Quetiapine and Drug Interactions: Evidence From a Routine Therapeutic Drug Monitoring Service

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Objective: The objective of the present study was to investigate the effect of age, gender, and various comedications on the pharmacokinetics of quetiapine in a naturalistic setting.

Method: In total, 2111 serum samples analyzed for quetiapine during the period from June 2001 to December 2004 were included in the study. The samples had been collected for routine therapeutic drug monitoring purposes from 1179 patients treated with quetiapine. A log-linear mixed model was used to identify factors influencing the dose-corrected quetiapine serum concentration, expressed as the quetiapine concentration-to-dose (C/D) ratio. Variables included in the analysis were age, gender, and concomitant treatment with a total of 41 drugs most often used in combination with quetiapine.

Results: Age ≥ 70 years ($p = .001$) and comedication with alimemazine ($p = .002$), fluvoxamine ($p = .001$), citalopram/escitalopram ($p = .041$), or clozapine ($p < .001$) significantly increased the serum concentrations of quetiapine, while age < 18 years ($p = .044$) and comedication with lamotrigine ($p = .024$), levomepromazine ($p = .011$), oxazepam ($p < .001$), or carbamazepine ($p < .001$) significantly decreased the serum concentrations. The effects were most pronounced for fluvoxamine (+159%), clozapine (+82%), age ≥ 70 years (+67%), and carbamazepine (–86%). In 18% of the samples, the daily dose exceeded the currently recommended maximum of 800 mg/day.

Conclusion: Due to the increased serum levels of quetiapine, a lower dose than usual should be considered when quetiapine is administered to elderly patients and to patients comedicated with clozapine or fluvoxamine. As the inducing effect of carbamazepine on quetiapine metabolism is very potent, cotreatment with carbamazepine cannot be recommended. On the basis of our data and pharmacokinetic considerations, the majority of drugs commonly used in psychiatry can safely be given in combination with quetiapine.

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The second-generation antipsychotic drug quetiapine is a multiple receptor antagonist with many features in common with other second-generation antipsychotics. It has a modest affinity for the dopamine D_2 receptor, to which it shows only a transiently high occupancy,[1,2] and a higher affinity for serotonin-2A ($5\text{-}HT_{2A}$), α_1-adrenergic, histaminergic, and muscarinic receptors. It has a very low affinity for $5\text{-}HT_{2C}$, α_2, and D_1 receptors.

Multiple-dose pharmacokinetic studies have demonstrated linear pharmacokinetics in a dose range up to 750 mg/day. No gender differences in the pharmacokinetics have been found, but considerable intraindividual and interindividual variability in serum concentrations has been shown.[3,4]

Quetiapine is extensively metabolized and has 11 confirmed metabolites. Two of these, 7-hydroxy-quetiapine and 7-hydroxy-N-desalkyl-quetiapine are pharmacologically active. They are, however, found in low concentrations, and are not thought to contribute to the pharmacologic effects of quetiapine. The mean terminal half-life of quetiapine has been shown to be approximately 7 hours, but this estimation has been questioned, as difficulties in detecting low levels of the drug after the distribution phase may have influenced the data.[5]

Quetiapine is metabolized primarily by cytochrome P450 3A4 (CYP3A4), and pharmacokinetic interactions with drugs that inhibit or induce this enzyme can be anticipated. Such an effect has been shown for the CYP3A4 inhibitor ketoconazole, which causes a decrease in quetiapine clearance by 84% in healthy volunteers.[6] The CYP3A4 inducer carbamazepine has been shown to

increase quetiapine clearance 7.5-fold in a small study on patients with psychiatric disorders.[6] A case report has been published in which carbamazepine caused a 14-fold reduction and phenytoin a 24-fold reduction in the quetiapine blood level.[7]

CYP2D6 contributes to the 7-hydroxylation of quetiapine, but as the 7-hydroxy metabolite constitutes such a small fraction of the metabolic product, genetic polymorphism of CYP2D6 or drug interactions with this enzyme is not considered clinically important.[3] In a small open-label study on psychiatric patients, imipramine was shown not to affect quetiapine metabolism, whereas fluoxetine, which moderately inhibits several CYP isozymes, was associated with a small, clinically insignificant increase in quetiapine plasma levels.[8] However, contrary to what one would expect, the CYP2D6 inhibitor thioridazine increased the oral clearance of quetiapine by 68% in an open-label study on 11 patients with psychiatric disorders.[9]

One study looking at the influence of comedication on quetiapine serum concentrations in psychiatric patients found no significant differences between a group of 38 patients comedicated with drugs competing for metabolism by CYP3A4 and a group of 16 patients comedicated with drugs metabolized by CYP2D6, as compared to 8 patients on monotherapy.[4] Two patients comedicated with carbamazepine had very low serum levels of quetiapine, however, with concentration-to-dose ratios 90% to 95% lower than the ratio in a control group of 60 patients.[4] Another study found that valproate comedication was associated with a 77% increase in quetiapine plasma levels in 9 psychiatric patients,[10] and attributes this effect to valproate inhibition of CYP2D6 and CYP3A4 activity.

Therapeutic drug monitoring (TDM) has been regarded as a useful tool in the optimization of quetiapine treatment.[11] To our knowledge, no extensive studies on quetiapine pharmacokinetics have been performed on the basis of data from a large routine TDM service. Moreover, previous studies on drug interactions with quetiapine have been carried out in small groups of patients, and with only a few potentially interacting drugs investigated. Thus, there is a lack of comprehensive studies on factors influencing quetiapine serum concentrations in a naturalistic setting. The aim of the present study was to use data from a large routine TDM database to investigate possible influences of age, gender, and various comedications on the serum levels of quetiapine.

METHOD

A total of 3579 samples were sent to our laboratory for routine TDM of quetiapine in the period from June 2001 to December 2004. Samples for which the request forms lacked information about dose and/or time interval between last intake of medication and blood sampling, samples obtained less than 6 hours or more than 24 hours after last dose, samples in which the quetiapine dose had been changed less than 1 week before sampling, or samples with nontraceable levels of quetiapine were excluded. A total of 2111 samples from 1179 subjects were then included in the study.

All samples were analyzed with a liquid chromatography–mass spectrometry method. In brief, quetiapine was extracted from 1 mL serum with 4 mL solution of hexane:butanol:acetonitrile (93:5:2 ratio) after addition of internal standard solution (50 μL of 10 μmol/L flurazepam in methanol) and alkalinization with 0.2 mL of 1 mol/L sodium carbonate. After mixing and centrifugation, the organic extract was evaporated to dryness with air, and the residue was reconstituted in 50 μL methanol, transferred to vials, and injected on an Agilent MSD 1100 liquid chromatography–mass spectrometry system (Agilent, Palo Alto, Calif.). The liquid chromatography–mass spectrometry system consisted of a G1379A degasser, a G1311A quaternary pump, a G1313A autosampler, a G1316A column oven, and a G1946A mass spectrometer. Separation was performed on a Supelco LC18-DB (Supelco, Bellefonte, Pa.) (20 × 4.6 mm) column with a mobile phase consisting of a solution of methanol:ammonium acetate in a ratio of 55:45. Quetiapine was monitored after positive electrospray ionization at a mass-to-charge ratio (m/z) of 384.1 and the internal standard flurazepam at m/z 388.1. The calibrated range was 4 to 1150 ng/mL, and linearity was shown through this interval. Six quality-control samples covering the range from 57 to 575 ng/mL were analyzed with every batch of unknown samples. Between-day coefficient of variation calculated from quality-control samples was better than 4.7% at 19 ng/mL and 3.8% at 192 ng/mL. The limit of quantification of the method was 4 ng/mL. The conversion factor for quetiapine from ng/mL to nmol/L is 2.61.

The primary target variable for most analyses and calculations was the quetiapine serum concentration-to-dose ratio (C/D ratio), which is the serum concentration divided by the daily dose and thus corresponds to the serum concentration per mg quetiapine administered daily. By using this measure, the estimated values can be compared directly within as well as between subjects without taking variations in the dosage into consideration. Basic descriptive statistics analysis of the raw data was performed with Microsoft Excel 2000 (Microsoft Corp., Redmond, Wash.) and SPSS 12 for Windows (SPSS Inc., Chicago, Ill.). Data are presented as means with standard deviations or with 95% confidence intervals, or as medians with ranges, as appropriate. The mean quetiapine dose and concentration in each patient was compared with respect to gender using the Wilcoxon nonparametric test. A p value less than .05 was considered statistically significant in all analyses.

We assumed a 1-compartment exponential model for the elimination phase of quetiapine. The observed quetia-

Table 1. Number of Samples Included in the Study With Gender, Age, and Reported Doses and Measured Serum Concentrations of Quetiapine

Variable	Total	Female (N = 605)	Male (N = 574)	p Value[a]
No. of samples	2111	1023	1088	…
Age, y				
Mean	36	37	35	< .001
Median (range)	33 (14–89)	35 (14–89)	32 (16–88)	
Dose, mg/d				
Mean	638	595	679	< .001
Median (range)	600 (12.5–2600)	600 (25–2600)	600 (12.5–2200)	
Serum concentration, ng/mL				
Mean	146	132	159	< .001
Median (range)	101 (< 4–1816)	89 (< 4–1487)	112 (< 4–1816)	

[a]p Values presented for comparison between genders.
Symbol: … = not applicable.

pine concentration at t hours since intake was converted to a standardized 12-hour concentration according to the following equation:

$$C_{12} = C_t e^{-k(12-t)}$$

The rate constant k was set according to the equation $k = \log_e 2/t_{1/2}$, with a half-life of 7 hours.[3] Specifically, quetiapine C/D ratio was calculated by dividing this standardized serum concentration by the total daily dose in mg. Information on body weight was available only in a small number of cases; thus, it was not possible to normalize quetiapine C/D ratio to the dose per kg of body weight. The distribution of quetiapine C/D ratio was found to be heavily right-skewed, and to achieve near normality, the natural logarithm ($\log_e$) of the quetiapine C/D ratio was employed as the outcome variable in the statistical model.

Multiple samples were often available from the same patient; thus, a linear mixed model allowing correlation between repeated observations was employed. This model assumes that each individual patient possesses a random intercept (i.e., an individual "offset") in addition to being affected by fixed factors. The factors included in the model were gender, age (3 age groups were considered: < 18 years, 18–69 years, and ≥ 70 years), and concomitant treatment with a total of 41 drugs often used in combination with quetiapine. Model parameters, including variance components, were estimated by the method of restricted maximum likelihood using the *nlme* (nonlinear mixed effects) package of the software R, version 2.4.0.[12] Model estimation proceeded backward, starting with all potential explanatory variables (gender, age, and comedication) in the model. At each successive step, the least significant factor was removed and the model was refitted until only statistically significant factors were left.

RESULTS

The 2111 samples included in the present study were collected from 1179 patients of whom 605 were female and 574 were male. Total and gender-specific values for age and quetiapine doses and serum concentrations are given in Table 1. The mean dose and the mean serum concentrations were significantly higher in samples from males than in samples from females, but the quetiapine C/D ratio did not differ between genders.

Doses above 800 mg/day were used in 373 (18%) of the 2111 samples included (range, 850–2600 mg/day), corresponding to 214 individual patients.

Simultaneous prescription of other antipsychotics was not associated with lower quetiapine doses. In 736 samples represented by 339 patients who were given 1 or more antipsychotics concomitantly, the mean quetiapine dose was 715 mg/day. In 1353 samples representing 968 patients who were given no antipsychotic other than quetiapine, the mean dose was 596 mg/day.

Age was found to influence quetiapine C/D ratio significantly. In patients under 18 years of age, the expected quetiapine C/D ratio is 31% lower than in those aged 18 to 69 years (the reference group), whereas in patients 70 years of age or above, the expected quetiapine C/D ratio is 67% higher than in those aged 18 to 69 (Table 2).

Other drugs were used concomitantly in 74% of the cases. The mean number of concomitant medications was 1.6 (range, 0–7; median, 1). The most frequently used comedications were valproic acid (N = 237), oxazepam (N = 228), and zopiclone (N = 194). Of the 41 drugs most often used in combination with quetiapine, 9 were found to influence the quetiapine C/D ratio significantly (Table 2), whereas the other 32 (Table 3) did not. Alimemazine, clozapine, citalopram/escitalopram, and fluvoxamine were associated with increased quetiapine C/D ratios, whereas carbamazepine, lamotrigine, levomepromazine, and oxazepam were associated with decreased quetiapine C/D ratios.

According to our model, the expected C/D ratio can be calculated by the following equation:

$$\text{quetiapine C/D ratio} = e^{\beta 0 + \beta 1 + \ldots \beta i}$$

The intercept β_0 represents the reference group of both genders aged 18 to 69 years not taking any of the inter-

Table 2. Model Parameter Estimates Showing the Effects of Explanatory Factors (one by one) on the Log_e-Transformed Quetiapine Serum Concentration-to-Dose Ratio (quetiapine C/D ratio)[a]

	Log_e (quetiapine C/D ratio)				Expected Quetiapine C/D Ratio	
Variable (N)[b]	Estimate	p Value	95% CI Lower Bound	95% CI Upper Bound	(ng/mL)/(mg/d) mean (95% CI)	Percent Change
Intercept (1123)	–1.745	< .001	–1.802	–1.688	0.18 (0.17 to 0.19)	…
Age 14–17 years (29)	–0.373	.044	–0.735	–0.010	0.12 (0.08 to 0.17)	–31
Age 70–89 years (49)	0.512	.001	0.206	0.818	0.29 (0.22 to 0.40)	+67
Alimemazine (115)	0.248	.002	0.088	0.407	0.22 (0.19 to 0.26)	+28
Carbamazepine (39)	–1.987	< .001	–2.266	–1.708	0.02 (0.02 to 0.03)	–86
Citalopram/ escitalopram (181)	0.149	.041	0.007	0.292	0.20 (0.18 to 0.23)	+16
Clozapine (70)	0.598	< .001	0.371	0.825	0.32 (0.25 to 0.40)	+82
Fluvoxamine (11)	0.952	.001	0.398	1.507	0.45 (0.26 to 0.79)	+159
Lamotrigine (147)	–0.189	.024	–0.354	–0.025	0.15 (0.12 to 0.17)	–17
Levomepromazine (119)	–0.228	.011	–0.403	–0.053	0.14 (0.12 to 0.17)	–20
Oxazepam (228)	–0.234	< .001	–0.356	–0.112	0.14 (0.12 to 0.16)	–21

[a]The reference group (intercept) consists of patients of both genders aged 18 to 69 years, not taking any of the interacting drugs. To estimate the combined effect of 2 or more factors, use the equation [quetiapine C/D ratio = $e^{\beta 0+\beta 1+\ldots\beta i}$].

[b]N = number of samples included in the analyses.

Abbreviation: CI = confidence interval.

Symbol: … = not applicable.

Table 3. Drugs Found Not to Affect Quetiapine Serum Concentration-to-Dose Ratio Significantly

Anxiolytics (N)[a]	Antidepressants (N)[a]	Antipsychotics (N)[a]	Other Psychotropics (N)[a]	Other Drugs (N)[a]
Alprazolam (15)	Amitriptyline (13)	Amisulpride (21)	Lithium (174)	Biperiden (84)
Buspirone (16)	Fluoxetine (33)	Chlorpromazine (126)	Valproic acid (237)	Cetirizine (54)
Clonazepam (176)	Mianserin (33)	Chlorprothixene (90)	Zolpidem (48)	Omeprazole/ esomeprazole (63)
Diazepam (118)	Mirtazapine (63)	Flupenthixol (25)	Zopiclone (194)	
Flunitrazepam (33)	Paroxetine (48)	Haloperidol (49)		
Hydroxyzine (15)	Sertraline (90)	Olanzapine (105)		
Nitrazepam (31)	Venlafaxine (143)	Perphenazine (115)		
		Risperidone (62)		
		Ziprasidone (22)		
		Zuclopenthixol (97)		

[a]N = number of samples included in the analyses.

acting drugs, and β_1 to β_i represents the coefficients of additional fixed factors, as given in Table 2. The coefficient estimate in the reference group was –1.745, yielding a quetiapine C/D ratio of 0.18 (ng/mL)/(mg/d).

Figure 1 displays the expected quetiapine serum concentrations in patients of various age groups and with different comedications, on the basis of the current model and assuming a daily quetiapine intake of 600 mg.

DISCUSSION

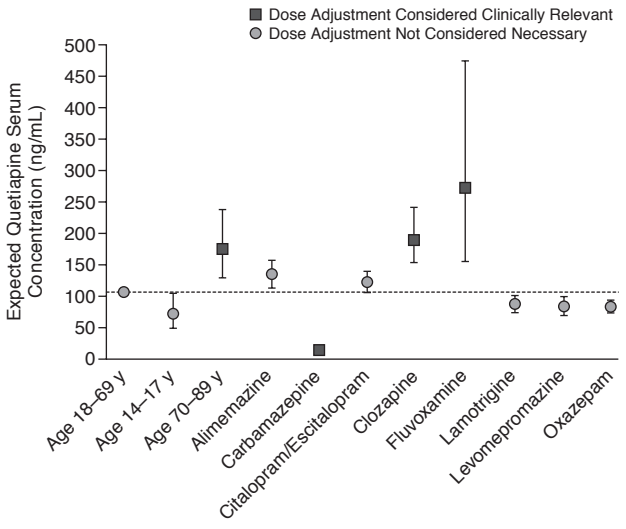
This study presents an overview of the serum concentrations of quetiapine achieved in a naturalistic setting, including the pharmacokinetic interaction potential of 41 drugs often used concomitantly.

Although we assume that the increases in quetiapine C/D ratio shown in this study are associated with an increased risk of adverse effects and the decreases are associated with a reduced clinical effect, it should be emphasized that the risk of adverse effects or diminished clinical efficacy has not been directly evaluated. Instead, we have used the quetiapine C/D ratio as a surrogate variable of these outcomes.

This study has several limitations. Most importantly, it is unknown to what degree the patients were compliant to the prescribed doses and medications. Consequently, a differentiated degree of noncompliance related to cotreatment with the other drugs cannot be ruled out, and might explain our findings. Coprescription of a drug that increases the serum levels of quetiapine and subsequently the concentration-dependent adverse effects of the drug could, at least in theory, increase noncompliance. As the factors expected to increase quetiapine C/D ratio in this study (age and fluvoxamine coadministration) in fact do exactly that, we do not consider this a severe problem. It could, however, mean that the observed increase in the C/D ratio is a conservative estimate of the changes actually taking place.

Furthermore, it is uncertain whether the subjects included in the study are representative of the whole population of quetiapine users, and we did not cross-check the information given in the request forms about dose, time of last ingestion, etc. We do, however, believe that the possibly inaccurate nature of this information is counterbalanced by the large number of observations. We therefore assume our data to mirror clinical reality. Another indica-

Figure 1. Expected Quetiapine Serum Concentration With 95% Confidence Interval for Different Age Groups in Monotherapy and With Various Comedications, With a Daily Dose of 600 mg Quetiapine[a]



[a]The calculated values are derived from the factor coefficient estimates presented in Table 2. The dotted line represents the intercept value of 108 ng/mL, calculated as the product of the estimated concentration-to-dose ratio [0.18 (ng/mL)/(mg/d)] and the dose (600 mg/d).

tion of this assumption is the fact that in the present study, the extent of the changes in the C/D ratios caused by the drugs previously known to affect the metabolism of quetiapine was in the same range as previously reported.[4,6,7]

The most pronounced pharmacokinetic interaction was found with carbamazepine, which decreased the quetiapine serum levels by as much as 86%. On the basis of experience from our TDM service, we assume neither an increase in quetiapine dose nor a decrease in carbamazepine dose will be sufficient in order to reach an adequate quetiapine serum level unless the quetiapine dose is increased by a factor of 5 or more. According to our experience, this is not done in clinical practice.

The concomitant use of alimemazine, fluvoxamine, clozapine, and citalopram/escitalopram increased the quetiapine C/D ratios. Whereas fluvoxamine is known to inhibit CYP3A4,[13] the effect on quetiapine C/D ratio for clozapine, which is not a known enzyme inhibitor, was more surprising. Also, the effect of clozapine should clearly be considered clinically relevant, inasmuch as the addition of clozapine to ongoing quetiapine treatment would be equivalent to almost doubling the quetiapine dose. It is possible that adherence to quetiapine medication is better than average in patients taking clozapine. The frequent contact with health professionals required for the monitoring of clozapine treatment may have an impact on the adherence to treatment with other drugs that these patients are prescribed. The finding should be verified in a more controlled setting. Concomitant treatment with citalopram/escitalopram also gave an unexpected increase in the quetiapine C/D ratio. These substances are not clinically significant CYP2D6 or CYP3A4 inhibitors.[14] If this result can similarly be explained by better adherence to therapy when an antidepressant is taken concomitantly, it remains unclear why it does not apply to other selective serotonin reuptake inhibitors as well.

Contrary to what one might expect, the concomitant use of levomepromazine, a known CYP2D6 inhibitor, decreased the quetiapine C/D ratio. There is no clear-cut explanation for this possible interaction, and the finding may be coincidental. Another study found that the concomitant use of levomepromazine had no apparent influence on the quetiapine C/D ratio.[4] However, as that study included only 5 patients taking levomepromazine in contrast to the 119 samples included in our study, it might have been too small to detect influences that were possible to reveal in the present study.

Lamotrigine and oxazepam, neither of which is a known CYP enzyme inducer, also caused statistically significant decreases in quetiapine C/D ratio. The effects were, however, not of a magnitude that warrants special consideration when combination therapy with quetiapine is indicated. It is unlikely that possible noncompliance caused by the sedating effects of oxazepam could explain the decrease in C/D ratio, as this effect was not seen with concomitant medication with other benzodiazepines or sedating drugs like olanzapine.

Some of the statistically significant but clinically insignificant changes (Figure 1) might also be due to chance, since more than 40 potentially explanatory variables were screened and there is thus an obvious risk of mass significance.

Age 70 years or above was associated with a significant increase in the quetiapine C/D ratio. The increase is of the same magnitude as shown in a small and unpublished study (N = 9) conducted by the manufacturer of quetiapine in which the plasma clearance was reduced by 30% to 50%.[15] The mechanism behind this effect has not been specifically studied, but it is probably to a large degree caused by age-related reduced hepatic drug clearance.[16] Special precautions may be warranted when quetiapine is prescribed in this age group, both due to the increased serum levels of quetiapine and because the elderly are often prone to pharmacodynamic side effects of quetiapine such as orthostatic hypotension.

Patients aged 14 to 17 years had a mean reduction of 31% in their quetiapine C/D ratio as compared to the reference group. A previous study on 10 adolescents aged 12 to 16 years reported that although there was a small decrease in the elimination half-life of quetiapine, the pharmacokinetic profile in adolescents was similar to the profile previously observed for adults.[17] The present study

thus confirms, in a larger population, that there is no need for dose reductions among subjects aged 14 to 17 years; in fact there is evidence to suggest that adolescents should be treated with somewhat higher quetiapine doses in order to achieve the same plasma concentrations as in adults.

We found that gender did not have any statistically significant impact on the quetiapine C/D ratio. This result is in accordance with the results found in a smaller study investigating quetiapine serum levels under routine conditions.[4]

Valproate and fluoxetine, which have previously been reported to increase quetiapine serum levels significantly,[8,10] had no statistically significant influence on quetiapine C/D ratio in the present study (estimate for valproic acid: –0.065, 95% CI = –0.204 to +0.073, p = .35; estimate for fluoxetine: –0.199, 95% CI = –0.545 to +0.147, p = .26). These drugs were used in a high number of cases (237 and 33, respectively). Moreover, the confidence intervals were relatively narrow, and the upper confidence limits, which are the most relevant in relation to the previous studies in which the quetiapine concentrations were found to increase, were close to zero in both cases. Therefore, we consider that our study was sufficiently powered to reveal significant influences on the quetiapine C/D ratio caused by these drugs if they exist.

The dosing of quetiapine in clinical practice has earlier been shown to be higher than what has been established in preclinical trials.[18] In our study the mean dose of quetiapine was 638 mg/day. The U.S. Food and Drug Administration states that the safety of doses above 800 mg/day has not been evaluated in clinical trials.[15] In the present study, however, doses above 800 mg/day were used in 18% of the patients at the time of sampling (range, 850–2600 mg/day). This percentage is remarkably high, but it cannot be excluded that clinicians use TDM more frequently when they prescribe doses above the recommended dose range.

In conclusion, due to the increased serum levels of quetiapine, a lower dose should be considered when quetiapine is administered to elderly patients and to patients comedicated with clozapine or fluvoxamine. As the enzyme-inducing effect of carbamazepine on quetiapine metabolism is very powerful, concomitant treatment with quetiapine and carbamazepine cannot be recommended. Doses above the recommended maximum dose of 800 mg/day are used in almost 20% of the patients in a naturalistic setting. Although it cannot be completely ruled out that our negative findings are due to differences in noncompliance between users of the various concomitant medications, we consider that on the basis of our data and pharmacokinetic considerations, the majority of drugs commonly used in psychiatry can safely be administered in combination with quetiapine.

Drug names: alprazolam (Xanax, Niravam, and others), biperiden (Akineton), buspirone (BuSpar and others), carbamazepine (Carbatrol, Equetro, and others), cetirizine (Zyrtec), chlorpromazine (Thorazine, Sonazine, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), diazepam (Diastat, Valium, and others), escitalopram (Lexapro and others), esomeprazole (Nexium), fluoxetine (Prozac and others), flurazepam (Dalmane and others), haloperidol (Haldol and others), hydroxyzine (Vistaril and others), imipramine (Tofranil and others), ketoconazole (Ketozole, Nizoral, and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), omeprazole (Prilosec and others), paroxetine (Paxil and others), phenytoin (Dilantin, Phentytoin, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others), valproic acid (Depakene and others), venlafaxine (Effexor and others), ziprasidone (Geodon), zopiclone (Lunesta), zolpidem (Ambien, Tovalt, and others).

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