Estimating the effects of co-medications on plasma olanzapine concentrations by using a mixed model

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A B S T R A C T

The purpose of this study was to estimate the effect sizes of drug interactions on plasma olanzapine concentrations while adjusting for potentially confounding factors such as smoking. The estimation was performed by using a mixed model, data from a series of previously published studies of lamotrigine, oxcarbazepine, topiramate, and mirtazapine, and unpublished data from patients under clinical therapeutic drug monitoring (TDM). The total sample included 163 adult patients (age ≥ 18 years) who provided both steady-state plasma olanzapine concentrations and smoking information. They provided a total of 360 olanzapine concentrations (1 to 11 measures per patient).

Smoking and concomitant carbamazepine or lamotrigine use were found to have significant effects on median plasma olanzapine concentrations. The effects of lamotrigine on plasma olanzapine concentrations were modified by smoking. After adjusting for olanzapine dose and carbamazepine intake, plasma olanzapine concentrations were 10% lower in non-smokers who were taking lamotrigine than in non-smokers who were not taking lamotrigine; olanzapine concentrations were 35% higher in smokers who were taking lamotrigine than in smokers who were not taking lamotrigine; olanzapine concentrations were 41% lower in smokers who were not taking lamotrigine than in non-smokers who were not taking lamotrigine; olanzapine concentrations were 11% lower in smokers who were taking lamotrigine than in non-smokers who were taking lamotrigine; olanzapine concentrations were 35% higher in smokers who were taking lamotrigine than in non-smokers who were not taking lamotrigine; and olanzapine concentrations were 10% lower in non-smokers who were taking lamotrigine than in non-smokers who were not taking lamotrigine.

1. Introduction

1.1. Olanzapine metabolism

Olanzapine is metabolized by a number of metabolic enzymes. The cytochrome P450 1A2 (CYP1A2) isozyme accounts for approximately 50–60% of olanzapine metabolism (de Leon et al., 2005; Spina and de Leon, 2007). The uridine 5′-diphosphate glucuronosyltransferase 1A4 (UGT1A4) is probably the second most important enzyme. Other minor metabolic pathways may include the flavin-containing monooxygenase (FMO) system and CYP2D6 (de Leon et al., 2005). CYP1A2 inducers such as smoking and carbamazepine increase olanzapine metabolism. These agents may also induce UGT1A4, contributing to their effect on
olanzapine metabolism. Likewise, inhibitors of CYP1A2 such as fluvoxamine may be clinically relevant inhibitors of olanzapine metabolism (de Leon et al., 2005; Spina and de Leon, 2007).

1.2. The use of mixed statistical models to study drug–drug interactions

In recent years, there has been a growing interest in the application of statistical mixed regression models in medical and pharmacological research (Brown and Prescott, 2001; Diaz et al., 2007, 2008; Fitzmaurice et al., 2004). These models are flexible tools that allow describing the overall features of a population of patients, as well as the features of individual patients. In particular, mixed models consider each patient as an individual entity, and not just as an interchangeable element in a sample of patients. This approach may open up new possibilities in the continuing quest for personalized medical treatments (Diaz et al., 2007). Mixed models are also the right statistical approach for analyzing data consisting of repeated measures of a biological or clinical variable in the same subject, as opposed to better known classical regression methods which were developed to deal with only one observation per patient.

By using data from a large U.S. clinical trial of clozapine, Diaz et al. (2007) developed a random intercept linear model (a special type of mixed model), which relates the log of plasma clozapine concentrations to clozapine doses while adjusting for the potential confounding effects of relevant demographic and clinical variables such as gender and smoking.

The purpose of this study was to estimate the effect size of DDI on steady-state plasma olanzapine concentrations, controlling for potentially confounding factors known to influence olanzapine metabolism such as smoking. The estimation was performed by using the same approach as that in a clozapine DDI study (Diaz et al., 2008), using data from a series of previously published studies of lamotrigine (Spina et al., 2006), oxcarbazepine (Muscatello et al., 2005), topiramate (Migliardi et al., 2007) and mirtazapine (Zoccali et al., 2003), and unpublished data from patients under clinical TDM.

2. Methods

2.1. Subjects

The current analyses combined the samples from 3 studies conducted in usual care environments and unpublished data on clinical TDM (Table 1). Only adult patients (age ≥18 years) who provided both steady-state plasma olanzapine concentrations and smoking information were included. A total of 163 patients (116 and 47 patients from the unpublished and published data, respectively) fulfilled these inclusion criteria. The 163 patients provided a total of 360 steady-state plasma olanzapine concentrations, which are summarized in Table 1. The sample included 54 smokers and 109 non-smokers. The smokers and non-smokers provided a total of 110 and 250 plasma olanzapine concentrations, respectively. All 163 patients were Italian Caucasians and signed a written informed consent approved by an ethics committee.

### Table 1

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Age (years)</th>
<th>Olanzapine</th>
<th>Co-medications</th>
<th>Male gender</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(years)</td>
<td>(mg/day)</td>
<td>(ng/ml)</td>
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<tr>
<td>All</td>
<td>163</td>
<td>40.8±11.4</td>
<td>12±6 (10)</td>
<td>24±14 (23)</td>
<td>2.3±1.4 (2.2)</td>
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<tr>
<td>Fluoxetine</td>
<td>6</td>
<td>38.2±11.1</td>
<td>8±3 (10)</td>
<td>16±9 (14)</td>
<td>2.1±0.8 (1.9)</td>
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<tr>
<td>Carbamazepine</td>
<td>2</td>
<td>46.2±8.5</td>
<td>25±7 (25)</td>
<td>12±5 (12)</td>
<td>0.48±0.077 (0.48)</td>
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<tr>
<td>Citalopram</td>
<td>7</td>
<td>43±14.5</td>
<td>11±7 (7.5)</td>
<td>20±9 (25)</td>
<td>2.7±2.0 (1.65)</td>
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<tr>
<td>Lamotrigine</td>
<td>28</td>
<td>43±10.4</td>
<td>13±6 (10)</td>
<td>28±14 (29.25)</td>
<td>2.4±0.97 (2.23)</td>
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<tr>
<td>Sertirazine</td>
<td>3</td>
<td>40±13.1</td>
<td>18±8 (20)</td>
<td>29±7 (27)</td>
<td>1.7±0.59 (1.9)</td>
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<tr>
<td>Valproic acid</td>
<td>19</td>
<td>41±10</td>
<td>13±6 (10)</td>
<td>22±14 (20)</td>
<td>2.0±1.0 (2)</td>
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<tr>
<td>Lorazepam</td>
<td>11</td>
<td>44±5.2</td>
<td>13±8 (10)</td>
<td>26±18 (21)</td>
<td>2.4±1.5 (2.1)</td>
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<tr>
<td>Mirtazapine</td>
<td>10</td>
<td>41±7.4</td>
<td>14±5 (12.5)</td>
<td>33±9 (32.25)</td>
<td>2.4±0.7 (2.5)</td>
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<tr>
<td>Oxcarbazepine</td>
<td>15</td>
<td>46.1±13.4</td>
<td>10±4 (10)</td>
<td>27±6 (28)</td>
<td>3.0±1.1 (2.9)</td>
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<tr>
<td>Paroxetine</td>
<td>3</td>
<td>49±4.0</td>
<td>23±7 (25)</td>
<td>69±31 (60)</td>
<td>3.6±2.9 (2.4)</td>
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<tr>
<td>Topiramate</td>
<td>16</td>
<td>39.4±9.2</td>
<td>13±5 (10)</td>
<td>29±10 (28)</td>
<td>2.4±0.63 (2.5)</td>
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<tr>
<td>Olanzapine monotherapy and no smoking</td>
<td>67</td>
<td>41±12</td>
<td>12.6±3 (10)</td>
<td>28±15 (27)</td>
<td>2.6±0.97 (2.6)</td>
</tr>
</tbody>
</table>

SD: Standard deviation; C/D: Olanzapine plasma concentration to dose ratio.

For olanzapine dose, plasma olanzapine concentrations, olanzapine C/D and co-medication doses, the table shows the means (±SDs) of the average of the repeated observations of the patients.

Some of the patients also provided plasma olanzapine concentrations when they were taking the following co-medications: clozapine (N=1), doxepin (N=2), aripiprazole (N=4), Bromazepam (N=4), Chlorpromazine (N=1), Haloperidol (N=2), Diazepam (N=2), Biperidine (N=1), Clonazepam (N=1), Lorazepam (N=5), Estacloploram (N=5), Trizolam (N=3), Haloperidol (N=2), Triazolone (N=3), Levopromazine (N=1), Flurazepam (N=1), Lithium (N=4), Chlorodesmethyldiazepam (N=2), Alprazolam (N=1), Risperidone (N=1), Venlafaxine (N=1), Zopolpidem (N=3).

Patients’ age at first plasma olanzapine concentration measurement.

All patients who took mirtazapine received 30 mg/day; thus, the standard deviation of mirtazapine dose was 0 mg/day.

The numbers on this row were computed by using 100 blood samples that were taken in the absence of any co-medication and smoking. A total of 67 patients provided these samples.
2.2. Samples

Blood samples were drawn early in the morning before olanzapine or co-medication morning dose, approximately 12 h after the last dose. All blood samples were analyzed by the same laboratory. Olanzapine concentrations were measured using high-performance liquid chromatography (D’Arrigo et al., 2006). The lowest limit of quantification was 2 ng/ml.

2.3. Statistics

Pharmacokinetic studies exploring the changes in plasma concentrations provide an idea of the magnitude of the effect, that is, the effect size of the DDI. Many drugs in usual doses, including the atypical antipsychotics, follow linear pharmacokinetics. The concentration (C) increases linearly with the dose (D). This linear relationship can be represented by a number, the C/D ratio. Inhibitors increase the C/D ratio and inducers decrease it. Thus, pharmacokinetic studies can provide information on the changes in C/D ratio due to DDIs, but studies using single doses or studies that are too short to see the maximum effects of inhibition or induction may undervalue DDIs. Furthermore, these studies are usually performed to determine the effect size of a single medication and do not provide information on situations where multiple inducers and/or inhibitors may be present. This leaves a gap in the knowledge that is necessary for prescribers to effectively manage potential DDIs in routine clinical care.

DDI studies performed in the clinical environment usually focus on finding significant differences in clearance or elimination of a drug under partially controlled conditions. Clinicians are not only interested in detecting whether a significant interaction occurs but also whether the magnitude (effect size) of that interaction amidst the noise of the clinical setting (e.g., multiple medications, smoking, gender differences) warrants modification of dosing or use of the agents together. Effect sizes can be better interpreted by clinicians by providing a dose–correction factor. For example, an inhibitor that decreases a drug’s metabolism by 50% will result in an increased plasma C by a factor of 2 and an increased C/D ratio by a factor of 2. The dose–correction factor in this situation is 0.5. So in the presence of the inhibitor, the clinician has to divide the dose of the study drug in half to obtain the plasma C that would be obtained in the absence of the inhibitor.

For each patient, the repeated measures of plasma olanzapine concentration were averaged to obtain a representative value from the patient. Medians, means and standard deviations (SDs) of the obtained values were used to describe plasma olanzapine concentrations within sub-samples of patients (Table 1). Similar procedures were used to describe olanzapine and co-medication doses, and olanzapine plasma concentration to dose (C/D) ratios (Table 1).

A random intercept linear model was built by using the total sample (Table 2) (Brown and Prescott, 2001; Diaz et al., 2008; Fitzmaurice et al., 2004). The model included the natural log of plasma olanzapine concentration as the dependent variable and had the form

\[
\log(C) = \alpha + \sum_i \beta_i X_i + \gamma \log(D) + e, 
\]

where C stands for plasma olanzapine concentration, D for olanzapine dose, \(\alpha\) is a characteristic constant of each patient that varies across patients, and the \(\beta_i\) and \(\gamma\) are population-constant regression coefficients. The \(X_i\)s are significant independent variables that were obtained through a backward selection procedure. The potential independent variables considered were gender, smoking, patient’s age at the time of first plasma olanzapine concentration measurement, and use of the following co-medications: fluoxetine, carbamazepine, cita-

### Table 2

Regression coefficients (B), effect sizes (E) and correction factors of variables significantly associated with the natural log of plasma olanzapine concentration according to a random intercept linear model (N=163)

<table>
<thead>
<tr>
<th>Variable (interaction)</th>
<th>Bp</th>
<th>95% CI</th>
<th>p-value</th>
<th>E</th>
<th>95% CI</th>
<th>Correction factor</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking carbamazepine†</td>
<td>−0.92</td>
<td>(−1.6,−0.27)</td>
<td>0.006</td>
<td>−603</td>
<td>(−79,−24)</td>
<td>2.5</td>
<td>(1.3, 4.8)</td>
</tr>
<tr>
<td>Taking lamotrigine‡</td>
<td>−0.11</td>
<td>(−0.25,0.04)</td>
<td>0.2</td>
<td>−10</td>
<td>(−22, 4)</td>
<td>1.1</td>
<td>(0.96, 1.3)</td>
</tr>
<tr>
<td>−Smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking°</td>
<td>−0.53</td>
<td>(−0.68,−0.38)</td>
<td>&lt;0.001</td>
<td>−41</td>
<td>(−49, −32)</td>
<td>1.7</td>
<td>(1.5, 2.0)</td>
</tr>
<tr>
<td>−Not taking lamotrigine</td>
<td></td>
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<tr>
<td>−Taking lamotrigine</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Log(dose)</td>
<td>0.77</td>
<td>(0.60, 0.88)</td>
<td>0.001</td>
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</tbody>
</table>

**Note:**
- **p** Confidence interval.
- † Correction factors for olanzapine doses were computed with the formula \(E/100+1\)\(^\text{−1}\).
- ‡ 95% CI for B.
- § p-value that tests the null hypothesis that B equals 0 versus the hypothesis that B is different from 0.
- † The effect size E measures the percentage change in the mean or median (or any other percentile) of plasma olanzapine concentrations due to co-administration of the corresponding drug.
- ‡ 95% CI for E.
- † Correction factors for olanzapine doses were computed with the formula \(E/100+1\)\(^\text{−1}\).
- § 95% CI for correction factor.
- b The dichotomous variable was defined as 1 if the patient was taking carbamazepine, 0 otherwise.
- c The effect size (or correction factor) is adjusted for olanzapine dose, taking lamotrigine and smoking. Table 2 reports an olanzapine dose correction factor of 2.5 when olanzapine is coadministered with carbamazepine. We do not consider this correction factor needs to be validated in larger samples since our data included only 3 plasma olanzapine concentrations measured under carbamazepine treatment which were provided by 2 smokers. However, a prior review of the literature indicated that the carbamazepine correction factor for olanzapine is between 2 and 3 (de Leon, 2004b). Thus, a factor of 2.5 may be reasonable and may indicate that carbamazepine induces both CYP1A2 and UGT1A4 activity (Linnet and Olsen, 2002).
- d The dichotomous variable was defined as 1 if the patient was taking lamotrigine, 0 otherwise.
- The effect size (or correction factor) is adjusted for olanzapine dose and taking carbamazepine.
- e The dichotomous variable was defined as 1 if the patient was a smoker, 0 otherwise.
- f The lamotrigine–smoking interaction variable was defined as the product of the dichotomous variables for taking lamotrigine and smoking.
- g After adjusting for olanzapine dose and taking carbamazepine, plasma olanzapine concentrations were 21% lower in smokers who were taking lamotrigine than in non-smokers who were not taking lamotrigine \((e^{−0.01}−0.53+0.64−1)×100=−21\%\); 95% CI, (−39, 4); correction factor, 1.3 (0.97, 1.6).
lopram, lamotrigine, sertraline, valproic acid (VPA), lorazepam, mirtazapine, oxcarbazepine, paroxetine, topiramate, duloxetine and clozapine. All 360 plasma olanzapine concentrations were used to fit the model. The model was fit by using SAS PROC MIXED (Littell et al., 2006) (Table 2). To assess the model’s goodness of fit, a plot of random-effect-adjusted observations versus expected observations was made (Diaz et al., 2008) (Fig. 1). The model fit well, p-values < 0.05 were considered significant.

The effect size of a particular co-medication on olanzapine levels was computed with the formula \( E=100\% \times \left(\frac{e^{B\beta}-1}{1}\right) \) (de Leon et al., 2007) where \( B \) is the coefficient corresponding to the presence–absence variable of the co-medication (Table 2). The limits of a 95% confidence interval (CI) for \( E \) were computed by applying the above formula to the corresponding limits of the CI for \( B \). A negative \( E \) suggests that the co-medication increases olanzapine metabolism, whereas a positive \( E \) suggests that the co-medication decreases it (Diaz et al., 2008).

For each model, olanzapine dose–correction factors were computed (de Leon, 2004a,b; Diaz et al., 2008) by using the formula \( E=100\% \times \left(\frac{e^{B\beta}-1}{1}\right) \). Effect sizes and correction factors were adjusted for confounding variables, including smoking (de Leon, 2004b).

3. Results

3.1. Sample description

Each patient provided 1 to 11 measures of plasma olanzapine concentration. Twenty percent (371/1885) of the patients provided olanzapine concentrations while taking at least one of the co-medications. Sixty–one percent (64/105) of the patients who took at least one co-medication also provided olanzapine concentrations when they were not taking any of the co-medications.

3.2. Variables influencing plasma olanzapine concentrations

Table 2 describes the obtained model of plasma olanzapine concentrations. Concomitant use of carbamazepine was found to have a significant effect on median plasma olanzapine concentrations (Table 2). After adjusting for olanzapine dose, taking lamotrigine and smoking, plasma olanzapine concentrations were 60% lower in patients taking carbamazepine than in patients not taking carbamazepine \( \left(\frac{e^{B\beta}-1}{1}\right)\times 100\% = -60\%; \) Table 2. There was a significant interaction between smoking and taking lamotrigine (Table 2). After adjusting for olanzapine dose and taking carbamazepine, plasma olanzapine concentrations were 10% lower in non-smokers who were taking lamotrigine than in non-smokers who were not taking lamotrigine \( \left(\frac{e^{0.31}-1}{1}\right)\times 100\% = -10\%; \) Table 2; in contrast, plasma olanzapine concentrations were 35% higher in smokers who were taking lamotrigine than in smokers who were not taking lamotrigine \( \left(\frac{e^{0.11+0.41}-1}{1}\right)\times 100\% = +35\% \). Thus, lamotrigine may induce mildly olanzapine metabolism in non-smokers, whereas it may inhibit olanzapine metabolism in smokers.

Moreover, after adjusting for olanzapine dose and taking carbamazepine, plasma olanzapine concentrations were 41% lower in smokers who were not taking lamotrigine than in non-smokers who were not taking lamotrigine \( \left(\frac{e^{0.53}-1}{1}\right)\times 100\% = -41\%; \) Table 2; and plasma olanzapine concentrations were 11% lower in smokers who were taking lamotrigine than in non-smokers who were taking lamotrigine \( \left(\frac{e^{0.53+0.41}-1}{1}\right)\times 100\% = -11\% \). Thus, lamotrigine co-medication may reduce the inducing effects of smoking on olanzapine metabolism. Fig. 1 suggests that the obtained model of plasma olanzapine concentrations fits well.

4. Discussion

4.1. Olanzapine inducers

After adjusting for olanzapine dose and potential confounding variables, median plasma olanzapine concentrations were significantly affected by smoking and concomitant use of carbamazepine or lamotrigine (Table 2). Smoking and carbamazepine are known inducers of olanzapine metabolism (de Leon, 2004a,b; de Leon et al., 2005; Spina and de Leon, 2007).

4.2. Olanzapine inhibitors

VPA may be an inhibitor of at least some UGTs and CYP2C9 (de Leon et al., 2005; Spina and de Leon, 2007). In this study, valproic acid did not have significant effects on olanzapine levels. This is consistent with the results of a prior study that failed to find an effect of VPA in 32 patients taking olanzapine (Gex-Fabry et al., 2003). In contrast, in only four cases (two smokers and two non-smokers), Bergemann et al.  

![Random Effect Adjusted Observation](image-url)

Fig. 1. Plot of random-effect-adjusted observations versus expected observations for the random intercept linear model of the log of plasma olanzapine concentrations described in Table 2. Each point on the plot represents one of the 360 observations provided by the 163 patients. The points approximately follow a straight line with slope 1 and intercept 0, suggesting that the model fit reasonably well.
In our sample of smokers, lamotrigine had significant inhibitory effects on olanzapine metabolism. Lamotrigine is primarily metabolized by UGT1A4 and is a mild inducer of its own metabolism when administered as monotherapy (de Leon, 2003). In vitro data suggests that lamotrigine competes with olanzapine glucuronidation via UGT1A4 but at relatively high lamotrigine concentrations (Linnet 2002). Two prior studies failed to demonstrate a DDI between olanzapine and lamotrigine (Jann et al., 2006; Sidhu et al., 2006). Of the 28 patients who took lamotrigine in this study, 14 were included in a previously published research study (Spina et al., 2006) that used traditional statistics. Spina et al. (2006) reported that lamotrigine caused a small but statistically significant (p<0.05) increase in olanzapine levels (mean baseline olanzapine level, 32 ng/ml; mean level at the 8th week of lamotrigine treatment, 36 ng/ml). The current study, which used a mixed model, adjusted for smoking, and added 14 TDM patients, confirmed a significant, relative increase in olanzapine levels associated with concomitant lamotrigine use in smokers. However, in non-smokers lamotrigine treatment was associated with a modest decrease in olanzapine levels. This may easily be seen by comparing C/D ratios. The median of the average C/D ratios was 1.6 in smokers not taking carbamazepine or lamotrigine (N=51), 2.3 in smokers taking lamotrigine but not taking carbamazepine (N=7), 2.2 in non-smokers not taking lamotrigine (N=21) and 2.5 in non-smokers not taking lamotrigine (N=103). After adjusting for olanzapine dose and taking carbamazepine, the correction factor comparing smokers taking lamotrigine versus non-smokers who were not taking lamotrigine was 1.3 ([(e−0.11−0.65+0.41)−1]×100=21%; 95% CI, (−39, 4)) (Table 2, footnote o).

The differential effect of lamotrigine on olanzapine concentrations in smokers versus non-smokers is not totally surprising. We also found a differential effect of VPA on clozapine concentrations in a similar study (Diaz et al., 2008). VPA appeared to increase clozapine metabolism in smokers and decrease it in non-smokers (Diaz et al., 2008). Both VPA and lamotrigine influence UGT metabolism. Whereas VPA is a broad inhibitor, lamotrigine may act as a modest inducer or competitive inhibitor of UGT1A4. (Linnet, 2002) Smoking is a significant inducer of CYP1A2 and may induce UGT metabolism to some extent. It is possible that smoking may influence the quantity of the drug (clozapine or olanzapine) metabolized by CYP1A2 and may change the relative importance of this pathway in comparison with the total metabolism of these drugs. UGT1A4 may be of greater importance in non-smokers than smokers taking olanzapine. In contrast, CYP1A2, which is induced by smoking, may play a greater role in smokers’ olanzapine metabolism. Thus, our finding that lamotrigine use in non-smokers resulted in a modest numerical decrease in olanzapine concentrations is consistent with a mild inducing effect of lamotrigine on UGT1A4. In smokers, however, lamotrigine appeared to have an inhibitory effect on olanzapine metabolism, elevating plasma C by 35%. It is possible that smoking may induce UGT1A4 (Nozawa et al., 2008) and the addition of lamotrigine does not result in further induction in this environment but rather results in competitive inhibition of olanzapine metabolism. Finally, the above results suggest the importance of performing an appropriate control for smoking when studying the effects of concomitant use of lamotrigine on plasma olanzapine concentrations. To demonstrate these effects, it is necessary to include appropriate lamotrigine-smoking interaction terms in regression models or to stratify by smoking.

4.3. Limitations

While dose correction factors seem to simplify the management of known DDIs, three underlying assumptions need acknowledgment. First, since correction factors are usually computed by combining data from a group of patients, an assumption when a correction factor is applied to a particular patient is that he/she is an “average” patient. It is likely that some patients will not respond as an “average patient” due to genetic differences, environmental factors, or the presence of other co-medications. In these cases, inhibitors or inducers may have greater or lesser effects than on the average patient. The second assumption is that the effect of the inhibitor or inducer on the average patient is independent of the dose of the inhibitor or inducer (e.g., smoking 1 pack of cigarettes per day results in the same metabolic induction as smoking 2 packs per day). This may be correct for the majority of potent inhibitors and inducers, but it may not be true for less potent inhibitors and inducers. The third assumption is that the effects of the log-transformed olanzapine dosing are the same across all dosage levels, including high and low dosages. The relatively good fit observed in Fig. 1 suggests that the third assumption may be reasonable.

Our results reflect the doses and time frames used in the studies (Migliardi et al., 2007; Muscatello et al., 2005; Spina et al., 2006; Zoccali et al., 2003). Both co-medication dosing and duration of administration influence the amount of olanzapine metabolism inhibition or induction caused by co-medications. An inducer drug may require several weeks of administration to reach the highest rate of synthesis of a new metabolic enzyme. The oxcarbazepine study provided oxcarbazepine doses of 900 or 1200 mg/day for 5 weeks (Muscatello et al., 2005). The possibility that higher oxcarbazepine dosages or longer oxcarbazepine treatment durations may have significant effects on olanzapine levels cannot be completely ruled out.

The literature suggests that neither paroxetine nor fluoxetine (de Leon et al., 2005; Spina and de Leon, 2007) is likely to cause clinically relevant inhibition of olanzapine metabolism. However, we need to acknowledge that our sub-samples of patients who took paroxetine (N=3) and fluoxetine (N=6) were too small, which makes it difficult to confirm the irrelevance of paroxetine and fluoxetine in olanzapine metabolism.

We cannot rule out that mirtazapine may have some mild inhibitory properties of olanzapine metabolism. In our sub-sample of males, mirtazapine appeared to increase significantly plasma olanzapine concentrations. Mirtazapine effect size, adjusted for dose, smoking, and taking oxcarbazepine and carbamazepine, was +31% [95% CI, (0.50, 0.70); correction factor, 0.76 (0.59, 0.99)]. Larger samples will be needed to explore more thoroughly this issue.

The described effect sizes reflect the average influences of co-medications on the patient population. We cannot rule out the possibility that, in some specific patients, perhaps due to genetic differences, co-medication effects may be stronger or weaker than those described in this article. We are unable to assess the population variability of the reported DDI effects of carbamazepine and lamotrigine, since a small number of patients taking these co-medications was used. We can assess the variability of the effect of smoking on olanzapine in the population of patients who did not take carbamazepine or lamotrigine. Among these patients, the non-smokers and smokers had median olanzapine C/D ratios of 2.5 and 1.6, respectively. The relationship between these C/D ratios (2.5/1.6=1.6) provides a correction factor for smoking that is very close to the (carbamazepine-adjusted) correction factor within patients not taking lamotrigine (1.7; see Table 2). Assuming that a C/D change from 2.5 to a value ≤2.0 is a clinically relevant increase in olanzapine metabolism, approximately 26% (27/103) of the non-smokers who were not taking lamotrigine had an increased metabolism (C/D≥2), while 67% (34/51) of the smokers who were not taking carbamazepine or lamotrigine had an increased metabolism. (Please remember that none of our non-smokers took carbamazepine.) This suggests that there is a great overlap between smokers and non-smokers and that our reported average correction factors represent an average and somewhat “ideal” subject.

A limitation of this study was that the original purpose of the studies was not to build a model, but the independent studies were completed in the same research center and combined and re-analyzed with a different statistical approach. The main limitation of this clinical
design is the unavoidable substantial “noise” that characterizes (usually uncontrolled) clinical environments, which may make it difficult to detect the effects of some variables. Another limitation was the lack of tests for plasma olanzapine metabolites.

5. Conclusion

The main contribution of this analysis of previously published studies combined with new data is that a statistical mixed model of plasma olanzapine concentrations was used to estimate the effect sizes of co-medications, adjust for relevant confounders, and compute effect sizes Cls. The adjustment for confounding factors, including smoking, contributes to understanding the effects of these co-medications in clinical environments where olanzapine metabolism, and therefore plasma olanzapine concentrations, is influenced simultaneously by several relevant factors.

Olanzapine has a wider therapeutic window or index than clozapine. Thus, it is possible that clozapine DDIs may have more clinical relevance than olanzapine DDIs (de Leon et al., 2005). In fact, in the clinical environment, olanzapine pharmacokinetics does not appear to be a major determinant of olanzapine dosing. Clinician beliefs and attitudes may have more obvious influences on olanzapine dosing than pharmacokinetic factors such as smoking induction or DDIs (Botts et al., 2004). Two recent reviews comment on the limited information available on olanzapine’s therapeutic window (Hiemke et al., 2004; Mauri et al., 2007).

This study verified that smoking and carbamazepine significantly induce olanzapine metabolism. Lamotrigine decreases olanzapine metabolism in smokers, and may increase it slightly in non-smokers. Future olanzapine DDI studies need to pay careful attention to smoking, and may need to control this important confounder by inclusion of interaction terms in statistical models or by stratification.

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References


