

## ORIGINAL ARTICLE

# Metamizole but not ibuprofen reduces the plasma concentration of sertraline: Implications for the concurrent treatment of pain and depression/anxiety disorders

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**Aim:** Comorbidity of pain and depression or anxiety is a challenging clinical phenomenon, often requiring the concurrent application of antidepressant and analgesic drugs. Growing evidence suggests that the analgesic metamizole exhibits cytochrome P450 inducing properties. In the present study, we assessed the impact of metamizole and ibuprofen on plasma concentrations of the selective serotonin reuptake inhibitor sertraline.

**Methods:** Out of a therapeutic drug monitoring (TDM) database, three groups of patients were compared: patients receiving sertraline and metamizole ( $n = 15$ ), patients receiving sertraline and ibuprofen ( $n = 19$ ), and a matched control group without one of the analgesics ( $n = 19$ ).

**Results:** Metamizole was associated with 67% lower median sertraline plasma concentrations compared to the control group (14 vs 42 ng/mL,  $P < 0.001$ ). In contrast, differences between the ibuprofen group and the control group did not reach statistical significance (31 vs 42 ng/mL,  $P = 0.128$ ). Moreover, the metamizole group demonstrated lower dose-adjusted drug concentrations than the ibuprofen group (0.10 vs 0.26 (ng/mL)/(mg/day),  $P = 0.008$ ). Finally, the metamizole group exhibited a higher proportion of patients whose sertraline concentrations were below the therapeutic reference range (40% in the metamizole group, 5% in the ibuprofen group, 0% in the control group,  $P = 0.005$ ) indicating therapeutically insufficient drug concentrations.

**Conclusion:** Our findings support preliminary evidence that metamizole acts as a potent inducer of cytochrome P450 isoenzymes CYP2B6 and CYP3A4. We observed a clinically meaningful pharmacokinetic interaction between metamizole and sertraline, leading to insufficiently low sertraline drug concentrations. Clinicians should therefore consider alternative drug combinations or apply TDM-guided dose adjustment of sertraline.

## KEYWORDS

depression, dipyrrone, metamizole, pain, pharmacokinetics, sertraline, therapeutic drug monitoring

## 1 | INTRODUCTION

The combination of pain and mental disorders such as depression and anxiety disorders is a frequently challenging clinical situation as both mutually reinforce.<sup>1–4</sup> Severe pain is associated with increased depressive and anxious symptomatology as well as worse treatment outcomes.<sup>4,5</sup> In addition, the presence of pain impedes the recognition and treatment of major depressive and anxiety disorders.<sup>4,5</sup> Accordingly, depressive and anxious symptoms are often associated with increased pain perception and greater impairment in patients suffering from pain. Besides psychological factors, depression, anxiety and pain also exhibit converging neural mechanisms, which may have implications for future strategies of drug development.<sup>5,6</sup>

The treatment of patients suffering from both pain and depression or anxiety disorders often requires a simultaneous administration of antidepressant and analgesic drugs,<sup>7</sup> therefore clinicians have to be aware of relevant pharmacodynamic and pharmacokinetic drug-drug interactions (DDI). Since the approval of fluoxetine in the USA in 1987, selective serotonin reuptake inhibitors (SSRIs) have incrementally become the most widely prescribed antidepressant drugs.<sup>8</sup> Sertraline represents a potent inhibitor of serotonin reuptake and a modest inhibitor of dopamine and norepinephrine reuptake.<sup>9</sup> Converging evidence from meta-analyses indicates a trend in favour of sertraline over other antidepressants, concerning both, efficacy and tolerability.<sup>10</sup> Based on this finding, the drug is recommended as the initial choice of an antidepressant in people with major depression<sup>10</sup> or anxiety disorders.<sup>11</sup> Sertraline's metabolism involves *N*-demethylation (mediated by cytochromes P450 [CYP] 2B6, CYP2C19, CYP2C9, CYP3A4, and CYP2D6), deamination (mediated by CYP3A4, CYP2C19 and monoamine oxidases A and B) as well as *N*-carbamoyl glucuronidation catalysed by UGT2B7.<sup>12</sup> Sertraline's elimination half-life is between 22 and 36 hours<sup>13</sup> and plasma concentrations from 10 to 150 ng/mL are considered to be therapeutically effective.<sup>13</sup>

Nonopioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol and metamizole (dipyrone) are effective agents for the treatment of mild to moderate chronic pain and serve as first-line treatment for the management of chronic cancer pain according to the recommendations of the World Health Organization.<sup>14,15</sup> NSAIDs represent one of the most commonly prescribed drug classes.<sup>16</sup> Combining NSAIDs with SSRIs, however, increases the risk of gastrointestinal bleeding.<sup>17</sup> According to a meta-analysis by Anglin et al,<sup>18</sup> the combined odds ratio of upper gastrointestinal bleeding under a concomitant treatment with SSRIs and NSAIDs was estimated as 4.25 (95% CI = 2.82, 6.42), whereas the respective odds ratios under SSRI or NSAID treatment alone were estimated as 1.66 (95% CI = 1.44, 1.92) and 2.80 (95% CI = 2.20, 3.56), respectively. Therefore, metamizole may be a promising alternative when considering a simultaneous treatment with analgesics and SSRIs. The pyrazolone derivative metamizole is an effective analgesic agent exhibiting both antipyretic and antispasmodic properties.<sup>19</sup> Following reports of lethal agranulocytosis, the drug was withdrawn from the market in the United States and several European countries. However,

### What is already known about this subject

- The nonopioid analgesic metamizole exhibits inducing properties of cytochrome P450 (CYP) 2B6 and 3A4.
- Metamizole may be preferred over nonsteroidal anti-inflammatory drugs for patients who are under treatment with selective serotonin reuptake inhibitors (SSRIs).
- There is no data available on the impact of metamizole and ibuprofen on the SSRI sertraline, which is metabolized—among others—by CYP2B6 and CYP3A4.

### What this study adds

- Treatment with metamizole—but not ibuprofen—is associated with significantly lower plasma concentrations of sertraline.
- Under treatment with metamizole, plasma concentrations of sertraline are more likely to be below the therapeutic reference range.
- Clinicians should consider alternative drug combinations or apply therapeutic drug monitoring for dose adjustment of sertraline.

in many other countries in Europe, South America and Asia metamizole is still available and remains a popular analgesic agent.<sup>20</sup> In Germany, the prescription of metamizole increased nearly 3-fold from 2005 to 2015, yielding a total amount of 142 million defined daily doses (DDD) in 2012, by far exceeding the amount of COX-2-selective inhibitors, which amounted to 98 million DDD.<sup>21</sup>

Growing evidence indicates that metamizole may exhibit relevant pharmacokinetic interactions. More precisely, the intake of metamizole was associated with increased metabolism of both cyclosporin and bupropion in humans<sup>22,23</sup> which may be explained by the induction of CYP2B6 (bupropion) and CYP3A4 (cyclosporin), respectively.<sup>24</sup> Since both cytochrome isoenzymes are involved in sertraline metabolism, the aim of the current study was to address the impact of metamizole on sertraline pharmacokinetics.

We hypothesized that the co-administration of metamizole to an antidepressant treatment with sertraline leads to reduced drug concentrations compared to patients who did not receive metamizole. Moreover, we assumed that the NSAID ibuprofen is devoid of pharmacokinetic drug-drug interactions with sertraline due to lacking inducing or inhibiting properties on distinct cytochrome isoenzymes. We therefore conducted a retrospective analysis of sertraline drug concentrations obtained from a database dedicated to therapeutic drug monitoring (TDM). To the best of our knowledge, this is the first study to investigate pharmacokinetic effects of metamizole and ibuprofen on sertraline drug concentrations in blood.

## 2 | METHODS

Konbest, a web-based laboratory information management system for TDM laboratories,<sup>25</sup> served as our source of data. A large dataset comprising 1295 sertraline plasma concentrations from 874 patients was analysed. Data collection took place between 2006 and 2015 as part of the clinical routine in different institutions of the AGATE (Arbeitsgemeinschaft Arzneimitteltherapie bei psychischen Erkrankungen). AGATE is a co-operative for drug safety in the treatment of psychiatric diseases (for details see [www.amuep-agate.de](http://www.amuep-agate.de)). Retrospective analysis of clinical data was in accordance with the local regulatory authority of the Faculty of Medicine of the RWTH Aachen University. In this naturalistic database, patients were under medication with sertraline for different reasons. Patients receiving concomitant medication with possible inhibitory or inducing properties for CYP2B6, CYP2C19, CYP3A4 or inhibitory properties for CYP2D6, according to the suggestions by the US Food and Drug Administration,<sup>13,26</sup> were excluded. Among patients with more than one determination of sertraline plasma concentration, we only selected the most recent measurement.<sup>27</sup> Hence, the TDM data of 794 in- and outpatients with a broad spectrum of mental disorders were eligible for analysis. Based on this sample, we considered three groups: a group of patients receiving concomitant medication with metamizole (SERT<sub>Met</sub>, n = 15), a second group receiving concomitant medication with ibuprofen (SERT<sub>Ibu</sub>, n = 19), and a control group receiving only sertraline but neither metamizole nor ibuprofen (SERT, n = 19). In both the SERT<sub>Met</sub> and SERT<sub>Ibu</sub> groups, we considered only patients who were treated with the respective analgesic on a daily basis, ie, we excluded patients taking ibuprofen or metamizole as pro re nata medication. Information on the duration of

treatment was not available. Out of the remaining 760 patients who did not receive metamizole or ibuprofen, we matched the 19 best-fitting patients as the control group (SERT) with respect to age, gender, weight, nicotine and caffeine consumption as well as the daily dosage of sertraline. The demographic and clinical characteristics of the sample are provided in Table 1.

### 2.1 | Quantification of sertraline

Blood samples were asked to be drawn just before drug administration (trough levels) at steady-state conditions (>5 elimination half-lives under the same drug dose). All sertraline concentrations were determined in the same laboratory by high performance liquid chromatography with ultraviolet detection (HPLC/UV)<sup>28</sup>; unfortunately, no concentrations of desmethylsertraline were available. The method was validated according to DIN 32645 (Deutsche Industrie Norm 32,645, described in the guidelines of the GTFCh (Society of Toxicology and Forensic Chemistry) in consideration of ISO 5725 (International Organization for Standardization),<sup>29</sup> FDA (US Food and Drug Administration) guidance (US Food and Drug Administration, 2018),<sup>30</sup> and ICH (International Conference on Harmonization) requirements.<sup>31</sup> The laboratory regularly runs internal quality controls and participates in external quality assessment schemes set by INSTAND (Düsseldorf, Germany, [www.instandev.de](http://www.instandev.de)).

Inaccuracy, inter- and intraday imprecision were evaluated at sertraline concentrations of 300, 100 and 5 ng/mL, respectively.

- Inaccuracy: bias values were -2.14%, 2.80% and 8.60%.

**TABLE 1** Sociodemographic and clinical characteristics of the study sample consisting of three groups: patients receiving concomitant medication with metamizole (SERT<sub>Met</sub>), patients receiving ibuprofen (SERT<sub>Ibu</sub>) and a control group receiving only sertraline, but neither of the two analgesics (SERT)

Characteristic	SERT <sub>Met</sub> (n = 15)			SERT <sub>Ibu</sub> (n = 19)			SERT (n = 19)			Comparison	
	Median	q <sub>1</sub>	q <sub>3</sub>	Median	q <sub>1</sub>	q <sub>3</sub>	Median	q <sub>1</sub>	q <sub>3</sub>	$\chi^2$ (df = 2) <sup>a</sup>	P
Age (years)	58	49	75	49	49	57	55	49	69	3.35	0.187
Dose of sertraline (mg/day)	100	75	188	100	63	138	125	100	150	1.63	0.442
Weight (kg)	76	69	83	74	69	76	76	72	89	1.33	0.515
	n	%		n	%		n	%		$\chi^2$ (df = 2)	P
Sex										0.27	0.873
Female	9	60.0		13	68.4		12	63.2			
Male	6	40.0		6	31.6		7	36.8			
Nicotine consumption										3.33	0.189
Smokers	3	20.0		9	47.4		5	26.3			
Nonsmokers	12	80.0		10	52.6		14	73.7			
Caffeine consumption										0.19	0.910
Consumers	12	80.0		16	84.2		15	79.0			
Non-consumers	3	20.0		3	15.8		4	21.0			

<sup>a</sup>The Kruskal-Wallis test was calculated to assess group differences. The distribution of its test statistic was approximated by a  $\chi^2$  distribution.

- Interday imprecision: coefficients of variation (CV) were 3.8%, 8.9% and 13.9%.
- Intraday imprecision: CVs were 0.8%, 7.0% and 10.4%.

The limit of detection (LOD) and limit of quantification (LOQ) were 3.6 and 7.2 ng/mL, respectively.

## 2.2 | Statistical analysis

Statistical analysis was carried out using MATLAB 2015a (The MathWorks, Inc., Natick, USA) and SPSS 25, IBM, Armonk, USA). Drug concentrations of sertraline were compared between the three groups SERT ( $n = 19$ ), SERT<sub>Met</sub> ( $n = 15$ ) and SERT<sub>Ibu</sub> ( $n = 19$ ). Dose-adjusted drug concentrations (ratio of the drug concentration  $C$  and the applied daily dose  $D$ ,  $C/D$ , in [ng/mL]/[mg/day]) were also calculated. Histograms provided evidence of non-normal distribution of the analysed drug concentrations, which was also confirmed by a Kolmogorov-Smirnov test. The Kruskal-Wallis test was therefore chosen as a nonparametric test to compare the distributions of sertraline plasma concentrations between the three groups. Following the standard implementation in MATLAB, Tukey's honest significant difference test was conducted as a post hoc test for a pairwise comparison of the average group ranks.

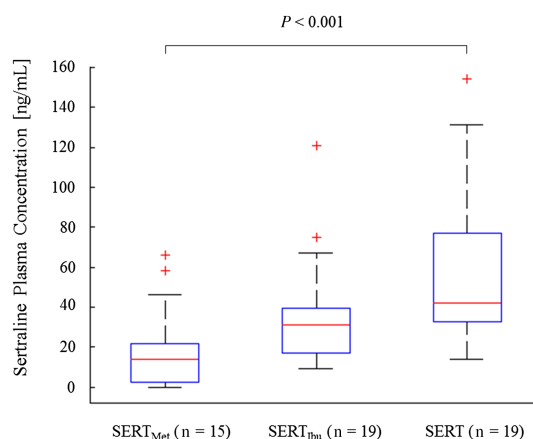
Finally, we calculated the proportion of plasma concentrations within every group that was found either inside or outside the so-called dose-related and therapeutic reference ranges, respectively.<sup>13</sup> The dose-related reference range (DRR) constitutes a theoretically expected drug concentration range for a given daily dose in drug-adherent patients without interacting co-medication or abnormalities concerning drug absorption, metabolism or clearance.<sup>13</sup> More precisely, the DRR is defined as the expected mean - standard deviation to mean + standard deviation range of the trough concentration of a drug under steady-state conditions for a given daily dose. DRRs are obtained by multiplying the daily dose by the dose-related concentration (DRC) factors for the lower limit (DRC low) and upper limit (DRC high) of the range, respectively. The DRC factors themselves can be calculated using the drug's apparent total clearance, half-life and the time interval between intake of the last dose and blood withdrawal. Thus, the clinician is able to evaluate a measured drug concentration from a pure pharmacokinetic perspective. In contrast, the therapeutic reference range (TRR) represents a concentration range for which a drug is expected to unfold its therapeutic effect and to exhibit acceptable tolerability. Consequently, drug concentrations below the TRR are unlikely to cause a drug response, whereas concentrations above the TRR are unlikely to further enhance drug response but likely to cause side effects.  $\chi^2$  tests were conducted to compare the proportions of patients whose plasma levels of sertraline were below, within or above the respective reference ranges (DRR and TRR) between groups. For all statistical tests, a two-tailed significance level of 0.05 was applied. The analysis of the clinical data was performed in accordance with the local regulatory authority of RWTH Aachen University Hospital (registration number EK: 110/20).

## 3 | RESULTS

The demographic data of the study groups are displayed in Table 1. No significant differences were found between the groups regarding daily dosage of sertraline, age, weight, gender distribution, and caffeine or nicotine consumption (all  $P$  values  $> 0.05$ ). The median daily dose of metamizole was 1500 mg (interquartile range 1000-2000 mg) and the median daily dose of ibuprofen was 800 mg (interquartile range 450-1200 mg).

Differences regarding the plasma concentrations of sertraline between the groups reached statistical significance ( $P < 0.001$ , Kruskal-Wallis test; see Figure 1; for detailed statistics see Table 2). Analysis of dose-adjusted drug concentrations yielded comparable results ( $P < 0.001$ , Kruskal-Wallis test, see Figure 2 and Table 2). Post hoc tests revealed that the group differences were driven by significantly lower plasma concentrations of sertraline in the metamizole group compared to the control group ( $P < 0.001$  for both drug concentrations and dose-adjusted drug concentrations). In contrast, plasma concentrations of sertraline in the ibuprofen group did not differ from those in the control group ( $P = 0.128$  for drug concentrations,  $P = 0.565$  for dose-adjusted drug concentrations). Group differences between the metamizole and ibuprofen group only reached statistical significance for the dose-adjusted drug concentrations ( $P = 0.008$ ). On a descriptive level, when compared to the control group, patients under a co-medication with metamizole exhibited 67% lower median plasma concentrations of sertraline. In contrast, median plasma concentrations of sertraline in the ibuprofen group were only 26% lower, compared to the control group.

We did not detect significant group differences in terms of the proportion of plasma concentrations that were inside or outside the



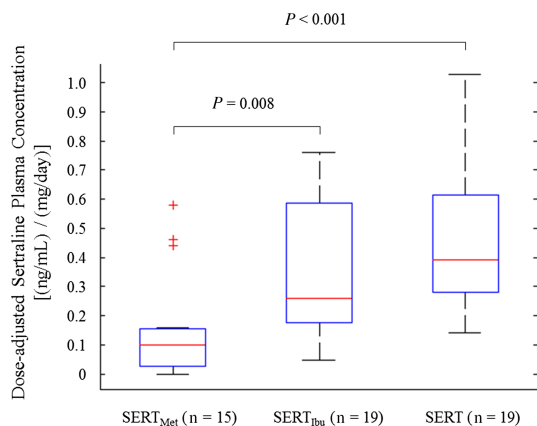
**FIGURE 1** Sertraline plasma concentrations in patients with sertraline (SERT), co-medicated with metamizole (SERT<sub>Met</sub>) or ibuprofen (SERT<sub>Ibu</sub>). The metamizole group exhibited significantly lower sertraline plasma concentrations than the control group ( $P < 0.001$ ). Group differences between SERT<sub>Ibu</sub> and SERT as well as differences between SERT<sub>Met</sub> and SERT<sub>Ibu</sub> did not reach statistical significance ( $P = 0.128$  each). Data points are considered as outliers (red crosses) if they are greater than  $q_3 + 1.5 \times (q_3 - q_1)$  or less than  $q_1 - 1.5 \times (q_3 - q_1)$ , where  $q_1$  and  $q_3$  are the 25th and 75th percentiles of the sample data, respectively

**TABLE 2** Sertraline plasma concentrations obtained from patients receiving concomitant medication with metamizole (SERT<sub>Met</sub>), ibuprofen (SERT<sub>Ibu</sub>) and a control group receiving only sertraline, but neither of the two analgesics (SERT)

Characteristic	SERT <sub>Met</sub> (n = 15)			SERT <sub>Ibu</sub> (n = 19)			SERT (n = 19)			Comparison	
	Median	q <sub>1</sub>	q <sub>3</sub>	Median	q <sub>1</sub>	q <sub>3</sub>	Median	q <sub>1</sub>	q <sub>3</sub>	$\chi^2$ (df = 2) <sup>a</sup>	P
Sertraline plasma concentration (ng/mL)	14.00	2.53	21.75	31.00	17.00	39.50	42.00	32.50	76.75	14.18	0.001
SERT <sub>Met</sub> vs SERT <sup>b</sup>											0.001
SERT <sub>Ibu</sub> vs SERT											0.128
SERT <sub>Met</sub> vs SERT <sub>Ibu</sub>											0.128
Dose-adjusted plasma concentrations (ng/mL)/(mg/day)	0.10	0.03	0.16	0.26	0.18	0.59	0.39	0.28	0.61	16.33	0.001
SERT <sub>Met</sub> vs SERT											0.001
SERT <sub>Ibu</sub> vs SERT											0.565
SERT <sub>Met</sub> vs SERT <sub>Ibu</sub>											0.008
	n	%	n	%	n	%	$\chi^2$ (df = 4)	P			
Dose-related reference range (DRR)							6.91	0.141			
Below DRR	12	80.0	10	52.6	7	36.8					
Within DRR	2	13.3	4	21.1	7	36.8					
Above DRR	1	6.7	5	26.3	5	26.3					
Therapeutic reference range (TRR)							14.89	0.005			
Below TRR	6	40.0	1	5.3	0	0.0					
Within TRR	9	60.0	18	94.7	18	94.7					
Above TRR	0	0.0	0	0.0	1	5.3					

<sup>a</sup>The Kruskal-Wallis test was calculated to assess group differences. The distribution of its test statistic was approximated by a  $\chi^2$  distribution.

<sup>b</sup>Tukey's honest significant difference test was conducted as a post hoc test on the rank-transformed data.



**FIGURE 2** Dose-adjusted sertraline plasma concentrations in patients co-medicated with metamizole (SERT<sub>Met</sub>), ibuprofen (SERT<sub>Ibu</sub>) and control patients (SERT). The SERT<sub>Met</sub> group exhibited significantly lower dose-adjusted sertraline concentrations than both the control group ( $P < 0.001$ ) and the ibuprofen group ( $P = 0.008$ ). We did not detect a significant group difference between the ibuprofen and the control group ( $P = 0.565$ ). Data points are considered as outliers (red crosses) if they are greater than  $q_3 + 1.5 \times (q_3 - q_1)$  or less than  $q_1 - 1.5 \times (q_3 - q_1)$ , where  $q_1$  and  $q_3$  are the 25th and 75th percentiles of the sample data, respectively

dose-related reference range ( $P = 0.141$ ; for detailed statistics see Table 2). However, groups significantly differed regarding the proportion of patients whose sertraline concentrations were inside or outside the TRR ( $\chi^2$  (df = 4) = 14.89;  $P = 0.005$ ; see Table 2): Only 60% of the patients receiving metamizole exhibited sertraline plasma concentrations within the TRR of 10–150 ng/mL. Forty per cent of the patients in the SERT<sub>Met</sub> group exhibited drug concentrations below the lower limit of the TRR and no patient in this group showed drug concentrations above the TRR. In contrast, 95% of the patients in the control group showed drug concentrations within the TRR and 5% of patients exceeded the upper threshold of the TRR. In the ibuprofen group, 95% of the patients showed sertraline concentrations within the TRR and only 5% of the patients showed drug concentrations below the lower limit of the TRR. Subsequently, we conducted a post hoc analysis to determine whether this effect was driven by a higher proportion of patients with insufficient sertraline drug concentrations in the metamizole group. We therefore classified each plasma concentration as being either below or above the lower threshold of the TRR and conducted a further  $\chi^2$  test revealing a significant group difference ( $\chi^2$  (df = 2) = 13.33,  $P = 0.001$ ). We then assessed differences between each pair of groups using  $\chi^2$  tests. The analysis showed that patients in the SERT<sub>Met</sub> group showed a significantly higher



proportion of potentially insufficient plasma concentrations as compared to both the control group SERT ( $\chi^2$  (df = 1) = 9.23,  $P = 0.006$  [Bonferroni corrected]) and the ibuprofen group SERT<sub>ibu</sub> ( $\chi^2$  (df = 1) = 6.19,  $P = 0.039$  [Bonferroni corrected]). In contrast, we did not detect significant differences between the SERT<sub>ibu</sub> and SERT groups ( $\chi^2$  (df = 1) = 1.03,  $P = 0.933$  [Bonferroni corrected]).

## 4 | DISCUSSION

Because of the growing evidence of metamizole's inducing properties on cytochromes P450 (CYP) 2B6 and CYP3A4, we assessed its impact on plasma concentrations of sertraline, a drug that is predominantly metabolized via CYP2B6 and CYP3A4. Thereto, we analysed a TDM database of a naturalistic sample of psychiatric patients receiving sertraline alone or in combination with metamizole. Patients who received a co-medication with ibuprofen served as a further control group. A main finding of our study is that the co-medication with metamizole—but not ibuprofen—is associated with statistically significant lower sertraline plasma concentrations. Moreover, and even more important, the metamizole group contained a significantly larger proportion of patients showing sertraline plasma concentrations below the lower threshold of the therapeutic reference range of 10–150 ng/mL.

To the best of our knowledge, the first evidence of metamizole's potential to cause pharmacokinetic drug-drug interactions was found in patients showing significantly reduced serum concentrations of cyclosporin when metamizole was added.<sup>22</sup> The authors suggested that metamizole leads to an enhanced gut CYP3A4 activity rather than hepatic CYP3A4 activity. Another study indicated that the intake of metamizole for 4 days significantly increased the CYP2B6-mediated hydroxylation of bupropion.<sup>23</sup>

Liver microsomes from patients receiving metamizole showed a selectively higher expression of cytochromes CYP2B6 and CYP3A4 as well as a higher bupropion hydroxylase activity compared to healthy controls.<sup>24</sup> Moreover, treatment of human primary hepatocyte cultures with varying concentrations of metamizole revealed a time- and concentration-dependent induction of CYP2B6 and CYP3A4 on both mRNA and protein levels. Importantly, other genes involved in drug metabolism, such as CYP2C9, CYP2C19, CYP2D6, NADPH:cytochrome P450 reductase, ABCB1, constitutive androstane receptor (CAR) and pregnane X receptor (PXR), were not substantially altered. Based on reporter gene assays, the authors suggested a phenobarbital-like mechanism of induction as it did not act as a direct ligand to PXR or CAR.<sup>24</sup> Consistently, another study confirmed CYP2B6 induction by metamizole in rats.<sup>32</sup>

Both CYP2B6 and CYP3A4 catalyse the *N*-demethylation of sertraline. Moreover, CYP3A4 also mediates its deamination. Therefore, it is likely that the reduced plasma concentrations found in patients under co-medication with metamizole reflect an increased metabolism of sertraline due to an induction of both CYP isoenzymes. This effect may be clinically relevant as sertraline's main metabolite, desmethylsertraline, exhibits a very weak potency as a serotonin

reuptake inhibitor (approximately 20-fold less compared to the parent compound) and can be neglected for clinical purposes.<sup>33</sup>

On a descriptive level, patients co-medicated with ibuprofen also exhibited slightly reduced plasma concentrations of sertraline. This effect, however, did not reach statistical significance. To the best of our knowledge, ibuprofen, which is metabolized via CYP2C8 and CYP2C9, is not known for CYP-inducing properties.<sup>34</sup> Future studies may clarify this issue.

The present study suggests that clinicians should prefer other analgesic drugs over metamizole for patients medicated with sertraline. A potential alternative might be paracetamol, which is assumed to be devoid of both pharmacokinetic interactions and the risk of gastrointestinal bleeding.<sup>35,36</sup> An alternative strategy may be the use of another antidepressant which is not metabolized by CYP2B6 or CYP3A4, such as fluvoxamine or duloxetine. Whereas the prescription of fluvoxamine should be carefully considered due to its strong inhibiting properties of CYP1A2,<sup>37</sup> duloxetine represents a promising alternative due to its benefits for treating painful neuropathy and different types of chronic pain.<sup>38</sup> If, for individual reasons, no appropriate alternative exists for the combination of sertraline and metamizole, clinicians should apply TDM-guided dose-adjustment of sertraline, which should be repeated when the dose of metamizole is changed or therapy is discontinued. Otherwise, discontinuation of metamizole therapy may bear the risk of potentially dangerous elevations of sertraline plasma levels.

### 4.1 | Conclusion

We identified statistically significantly lower sertraline plasma concentrations in patients who were under a co-medication with metamizole. This finding may be explained by an induction of the cytochrome P450 isoenzymes CYP2B6 and CYP3A4, which are involved in the metabolism of sertraline. However, our findings cannot distinguish between an increased gut and/or an increased liver activity of the involved cytochromes. Clinicians should therefore consider alternative drug combinations or apply TDM-based dose adjustment of sertraline when treating patients suffering from pain and comorbid depression or anxiety.

### 4.2 | Limitations

As we retrospectively studied a naturalistic clinical sample, patient information can be considered less reliable than in prospective studies. A major limitation of the present study is the limited number of patients, with each representing only one measurement of plasma concentration. Therefore, the quantitative estimates of metamizole's impact on sertraline plasma concentrations, ie, a 67% lowering of median sertraline plasma concentrations as compared to the control group, have to be considered as very uncertain. As a further shortcoming, plasma concentrations of desmethylsertraline, the main metabolite of sertraline, were not available. Moreover, many clinical parameters,

including the onset and duration of illness, clinical rating scales, adverse effects, comorbidities, renal function parameters, the patients' alcohol consumption as well as the duration of prior exposure to sertraline and the co-medication, were not available. Therefore, further analyses of confounding effects could not be conducted. Furthermore, we could not control for individual variations in sampling time (although clinicians were asked to draw blood at trough level times) as a result of the clinical setting, which may account for the pronounced interindividual variation in plasma concentrations. In the case of multiple plasma concentrations determinations, we minimized patient bias by including only the most recent analysis per patient. To eliminate the effect of additional pharmacokinetic interactions on sertraline plasma concentration, we excluded patients receiving concomitant potent modulators of CYP activity from the analysis. Moreover, the patients from the control group were carefully selected according to best matching properties with respect to potential confounding factors such as age, gender, body weight, nicotine and caffeine consumption. A part of our results depend on the definition of the dose-related and therapeutic reference ranges (DRRs and TRRs), respectively. However, the definition of these ranges is not unitary in the literature and the respective definitions entail different advantages and disadvantages. According to its present definition, the DRR represents a rather narrow range containing only one standard deviation below and above the expected mean plasma concentration. Therefore, in the present study, all three groups had a substantial proportion of patients with their plasma concentrations situated below the DRR. As a consequence, the  $\chi^2$  test did not achieve statistical significance. However, when defining the DRR as a wider range containing two standard deviations below and above the mean, there were still seven patients in the SERT<sub>Met</sub> group who had plasma levels below this adjusted limit as compared to only one patient in the SERT<sub>Ibu</sub> group and no patient in the SERT group, leading to a significant  $\chi^2$  test (see Supporting Information Table S1). For the therapeutic reference range, a generally accepted method to estimate its limits does not exist either. The present definition of sertraline's therapeutic reference range was adopted from the current consensus guidelines for TDM in neuropsychopharmacology presented by Hiemke et al.<sup>13</sup> The suggested lower limit of 10 ng/mL is in accordance with the results of positron emission tomography (PET) occupancy studies (eg, Meyer et al.<sup>39</sup>). The authors defined an IC<sub>50</sub> at 1.1 ng/mL and found 80% occupancy of striatal serotonin transporters at ~10 ng/mL with the minimal therapeutic dose of 50 mg sertraline. They demonstrated that across the different SSRIs, occupancy of 80% occurs at minimal therapeutic doses, suggesting that 80% blockade of striatal serotonin transporters is important for therapeutic effect.

Finally, the magnitude of the differences for the ibuprofen group did not reach statistical significance, potentially due to the small sample size. Ibuprofen effects may be mediated by mechanisms other than CYP isoenzymes<sup>40,41</sup> and the impact of ibuprofen prescription should be assessed in larger samples.

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## COMPETING INTERESTS

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## CONTRIBUTORS

A.J.G., G.S., M.P., C.H. and E.H. participated in research design. A.J.G. and M.P. performed data analysis. A.J.G., G.S., K.E., E.H., C.H. and M.P. wrote or contributed to the writing of the manuscript.

## DATA AVAILABILITY STATEMENT

Data are stored at RWTH Aachen University Hospital. The data are not publicly available due to privacy and ethical restrictions.

## PRINCIPAL INVESTIGATOR STATEMENT

Not applicable.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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