**Discovering Interactions in polypharmacy:   
Impact of Metamizole on the Metabolism of Quetiapine**

**Running Title: Induction of quetiapine metabolism by metamizole**

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**a) Running title page**

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**b)** **The number of text pages, number of tables, figures, and references, and the number of words in the Abstract, Introduction, and Discussion**

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**Abstract**

**Objective:**

Metamizole is quite an old drug with analgesic, antipyretic and spasmolytic properties. Recent findings have shown that it may induce several cytochrome P450 enzymes, especially CYP3A4 and CYP2B6. The clinical relevance of these properties is uncertain. We aimed to unravel potential pharmacokinetic interactions between metamizole and the CYP3A4 substrate quetiapine.

**Methods:**

Plasma concentrations of quetiapine from a large therapeutic drug monitoring database were analyzed. Two groups of 33 patients, either receiving quetiapine as a monotherapy (without CYP modulating co-medications) or with concomitantly applied metamizole were compared addressing a potential impact of metamizole on the metabolism of quetiapine being reflected in differences of plasma concentrations of quetiapine and dose-adjusted plasma concentrations (C/D).

**Results:**

Patients co-medicated with metamizole showed significantly lower plasma concentrations of quetiapine (median 45.2 ng/mL, Q1=15.5; Q3=90.5 vs. 92.0 ng/mL, Q1=52.3; Q3=203.8, p=0.003). Accordingly, plasma concentrations of quetiapine in the control group were more than twice of those in the metamizole group (+103% higher). The dose-adjusted plasma concentrations were 69 % lower in the co-medication group (p=0.001).

**Conclusions:**

The combination of metamizole and quetiapine leads to significantly lower drug concentrations of quetiapine, most likely via an induction of cytochrome P450 CYP3A4 by metamizole. Clinicians have to consider the risk of adverse drug reactions, especially treatment failure under quetiapine when adding metamizole.

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**Data Sharing**: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

**Key Words:** Therapeutic Drug Monitoring – Quetiapine – Metamizole – Pharmacokinetics – Cytochrome – Interaction

**Conflicts of Interest:** Dr. Haen received speaker’s or consultancy fees from the following pharmaceutical companies: Servier, Novartis, and Janssen-Cilag. He is managing director of AGATE. He is editor of an internet-based drug-drug interaction program (www.psiac.de). He reports no conﬂict of interest with this publication. Dr. Hiemke has received speaker’s fees from Otsuka. He is editor of an internet-based drug-drug interaction program (www.psiac.de). He reports no conﬂict of interest with this publication. Dr. Paulzen has received speaker’s fees from Janssen, ROVI, Neuraxpharm, Lundbeck and Otsuka. He has served as a consultant for Novartis, Otsuka and ROVI. He is editor of an internet-based drug-drug interaction program (www.psiac.de). He reports no conﬂict of interest with this publication. Dr. Schoretsanitis has served as a consult-ant for HLS Therapeutics and Thermo Fisher and has received speaker's fees from HLS Therapeutics. All other authors report no conflicts of interests.

**What is known:**

* Pharmacokinetic interactions are of high clinical relevance even in complex clinical situations.
* Little is known about pharmacokinetic interactions between metamizole and quetiapine.
* Metamizole is suspicious but not finally proven to be a potent inducer of distinct cytochrome P450 enzymes.

**What this study adds**:

* Metamizole leads to significantly lower plasma concentrations of quetiapine during a combined treatment.
* Dose adjusted plasma concentrations (C/D) of quetiapine decrease significantly under a combined treatment.
* Findings underscore evidence for a relevant pharmacokinetic interaction most likely via CYP 3A4 due to CYP inducing properties of metamizole that clinicians should be aware of.

**Limitations**

Our sample comprised a large naturalistic population and relies on retrospective data.

Our database consists only of quetiapine but not of N-desalkylquetiapine concentrations. Therefore, conclusions about the metabolic ratio (N-desalkylquetiapine / quetiapine) cannot be drawn.

**Authorship contributions**

Participated in research design: FW, MP, AG, CH, GS, EH.

Performed analytic tools: EH

Performed data analysis: FW, AG.

Wrote the manuscript: FW

Edited and corrected the manuscript: MP, AG, CH, GS, IN

**Introduction**

Polypharmacy and related adverse consequences are common in both, elderly patients as well as patients with severe mental illnesses. Accordingly, the combination of psychotropic drugs such as atypical antipsychotics and analgesics is especially common in elderly patients given that pain conditions often occur in old aged patients. These patients are often prone to delirium-like conditions affording antipsychotic treatment and the combination of polypharmacy, frailty and general medical conditions in elderly patients is the mainspring of treatment requiring conditions.

Besides the general increase in prescription rates of atypical antipsychotics, the off-label use, e.g. treatment indications without Food and Drug Administration (FDA) approval, increased significantly over the past years [1, 2]. One of the most frequently prescribed atypical antipsychotics is quetiapine [3], a dibenzothiazepine derivative, available in two different galenic formulations: as an immediate-release (IR) and an extended-release (XR) formulation [4].

Quetiapine is indicated in different psychiatric conditions such as bipolar disorder, schizophrenia and as augmentation strategy in the treatment of major depression, but has also a broad off-label prescription spectrum, although there are explicit warnings addressing the off-label use [3]. Quetiapine is also used under off-label conditions to treat generalized anxiety disorder, sleep disturbances, depressive disorders, Alzheimer's disease, delirium, borderline personality disorders, psychosis in Parkinson's disease, Tourette's syndrome and restless legs syndrome [5].

In a lot of different clinical conditions of these disorders, a treatment with analgesics is part of the treatment regimen. For example, patients with bipolar disorder have been found to have a significantly higher pain perception than people without bipolar disorder [6]. Moreover, treatment with analgesics is elementary for both, prevention and treatment of delirium in patients in intensive care units [7].

Metamizole (dipyrone) is one of the most frequently prescribed analgesics in Germany [3]. For more than a decade, there has been a continuous increase in prescription rates, although it has never been approved or is banned in many other European countries due to fatal agranulocytosis and severe allergic reactions [8]. Metamizole is a pro-drug, which is spontaneously converted after oral administration to the structurally related pyrazolone compounds 4-N-methylaminoantipyrine (4-MAA) and 4-aminoantipyrine (4-AA) that inhibit cyclooxygenase (COX)-1 and COX-2 [9, 10].

Metamizole is approved exclusively for the treatment of severe pain. This includes acute severe pain after an injury or surgery, pain from colic, and tumor pain [11]. Severe pain of other causes may only be treated with metamizole if other analgesic measures are not suitable [12]. Metamizole is considered a safe analgesic in acute therapy and, along with paracetamol, has the lowest additional mortality [12] [13]. It can be assumed that even in polypharmacy in elderly patients, the simultaneous use of quetiapine and metamizole is very common [14, 15]. Hence, prescribing physicians have to be aware of potentially occurring pharmacodynamic and pharmacokinetic interactions.

Data suggest that metamizole induces cytochrome P450 isoenzyme CYP2B6 as well as CYP3A4 [16, 17] and CYP1A2 [18]. *In vitro* analyses of liver microsomes from patients treated with metamizole, showed a selectively higher expression of cytochrome P450 CYP2B6 and CYP3A4 compared to drug-naive patients [16]. Accordingly, it can be expected that a co-medication with metamizole may lead to an enhanced clearance of drugs that are substrates of the isoenzymes CYP2B6 and CYP3A4. A rapid inducing effect was shown for CPY2B6 and the combination of the CYP2B6 substrate bupropion and metamizole [19]. Quetiapine is primarily metabolized via CYP3A4 to an inactive sulfoxide metabolite and to the major active metabolite, N-desalkylquetiapine [20]. Aim of the present study was to investigate the effects of metamizole on plasma concentrations of quetiapine in patients receiving the combination. We hypothesized that concomitantly applied metamizole may lead to reduced drug concentrations of quetiapine compared to patients, receiving quetiapine as a monotherapy. We therefore performed a retrospective analysis of quetiapine drug concentrations obtained from a large therapeutic drug monitoring (TDM) database. To our knowledge, this is the first study to examine the pharmacokinetic effects of metamizole on quetiapine blood concentrations.

**Methods**

KONBEST, a web-based laboratory information management system for therapeutic drug monitoring (TDM) served as the data source [21]. A large data set with quetiapine plasma concentrations obtained between 2006 and 2015 from more than 3,600 patients was analyzed. The data collection was part of clinical routine in different institutions of AGATE (Arbeitsgemeinschaft Arzneimitteltherapie bei psychischen Erkrankungen) and the University Hospital of RWTH Aachen and obtains plasma concentrations and respective dose information, as well as clinical information such as demographic parameters, data from clinical rating scales, and reports of adverse drug reactions. The retrospective analysis of clinical data was performed in accordance with the local regulatory authority of the Medical Faculty of RWTH Aachen University. In this naturalistic database, patients were under medication with quetiapine for various indications. Patients on concomitant medications with possible inhibitory or inducing properties for CYP3A4 and CYP2D6 were excluded according to the recommendations of the US Food and Drug Administration [22].

For patients with more than one determination of quetiapine plasma concentration, we selected only the most recent measure. Thus, TDM data from 2,439 in- and out-patients with a wide range of mental disorders were eligible for analysis. Based on this sample, we considered two groups: a group of quetiapine-treated patients who concomitantly received a medication with metamizole (QUETMet, n=33) and a control group that received only quetiapine but no metamizole (QUET, n=33). We selected only patients who received metamizole regularly, whereas patients who received metamizole as an on-demand medication were excluded from analysis. Information on the duration of metamizole treatment was not available. Out the remaining 2,406 patients that did not receive metamizole, we matched the 33 best-fitting patients as a control group (QUET). Patients were matched for age, sex, weight, nicotine and caffeine use, and for the daily quetiapine dosage.

**Quantification of quetiapine**

Blood samples were collected just before drug administration as trough level under steady-state conditions (>5 elimination half-lives at the same drug dose). All quetiapine concentrations were determined in the same laboratory by high-performance liquid chromatography with ultraviolet detection (HPLC/UV); unfortunately, no concentrations were available for the metabolite, N-desalkylquetiapine. The method was validated according to DIN 32645 (German Industrial Standard 32.645, described in the GTFCh (Society for Toxicology and Forensic Chemistry) guidelines, in consideration of ISO 5725 (International Organization for Standardization) [23], FDA (US Food and Drug Administration) guidance (US Food and Drug Administration, 2018) [24], and ICH (International Conference on Harmonization) requirements. The laboratory regularly performs internal quality control and participates in external quality assessment programs by INSTAND (Düsseldorf, Germany, www.instandev.de).

Inaccuracy, inter- and intraday imprecision were assessed for quetiapine of 600, 300 and 50 ng/mL, respectively.

- Inaccuracy: bias values were 1,61%, 1,61% and 1,45%

- Interday imprecision: coefficients of variation (CV) were 5,2%, 8,3% and 4,1%

- Intraday imprecision. CVs were 0,2%, 0,3% and 0,4%

The limit of detection (LOD) was 4,4 ng/mL and the limit of quantification (LOQ) was 8,8 ng/mL ng/mL, respectively.

**Statistical analysis**

Statistical analysis was based on the comparison of pharmacokinetic data from the KONBEST database and was performed using MATLAB 2015a (The MathWorks, Inc., Natick, USA) and SPSS 25 (IBM, Armonk, USA). Quetiapine concentrations were compared between the two groups, QUET (n=33) and QUETMet (n=33), as described above. The dose-adjusted drug concentrations (ratio of drug concentration C and applied daily dose D, C/D, in [(ng/mL)/(mg/day]] were also calculated [25].

Histograms provided evidence of a non-normal distribution of the analyzed drug concentrations, which was also confirmed by a Kolmogorov-Smirnov test. Therefore, the Mann Whitney-*U*-test with a two-sided significance level of 0.05 was chosen as a nonparametric test to compare the two groups.

Finally, we calculated the proportion of patients in each group whose plasma concentrations were either within or outside the therapeutic reference range (TRR). The therapeutic reference range (TRR) represents a concentration range for which a drug is expected to exert its therapeutic effect and to have acceptable tolerability. Consequently, drug concentrations below the TRR are unlikely to cause a drug effect, whereas concentrations above the TRR are unlikely to further enhance the drug effect but are more likely to cause adverse drug effects [26]. The clinical data was evaluated in accordance with the local regulatory authority of the University Hospital RWTH.

**Results**

No significant differences were found between the groups with regard to the daily dose of quetiapine, age, weight, sex distribution, and coffee or nicotine use (all P values > 0.05). The sociodemographic and clinical characteristics of the sample are shown in Table 1.

Table 1: Sociodemographic and clinical characteristics of the study sample consisting of patients receiving quetiapine with or without concomitant medication with metamizole.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| characteristic | quetiapine + metamizole (n=33) | | | quetiapine  (n=33) | | | comparison | |
|  | Median | Q1 | Q3 | Median | Q1 | Q3 | Wa | p |
| age [years] | 61 | 53 | 75 | 61 | 52 | 74 | 1096 | 0.908 |
| quetiapine dosage [mg/day] | 400 | 188 | 600 | 400 | 188 | 600 | 1095 | 0.892 |
| metamizole dosage [mg/day] | 1500 | 1250 | 2000 | 0 | 0 | 0 |  |  |
| Body weight [kg] | 83 | 72 | 91 | 79 | 67 | 92 | 1176 | 0.368 |
| BMI [kg/m2] | 28 | 25 | 33 | 27 | 26 | 31 | 1179 | 0.345 |
|  | n |  | % | n |  | % | χ2 (df = 1) | p |
| Sex |  |  |  |  |  |  | 0 | 1 |
| Female | 22 |  | 66.7 | 22 |  | 66.7 |  |  |
| Male | 11 |  | 33.3 | 11 |  | 33.3 |  |  |
| nicotine consumption |  |  |  |  |  |  | 1.63 | 0.202 |
| Smokers | 8 |  | 24,2 | 4 |  | 12.1 |  |  |
| non-smokers | 25 |  | 75.8 | 29 |  | 87.9 |  |  |
| caffeine consumption |  |  |  |  |  |  | 1.67 | 0.196 |
| Consumers | 24 |  | 72.7 | 19 |  | 57.6 |  |  |
| non-consumers | 9 |  | 27.3 | 14 |  | 42.4 |  |  |

The median daily dose for quetiapine was 400 mg/day (interquartile range 188- 600 mg) in both groups, the median daily dose for metamizole in the co-medication group was 1500 mg per day (interquartile range 1250-2000 mg). Because some of the variables were not normally distributed, we chose the Mann Whitney-*U*-test to compare the two groups pairwise. The differences in terms of plasma concentrations of quetiapine (ng/mL) between the two groups reached statistical significance (p=0.003, M W-*U*-test); see Figure 1 and for detailed statistics see Table 2.

Analysis of dose-adjusted drug concentrations, C/D [(ng/mL)/(mg/d)] yielded comparable results (p<0.001, M W-*U*-test, see Figure 2 and Table 2).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| characteristic | quetiapine +  metamizole (n=33) | | | quetiapine (n=33) | | | comparison | |
|  | Median | Q1 | Q3 | Median | Q1 | Q3 | Wa | p |
| quetiapine plasma concentration [ng/mL] | 45.2 | 15.5 | 90.5 | 92.0 | 52.3 | 203.8 | 876 | 0.003 |
| C/D [(ng/mL)/(mg/day)] | 0.10 | 0.07 | 0.18 | 0.32 | 0.17 | 0.50 | 796 | 0.001 |
| aDue to non-normality of these variables, Mann Witney-U-test was consistently chosen to assess group differences. W represents the smaller ranksum of the two groups, respectively. | | | | | | | | |

Table 2: Quetiapine plasma concentrations obtained from patients receiving quetiapine with or without concomitant medication with metamizole, respectively.

On a descriptive level, patients co-medicated with metamizole had 51% lower median plasma concentrations of quetiapine compared with the control group.

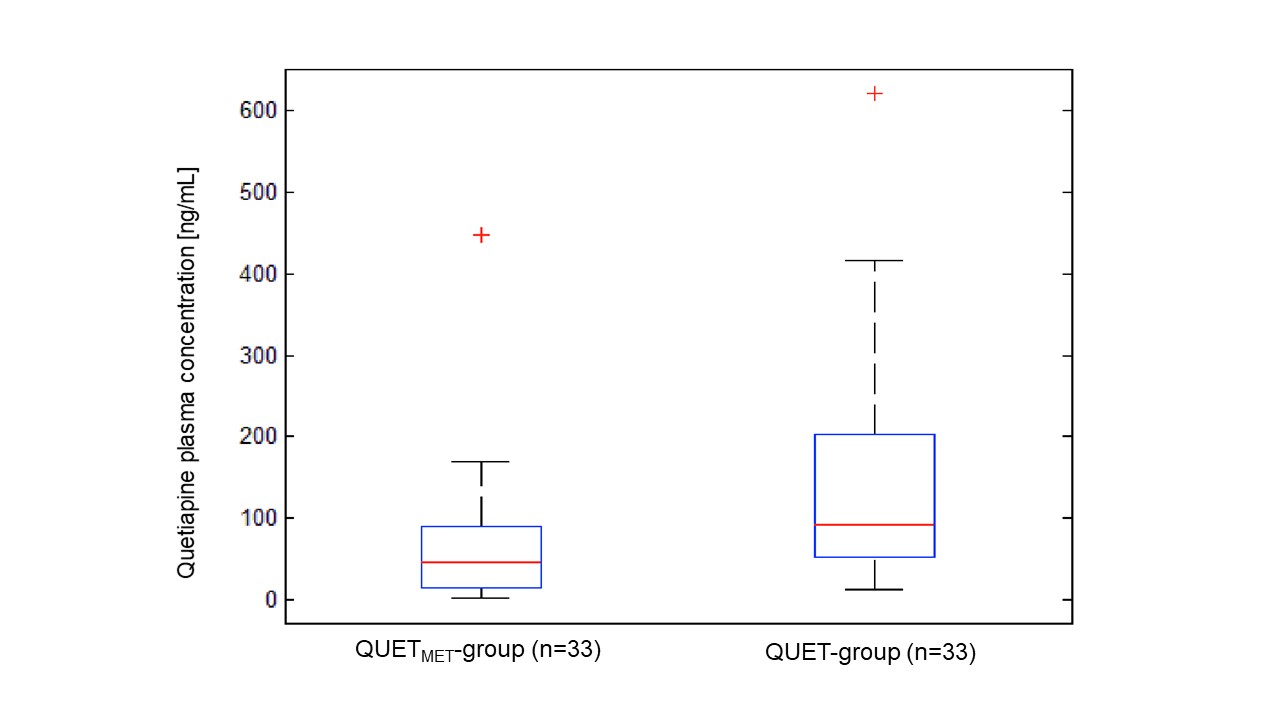


Figure 1: Median plasma concentrations of quetiapine between the two groups. Note the significantly lower drug concentrations in the co-medicated group (p=0.003).

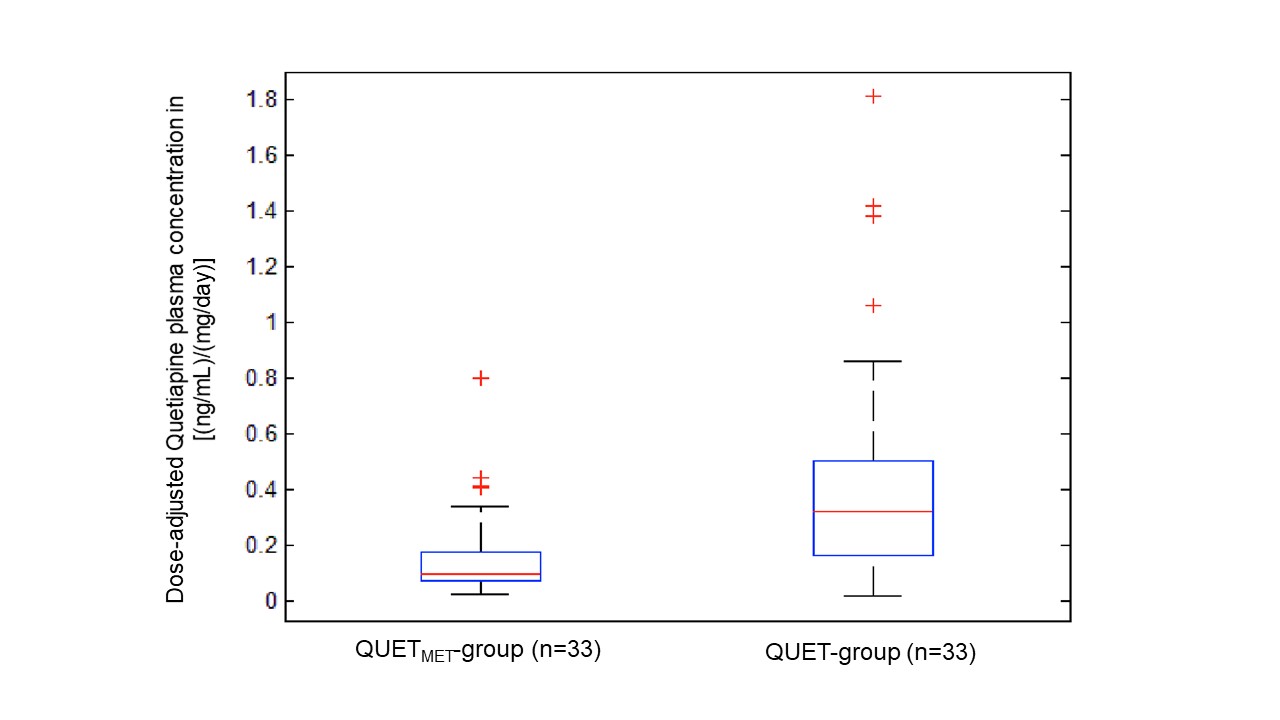


Figure 2: Comparison of the dose-adjusted plasma concentration of quetiapine (C/D) between the two groups. Note the significantly lower C/D values in the co-medicated group (p=0.001).

To further elucidate the effect of the co-administration of metamizole on the quetiapine concentrations with regard to the recommended therapeutic reference range, we compared the percentage of patients with plasma concentrations within the therapeutic reference range= TRR (100-500 ng/mL) as proposed by the AGNP consensus guidelines between the two groups [25].

Only 7 of 33 patients in the QUETMet group (21.2%) showed quetiapine plasma concentrations within the TRR, while 26 patients (78.8%) had drug concentrations below the lower limit of the TRR (100 ng/mL). None of the patients in the QUETMet showed drug concentrations above the TRR (500 ng/mL). In contrast, 14 of 33 patients in the control group (42.4%) showed drug concentrations within the TRR. 18 patients had drug concentrations below the lower limit of the TRR (54.5%) and one patient (3.0%) exceeded the upper limit of the TRR.

**Discussion**

Due to the well documented evidence of metamizole’s inducing properties on CYP isoenzymes 2B6 and 3A4, we assessed under real-life conditions its impact on plasma concentrations of quetiapine, a drug that is predominantly metabolized via CYP3A4. We therefore analyzed a TDM database of a naturalistic sample of psychiatric patients receiving quetiapine without any CYP inducing or inhibiting co-medications or in combination with metamizole.

Attention has to be paid when combining the two drugs from a pharmacodynamic as well as from a pharmacokinetic point of view. First, from a pharmacodynamic perspective, both drugs are known for their potential to cause agranulocytosis, second, from a pharmacokinetic perspective, metamizole may have an impact on the CYP3A4 mediated metabolism of quetiapine.

The probably first evidence for metamizole’s potential to cause pharmacokinetic drug-drug interactions was reported in patients showing significantly reduced serum concentrations of cyclosporin when metamizole was added [27]. 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 four days significantly increased the CYP2B6-mediated hydroxylation of bupropion [28].

To ensure efficacy and safety of treatment strategies, knowledge of potentially occurring pharmacokinetic interactions is elementary. The wide-spread use of quetiapine in a broad spectrum of different indications [3] and the increasing frequency of metamizole prescriptions over the years [3] [5] enhance the risk of pharmacokinetic interactions between the two compounds; thus, prescribers should be aware of adverse drug reactions or even a lack of efficacy.

While our study did not address the pharmacodynamic perspective, a main finding is that the co-medication with metamizole was associated with statistically significant lower quetiapine plasma concentrations. Moreover, and even more important, the metamizole group consisted of a significantly larger proportion of patients with quetiapine plasma concentrations below the lower threshold of the therapeutic reference range of 100-500 ng/mL that could lead to quetiapine treatment failure.

While the potential of metamizole to cause pharmacokinetic interactions via CYP2B6 and CYP3A4 has previously been described *in vitro* [16], knowledge from real-life data is missing. Only Gaebler et al. demonstrated that metamizole significantly decreased the plasma concentration of sertraline when taken concomitantly [17], most likely due to inducing properties on CYP2B6 and to a lesser extent on CYP2C19. Similarly, a case report series reported a decrease in tacrolimus plasma concentrations after initiation of a metamizole therapy. Tacrolimus, like quetiapine, is also a substrate of CYP3A4 [29]. In an older study, it was shown that metamizole decreased the plasma concentration of ciclosporin, especially in the first hours after taking metamizole [27].

Knowledge about both, pharmacodynamic and pharmacokinetic interactions of concomitantly prescribed metamizole becomes increasingly important due to the expanding use of metamizole in clinical practice [30].

In fact, a study on prescription rates of analgesics in German-speaking countries, metamizole was found to be very frequently used for acute and severe pain, but it was also by far the most frequently prescribed analgesic for the treatment of chronic pain [31]. Hoffmann et al. were able to demonstrate that metamizole is also very frequently used as long-term treatment in the elderly [32]. Although the prescripton of metamizole was considerably restricted in Germany in the mid-1980s due to the risk of agranulocytosis and high rates of adverse drug reactions after intravenous administration [3] [33], the drug becomes more and more prominent in recent times.

Due to polypharmacy in clinical routine, pharmacokinetic interactions, and reduced or even increased hepatic or renal clearance, optimal dosing is necessary, especially in the elderly, and the orientation on plasma concentrations and the therapeutic reference range rather than the orientation on the daily dosage, is a more precise way to maximize therapeutic efficacy [34].

Concomitant administration of a CYP3A4 inducer, as in our study, could shift the metabolite-to-parent-ratio (MPR), the ratio of N-desalkylquetiapine to quetiapine as a proxy for an increased metabolic capacity. In this context, Bakken et al. found that patients, concomitantly treated with a strong CYP3A4 inducer, showed significantly lower dose-adjusted drug concentrations (C/D values) of quetiapine. The effect on N-desalkylquetiapine was significantly smaller [35]. N-desalkylquetiapine is formed mainly by via CYP3A4 and to a lesser extent by CYP2D6 [36] [37]. Accordingly, a relatively higher level of N-desalkylquetiapine could have clinical implications for effects of quetiapine, when CYP3A4 inducers are concomitantly prescribed [38]. Unfortunately, we only measured plasma concentrations of quetiapine, but not of the metabolite N-desalkylquetiapine. N-desalkylquetiapine may account for the antidepressant activity of quetiapine [39] [40], although it may be hypothesized that it may be mainly responsible for quetiapine's side effects such as weight gain due to its strong antihistaminergic properties on H1-receptors. In addition, N-desalkylquetiapine is also suspected to be responsible for antipsychotic-induced hyperglycemia [41] via muscarinergic M3-antagonism, and for triggering other anticholinergic side effects such as dry mouth, mydriasis, increased intraocular pressure, urinary retention, and hyperthermia [39].

Anticholinergic drugs are also suspected to be involved in the pathogenesis of delirium [42]. In a case report, Almeida et al. reported a 95-year-old female who developed delirium while receiving quetiapine and carbamazepine, a potent CYP3A4 inducer. The authors hypothesized that – by increasing the metabolism of quetiapine – the anticholinergic potential of N-desalkylquetiapine may have contributed to the development of the delirium [43].

Due to the high pharmacokinetic variability of quetiapine and its main metabolite N-desalkylquetiapine, we recommend to clinicians prescribing analgesics in quetiapine-treated patients to reconsider the concomitant administration of metamizole. To prevent unwanted pharmacokinetic interactions, analgesics other than metamizole may be a better choice in quetiapine-treated patients. A good possible alternative could be the analgesic paracetamol, which is not subject to CYP P450 metabolism [17].

In complex cases, specifically in polypharmacy-treated patients, therapeutic drug monitoring offers a valuable tool for dose-adjusting addressing the individual pharmacokinetic characteristics or even the effects of pharmacokinetic drug-drug interactions. Measuring plasma concentrations can be helpful in situations when patients do not respond to standard doses of a drug and therapeutic effects are lacking or even when adverse drug reactions are suspected under supposedly low doses [25].

**Limitations**

There are several methodological limitations in using TDM data to describe individual pharmacokinetic variability and to identify pharmacokinetic determinants. These include lack of control for compliance, incomplete patient information on concomitantly prescribed medications and information on relevant comorbidities (e.g., renal or hepatic insufficiency), and possible ingestion of foods or dietary supplements that could affect the absorption or metabolism of quetiapine (grapefruit juice [44] or St. John's wort [45]). Similarly, information on a possible CYP3A4 polymorphism of patients is lacking in the literature [46] [47], and the influence of hormonal factors on CYP3A4 expression was also not considered. In addition, large individual temporal variations in blood sampling can be assumed (although clinicians were asked to draw blood at times of trough levels). This may have contributed to pronounced interindividual variations in plasma concentrations and metabolic ratios. Furthermore, we only measured plasma concentrations of quetiapine, but not of the metabolite N-desalkylquetiapine. However, these methodological limitations are often outweighed by the large number of observations possible in this type of naturalistic study.

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