, it has been suggested that beneficial clinical effects are linked to serum concentrations within the therapeutic reference range of 30–120 ng/mL,[10] as patients with higher serum concentrations showed greater improvements on the Clinical Global Impressions scale (CGI).[11] Whether serum duloxetine drug concentrations are within the therapeutic reference range depends sometimes on many factors and occasionally on only a single factor. For instance, concomitant treatment with duloxetine and fluvoxamine, a potent CYP1A2 inhibitor, has been shown to substantially increase plasma duloxetine concentrations.[12]

Duloxetine metabolism is hypothesized to be influenced by smoking; however, data from naturalistic settings are scarce. A recent systematic review[6] counted only 2 studies that focused on smoking and the pharmacokinetics of duloxetine.

To elucidate the impact of smoking on duloxetine pharmacokinetics, we used data from a therapeutic

Clinical Points

- Despite higher daily doses, smokers have significantly lower serum concentrations of duloxetine compared to nonsmokers. Dose-adjusted drug concentrations in smokers have been shown to be more than 50% lower compared to nonsmokers.
- CYP1A2 induction by tobacco smoke is a clinically relevant factor to be considered for a personalized psychopharmacotherapy, as smokers need higher daily doses of duloxetine.
- Therapeutic drug monitoring as a tool of precision medicine should be used to personalize duloxetine treatment, and psychiatrists should actively consider the smoking status of the patient.

drug monitoring (TDM) database to compare smoking and nonsmoking patients treated with duloxetine. TDM databases enable investigation of the concentration of psychotropic drugs in human serum or plasma, highlighting the influence of factors such as comedication,[13–16] sex, age, smoking behavior,[17] and adverse drug reactions[18,19] on pharmacokinetics.

Duloxetine is approved for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain.[20] It is administered once daily in a dose ranging from 30 to 120 mg. The elimination half-life is about 12 hours, and elimination involves CYP1A2 and CYP2D6.[21] Besides being a substrate, duloxetine has also been found to moderately inhibit CYP2D6.[22] Duloxetine is extensively metabolized, but metabolites have not been linked to pharmacologic activity. The bioavailability of duloxetine appears to be reduced by one-third in smokers, but the prescribing information does not currently recommend modified dosage for smokers.[20]

Duloxetine is prone to pharmacokinetic interactions because 2 CYP isoenzymes are involved in the metabolism. There is literature on drug-drug interactions between duloxetine and non-psychiatric drugs such as metoprolol.[23] However, surprisingly little data on pharmacokinetic aspects of duloxetine metabolism comparing smoking and nonsmoking patients are available. Therefore, we aimed to explore the effect of smoking on duloxetine metabolism. Serum concentrations and dose-adjusted serum concentrations (C/D) in (ng/mL)/(mg/d), collected in a TDM database, were analyzed.

MATERIALS AND METHODS

The study was conducted at the Department of Psychiatry, Psychotherapy and Psychosomatics of RWTH Aachen University Hospital, Aachen, Germany. A TDM database that was created for this study consists of serum concentrations of duloxetine from inpatients with different psychiatric diseases that were treated from January 2013 to June 2017. Data collection was performed as part of the clinical routine at steady-state conditions (> 5 half-lifetimes, trough level blood sampling). In some rare cases of multiple available serum concentrations for a 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 ethics committee.

We considered 2 study groups receiving duloxetine as an oral formulation: a group of nonsmoking patients (control group, V_N, n = 89) and a group of active smokers (V_S, n = 36). No matching processes for age, diagnoses, severity of the disease, duration, onset of disease, or sex were undertaken. Both groups consisted of patients without a comedication with known or previously described CYP2D6 inhibitory or CYP1A2, CYP3A4, CYP2C9, or CYP2C19 inhibitory or inducing properties according to established databases for CYP-influencing drugs.[10,24]

Quantification of Duloxetine

Blood samples were obtained just before drug administration (trough concentration) at steady state (> 5 elimination half-lives under the same drug dose). We used serum concentrations as the indicator for drug concentrations in blood. Serum was prepared by centrifugation of blood samples at 14,171 g for 15 minutes. A rapid, sensitive, and specific ultraperformance liquid chromatographic (UPLC) method (ACQUITY UPLC BEH Column, Waters Corporation, Milford, Massachusetts) was used for the quantitative determination of duloxetine. The method is linear from the designated limit of quantification of 2.0 ng/mL up to the upper limit of 111 ng/mL for duloxetine. Intraassay precision over a range from 14.0 ng/mL to 26.0 ng/mL is < 6.0%, and interassay precision is < 9.5%.

Statistical Analysis

Serum concentrations of duloxetine were compared between the 2 groups: the nonsmokers in the V_N group serving as the control group and smokers in the V_S group. Dose-adjusted serum concentrations (ratio of the drug concentration C and the applied daily dose D, C/D, in [ng/mL]/[mg/d]) for duloxetine were also calculated. As a primary outcome, we considered the serum duloxetine concentration. Histograms yielded evidence of a non-normal distribution of the analyzed serum concentrations. Hence, a non-parametric Mann-Whitney *U* test was conducted. Statistical analysis was carried out using IBM SPSS Statistics version 24.0 (SPSS Inc, Chicago, Illinois).

RESULTS

A total of 125 of the initial 152 patients were eligible for analysis. Twenty-seven patients had confounding comedications according to the US Food and Drug Administration classification of in vivo inhibitors or inducers of CYP enzymes and were excluded from the analysis. As noted, patients were assigned to the control group (V_N; n = 89) or the group of active smokers (V_S; n = 36). The demographic data are summarized in Table 1.

Table 1. Patient Demographic Characteristics

Group	n	Age, Median (Range), y	Sex, %		Duloxetine Daily Dose, Median (Range), mg/d
			Female	Male	
V_N	89	63 (19–88)	77.5	22.5	60 (30–120)
V_S	36	47* (20–78)	61.1	38.9	90* (60–150)

*Per the Mann-Whitney *U* test, patients in the V_S group were significantly younger ($P < .001$) and had significantly higher daily duloxetine doses ($P = .001$) than those in the V_N group.
Abbreviations: V_N = nonsmokers (controls), V_S = smokers.

Table 2. Median Serum Concentration (Range) and Concentration-to-Dose Ratio (C/D) for Duloxetine in the Study Groups

Group	Serum Duloxetine Concentration, Median (Range), ng/mL	Duloxetine C/D, Median (Range), (ng/mL)/(mg/d)
V_N	47.5 (6.5–230.0)	0.7 (0.1–3.5)
V_S	29.25* (5.7–141.0)	0.325* (0.1–1.2)

*Per the Mann-Whitney *U* test, patients in the V_S group had significantly lower serum concentrations of duloxetine ($P = .002$) and significantly lower C/D values ($P < .001$) than those in the V_N group.
Abbreviations: V_N = nonsmokers (controls), V_S = smokers.

Figure 1. Median (Interquartile Range) Serum Duloxetine Concentrations for the Control Group (V_N) and the Group of Active Smokers (V_S)

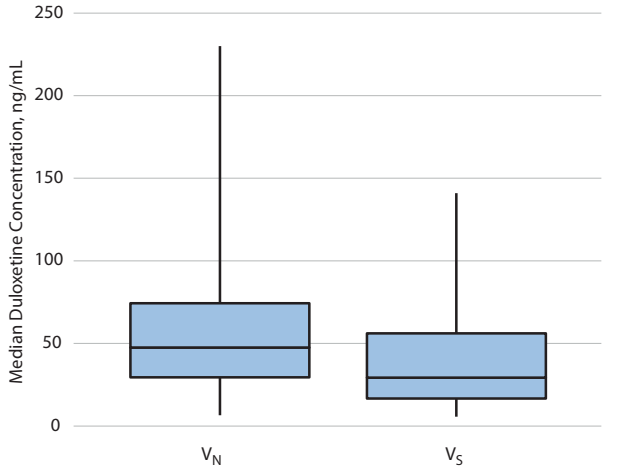
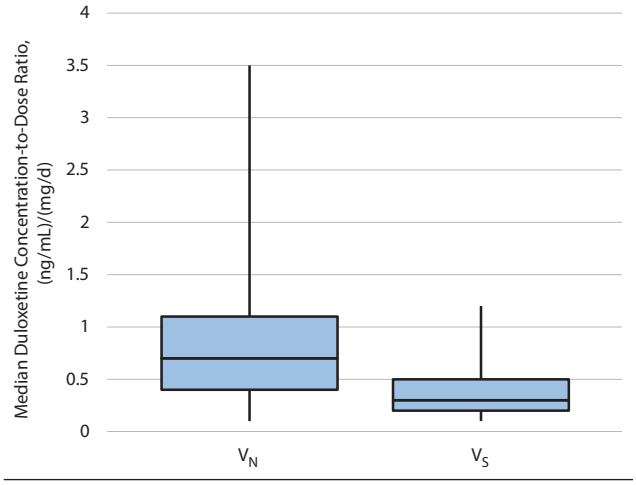


Figure 2. Median (Interquartile Range) Duloxetine Concentration-to-Dose Ratios for the Control Group (V_N) and the Group of Active Smokers (V_S)



The median serum concentrations (ng/mL) of duloxetine and the dose-adjusted serum concentrations, (C/D, [ng/mL]/[mg/d]) are displayed in Table 2.

The V_N group, and the V_S group, differed in terms of age ($P < .001$) and daily dose of duloxetine ($P = .001$) but not sex ($P = .063$). Smokers were significantly younger and had higher applied daily duloxetine doses.

Patients in the V_S group showed significantly lower serum concentrations of duloxetine ($P = .002$). Furthermore, dose-adjusted serum concentrations of duloxetine were found to differ significantly between the groups ($P < .001$), with lower values in the V_S group.

DISCUSSION

Smoking is prevalent in patients with depression, rendering this behavior a relevant factor in choosing the right dose of antidepressant drugs aiming to target drug concentrations within the therapeutic reference range. Our results show that smokers showed lower median serum duloxetine concentrations despite receiving significantly higher daily doses of duloxetine. The impact of CYP1A2 induction was remarkable. Although the median applied daily dose was higher (90 mg vs 60 mg), median duloxetine concentration values were about 38.4% lower in smokers compared to nonsmokers (see Figure 1). By controlling for the applied dose, we found that dose-adjusted serum concentrations were 53.6% lower in the group of smokers compared to nonsmokers (see Figure 2).

To our knowledge, and as was noted in a recent review,[6] only 2 studies[25,26] to date have addressed the effect of smoking on the pharmacokinetics of duloxetine. A first study[25] of 23 patients (8 smokers, 15 nonsmokers) showed significantly lower duloxetine concentrations in smokers, with smokers receiving higher daily doses of duloxetine in the course of antidepressant treatment. Concentration-to-dose ratios in smokers were in a range between 0.27 and 0.38, with higher values in nonsmokers (range between 0.61 and 0.81). Our analysis confirms these results in a considerably larger cohort.

A meta-analysis[26] of 594 patients from 5 clinical trials found the oral duloxetine clearance to be reduced by 30% in nonsmokers compared to smokers. Steady-state concentrations were 43% higher in nonsmokers compared to smokers. No specific dose recommendations were drawn based on smoking status. The majority of the patients were females (74%), nonsmokers (79%), and Caucasian (78%), but no information on exclusion of CYP-inducing or -inhibiting comedication was given. The authors applied a population pharmacokinetic modeling approach and found that sex, smoking status, age, duloxetine dose, and ethnic origin had a statistically significant effect on duloxetine pharmacokinetic

parameters. Besides presenting the impact of smoking on duloxetine metabolism, the study also addressed the impact of sex. It has been proposed that males have higher CYP1A2 expression in addition to the enhancing effect of smoking.[8,27] The authors of the meta-analysis[26] state that the combined effect of gender and smoking leads to an average duloxetine bioavailability that is 57% lower in male smokers compared to female nonsmokers. In our sample, median steady-state concentrations of duloxetine in smokers were significantly lower (29.25 vs 47.5 ng/mL), corresponding to a reduction of 38.4%. The TDM database used in this study was of particular value because data were collected by inpatients in the professional clinical setting of a university hospital. Patients were allowed to smoke in special areas inside the hospital, which excluded a potential bias effect due to an offset of CYP1A2 induction by smoking cessation. Therefore, the data quality is considered to be high, as all samples were collected at trough levels, extensive information on concomitant medication was available electronically, medication adherence was ensured, and clinical assessment of smoking status (yes/no; no extent of consumption) was possible.

Clinical implications of our findings are easy to address: whether a depressed person smokes or not is a clinically relevant factor in finding the right dose of duloxetine. Clinicians should actively assess smoking status in patients treated with duloxetine. To enhance treatment efficacy and safety, therapeutic drug monitoring is a valuable tool of precision medicine since it considers the high interindividual variability of pharmacokinetics for personalized psychopharmacotherapy. When a patient is treated with duloxetine with stable doses and stable serum concentrations, smoking cessation might be followed by a considerable increase in serum duloxetine concentrations and vice versa in the case when a patient starts smoking. An increase in drug concentrations can be expected nearly instantly, as the apparent half-life of CYP1A2 activity induction by tobacco smoke is around 38.6 hours.[28] Clinicians should use therapeutic drug monitoring in such cases to avoid adverse drug reactions due to increasing drug concentrations.

Given the interindividual variability in duloxetine metabolism and the range of serum duloxetine concentration values in our sample in both groups, it is difficult to draw general recommendations on how to dose duloxetine in patients who actively smoke. The prescribing information recommends a daily dose of 40 to 60 mg/d in major depressive disorder and states that the safety of doses above 120 mg/d has not been adequately studied.[20] Our results show that despite receiving higher daily doses, smoking patients had significantly lower median serum concentrations than nonsmoking patients. We therefore suggest higher maintenance doses of duloxetine in smoking patients with individually customized applied daily doses. To ensure adequate serum concentrations, treatment safety, and efficacy in patients whose psychotropic drug treatment consists of duloxetine, we highly recommend therapeutic drug monitoring. A level 2 recommendation for therapeutic drug monitoring of duloxetine is also supported by the 2017 update of the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology by Hiemke et al.[10] A level 2 recommendation means that therapeutic drug monitoring will increase the probability of response in nonresponders since at subtherapeutic drug concentrations, there is a risk of poor response while at supratherapeutic drug concentrations, there is an increased risk of intolerance or intoxication.

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 duloxetine use were not available, making further analyses for confounding effects impossible. Regrettably, there was no quantification of smoking status (eg, number of cigarettes per day). 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. To minimize the patient bias, only the most recent value was included in the analysis in the case of multiple available plasma concentrations for a single patient. Patients in the smoking group were considerably younger than those in the control group. Age may be an influential factor in drug metabolism as renal clearance and hepatic function decline in older patients. However, age accounts only for a small percentage of between-patient variability, and no dose adjustment for duloxetine based on the age of patients is recommended.[20]

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