Relationship Between Daily Dose, Plasma Concentrations, Dopamine Receptor Occupancy, and Clinical Response to Quetiapine: A Review

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Objective: To assess the relationships among quetiapine blood concentration, daily dose, dopamine receptor occupancy, and clinical outcome in order, if possible, to define a target plasma level range in which therapeutic response is enhanced and adverse events are minimized.

Data Sources: A search of the database Embase from 1974 to March 2009 and the databases MEDLINE and PubMed from 1966 to March 2009 was conducted. The drug name *quetiapine* was searched with each of the terms *plasma levels*, *plasma concentration*, *therapeutic drug monitoring*, and *dopamine occupancy*.

Study Selection: The search uncovered 42 relevant articles. All published reports of quetiapine plasma or serum concentration were considered for inclusion if reported in relation to a dose, clinical outcome, or dopamine occupancy. After application of exclusion criteria, 20 articles remained.

Data Extraction: Trials designed primarily to investigate an interaction between quetiapine and another medication were excluded, as were those designed to compare methods of blood sample analysis.

Data Synthesis: There was a weak correlation between quetiapine dose and measured plasma concentration (from trough samples). Quetiapine dose was correlated with central dopamine D_2 occupancy, although the relationship between plasma level and D_2 occupancy is less clear.

Conclusions: The dose-response relationship for (immediate-release) quetiapine is established. Data on plasma concentration-response relationships are not sufficiently robust to allow determination of a therapeutic plasma level range for quetiapine. Therapeutic drug monitoring procedures are thus probably not routinely useful in optimizing quetiapine dose. Further examination of the relationship between peak quetiapine plasma concentration and clinical response is necessary.

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Therapeutic drug monitoring (TDM) is a valuable tool for guiding treatment with drugs under particular circumstances. It is often used for drugs with a narrow therapeutic index, for drugs for which dosage is not directly correlated with clinical response, and for those patients in whom adherence to treatment is questioned. Therapeutic drug monitoring can also be utilized to guide dosing in the presence of likely drug interactions or in those whose physical illness (such as hepatic or renal disease) may affect the metabolism or excretion of the drug. Drugs known to have high interpatient variability in plasma concentration due to age, smoking status, gender, and metabolic enzyme genotype may also be candidates for TDM. In such cases, TDM can be used to avoid drug toxicity and to optimize therapeutic effect.

With the exception of clozapine and perhaps olanzapine, the routine monitoring of antipsychotic plasma concentration is rarely undertaken in practice. In order for TDM to be useful and appropriate, a relationship between blood concentration and clinical effect or toxicity must be established, and the absence of a clear dose-response relationship confirmed. Quetiapine has recently been suggested as a possible candidate for TDM[1] (pharmacokinetic details are shown in Table 1). In this review, we aimed to assess all available evidence regarding the relationships between blood quetiapine concentration, daily dose, dopamine receptor occupancy, and clinical outcome. We aimed, if possible, to establish the value of TDM for quetiapine and to define a therapeutic plasma level range in which therapeutic response is enhanced and adverse events are avoided.

DATA SOURCES

In December 2008, we searched the database Embase from 1974 to present and the databases MEDLINE and PubMed from 1966 to present for articles relevant to this review and written in English. The drug name *quetiapine* was searched with each of the terms *plasma levels*, *plasma concentration*, *therapeutic drug monitoring*, and *dopamine occupancy*. After retrieval of the relevant full texts, references were examined for appropriate citations. The search was repeated in March 2009 before the data were finally analyzed. Data from all studies were pooled to create graphs displaying the relationships between dose, plasma concentration, and dopamine occupancy. Graphs and trend lines were drawn using Microsoft Excel 2002 (Microsoft Corporation, Redmond, Washington).

STUDY SELECTION

The literature search uncovered 42 relevant articles. All published reports of plasma or serum quetiapine concentrations were considered for inclusion if reported in relation

Table 1. Quetiapine Pharmacokinetics

Recommended adult dosing	Schizophrenia: 50 mg, day 1; 100 mg, day 2; 200 mg, day 3; 300 mg, day 4. From day 4, titrate to the effective dose range 300–450 mg/d. Adjust within the range 150–750 mg/d Manic episodes associated with bipolar disorder: 100 mg, day 1; 200 mg, day 2; 300 mg, day 3; 400 mg, day 4. Adjust within the range 200–800 mg/d Twice daily dosing with or without food recommended[53]
Units of plasma concentration	ng/mL or µg/L (equivalent units)
Approximate elimination half-life	7 h (parent molecule)[53]
Approximate time to steady state	35 h (based on a half-life of 7 hours)
Plasma protein binding	83% bound to plasma proteins[53]
Approximate absolute bioavailability	70%[45]
Apparent volume of distribution	513–710 L[45]
Peak absorption	1 to 2 h[54]
Metabolism	Hepatic metabolism, primarily by CYP3A4 and also CYP2D6[54]
Active metabolites	Of the 11 metabolites identified, only 7-hydroxy-quetiapine and 7-hydroxy-*N*-desalkyl-quetiapine are active. Present in the plasma at 2%–12% of the parent, both are believed to have negligible pharmacologic effects[45]

Abbreviations: CYP2D6 = cytochrome P450 2D6, CYP3A4 = cytochrome P450 3A4.

Table 2. Excluded Studies

Reference	Reason for Exclusion
Fabre et al,[55] 1995	Peak concentration reported only
Wong et al,[56] 1996	Pharmacokinetic study reported in detail elsewhere by Jaskiw et al[21]
Wong et al,[57] 1996	Peak concentration reported only
Wong et al,[58] 1997	Peak concentration reported
Küfferle et al,[59] 1997	Plasma concentration not reported
Davis et al,[60] 1999	Description of analytic method. Plasma concentration reported elsewhere by Gefvert et al[31]
Kimko et al,[61] 2000	Simulation study using plasma concentration reported elsewhere by Small et al[17]
Gefvert et al,[30] 2001	Plasma concentration only displayed graphically
Stephenson et al,[62] 2000	Plasma concentration not reported
Sachse et al,[63] 2003	Full text not reported in English
Savasi et al,[64] 2002	Letter to editor describing drug interaction cases
Rothenhöfer et al,[65] 2005	Preliminary report for later-published study
Nemeroff et al,[54] 2002	Review article
Strakowski et al,[66] 2002	Interaction study
Potkin et al,[67] 2002	Interaction study
Li et al,[68] 2005	Interaction study
Härtter et al,[69] 2004	Interaction study
Kohnlein et al,[70] 2004	Full text not reported in English
Sachse et al,[71] 2006	Description of analytic method
Winter et al,[72] 2007	Interaction study
Schulz-Du Bois et al,[73] 2008	Interaction study
Catafau et al,[74] 2008	Plasma concentration drawn and SPECT scans completed at different times in dosing interval, and individual doses not available

Abbreviation: SPECT = single photon emission computed tomography.

to a dose, clinical outcome, or dopamine occupancy. After application of exclusion criteria, 20 articles remained. Excluded studies are shown in Table 2.

DATA EXTRACTION

Trials designed primarily to investigate an interaction between quetiapine and another medication were excluded, as were those designed to compare methods of blood sample analysis. Males and females of any age, psychiatric diagnosis, comorbidity, and bed status were included in the final selection of participants reviewed.

DATA SYNTHESIS

The reviewed articles reported blood quetiapine concentration of 2,034 participants enrolled in a range of study designs from health care systems across Europe, North America, China, and Canada between 1997 and 2009. Naturalistic therapeutic drug monitoring reports, pharmacokinetic investigations, efficacy studies, and positron emission tomography studies were all included in the group of articles to be included. Details of the design and method of each study are shown in Tables 3, 4, and 5. Together, the various studies suggest there is a weak interindividual relationship between trough plasma/serum concentration and quetiapine dose ($r^2 = 0.1518$, $P = .0142$; Figure 1). Individual studies are described here in detail.

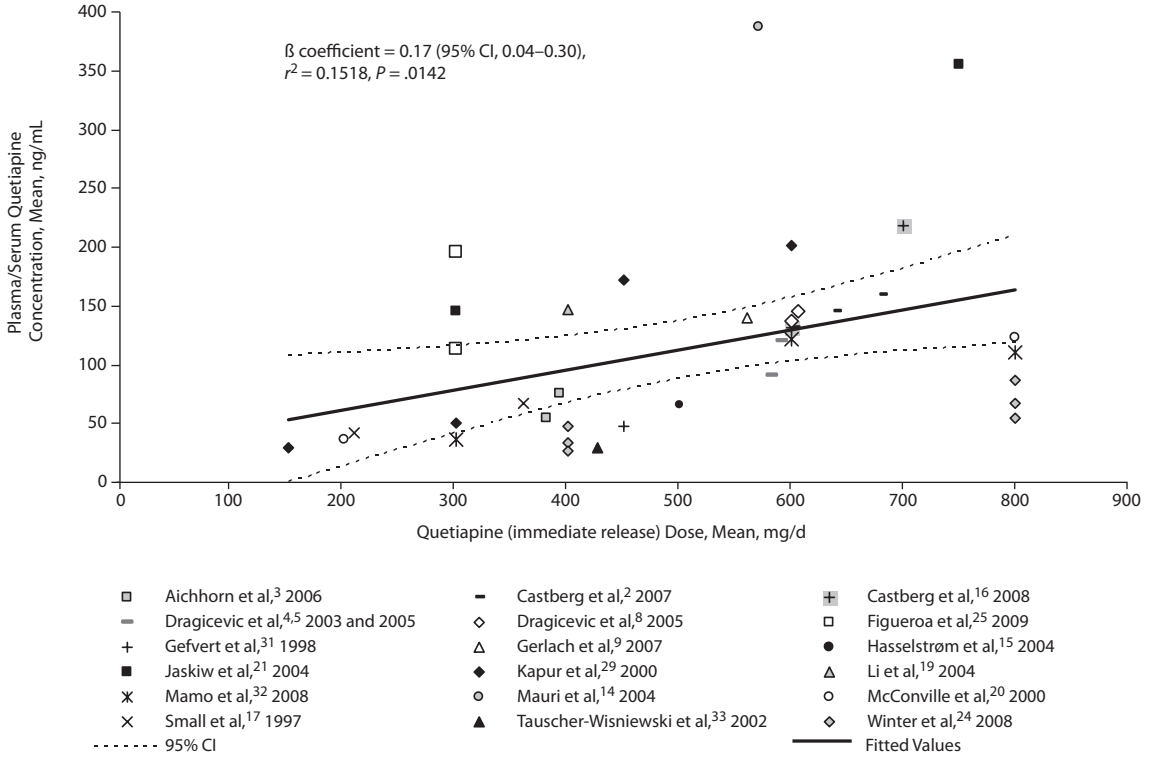
Therapeutic Drug Monitoring Studies

Ten TDM studies reported quetiapine plasma concentration of 1,578 participants, male and female, aged 13–89 years old. Details of the design and results of each study are shown in Table 3.

Castberg and coworkers[2] investigated the effect of age, gender, and comedication on the pharmacokinetics of quetiapine in a large naturalistic sample. Patients aged above 70 years and those aged below 18 years were compared with a reference group aged 18–69 years. Those aged above 70 years had increased serum quetiapine concentrations ($P = .001$), while those under 18 years had lower serum concentrations ($P = .044$) compared with the reference group. Mean dose and serum concentration were significantly higher in males than in females but there was no gender difference in the concentration/dose ratio. Several drugs were found to increase or decrease quetiapine concentration; details are shown in Table 3.

A similar TDM study conducted by Aichhorn and colleagues[3] studied the effects of age, gender, body weight, and comedication on plasma concentration of quetiapine in 94 patients whose plasma concentrations were monitored as part of their routine inpatient care. Mean daily doses were

Figure 1. Mean Quetiapine (immediate release) Dose Versus Mean Quetiapine Trough Plasma/Serum Concentration[a]



[a]In a weighted meta-regression, studies with less random variation are given greater weight than studies with more random variation. A typical meta-regression weights each study by the inverse of its variance. In general, it is logical to assume that the variance decreases as sample size increases. However, this is not a linear relationship, and variance cannot be estimated using sample size. The variance (or standard deviation) was not available for all of the studies examined here, and, for this reason, a nonweighted meta-regression has been performed.

similar for male and female participants and decreased significantly with age. Plasma concentration decreased slightly with increasing age, and female participants had higher mean plasma concentration than male participants, although the differences were not significant. Prescribed quetiapine doses appeared to decrease more with age than the corresponding plasma concentration, suggesting a reduction in metabolic capacity with age. Concentration/dose ratios were higher for female than male subjects, but the difference was statistically significant for uncorrected ratios only (35.4% higher for females, $P = .035$). Valproate was the only co-prescribed drug to have a significant effect on the concentration/dose ratio (mean 77% increase after adjustment for age and gender, $P = .016$). The overall results were not altered after exclusion of the 9 patients prescribed valproate, and the effect of age on weight-corrected concentration/dose ratio remained significant ($P = .012$), with a 9.5% average increase (95% CI, 2.0–17.5) per 10 years of age.

A German TDM study investigated serum quetiapine concentration and clinical response of 59 patients diagnosed with psychotic disorders. This study was reported in 2 separate publications by Dragicevic and coworkers.[4,5] A weak but significant correlation was found between dose and serum concentration, with female subjects having significantly lower concentrations than male subjects despite similar doses. Those patients coprescribed other medication in addition to quetiapine had higher serum quetiapine concentration than those taking quetiapine as a sole drug (122 ± 84 ng/mL vs 95 ± 92 ng/mL, $P = .023$). Patients were included for assessment of clinical response regardless of all other medication taken. Receiver operating characteristic curve analysis revealed that clinical improvement (measured using the Clinical Global Impressions [CGI] scale[6]) was significantly increased in those patients whose quetiapine concentrations were in excess of 77 ng/mL. There was a significant although weak correlation between quetiapine serum concentration and clinical improvement ($r_s = -0.26$, $P = .005$). Differences were found in the serum concentration of responders compared with nonresponders and between responders and "very good" responders, although details were not reported. There was no correlation between side effects (measured by the Udvalg for Kliniske Undersøgelser [UKU] side effect scale)[7] and quetiapine concentration.

A further TDM study[8] was reported by the same lead author in 2005. In this study, the authors investigated the effect of gender and age on quetiapine serum concentrations in 75 patients. Few details of the study design are available; therapeutic effect was monitored by the CGI scale[6] and side effects by the UKU side effects scale.[7] Male and female participants were prescribed similar doses, and, unlike in the authors' previous study, there was no significant gender difference in quetiapine concentration. Adverse effects,

Table 3. Quetiapine Therapeutic Drug Monitoring (TDM) Studies

Design	Method	Participants	Inclusion/Exclusion Criteria and Other Medication	Dose, Mean (range), mg/d	Plasma Level, Mean (range), ng/mL	Main Outcomes	Study
Naturalistic TDM study over 3 y Bed status and frequency of dosing not stated Serum analyzed 6–24 h postdose at steady state	HPLC- UV	N = 1,179 (2,111 samples) Age, mean (range), y: 36 (14–89) 574 male 605 female Diagnoses not stated	Exclusion: TDM samples lacking details of dose or sampling time Samples from patients not at steady state Other medication permitted due to naturalistic design	Total sample: 638 (12.5–2,600) Male: 679 (12.5–2,200) Female: 595 (25–2,600)	Total sample: 146 (< 4–1,816) Male: 159 (< 4–1,816) Female: 132 (< 4–1,487)	Quetiapine serum concentration increased by alimemazine ($P = .002$), fluvoxamine ($P = .001$), citalopram/escitalopram ($P = .041$), clozapine ($P < .001$) Quetiapine serum concentration decreased by lamotrigine ($P = .024$), levomepromazine ($P = .011$), oxazepam ($P < .001$), carbamazepine ($P < .001$)	Castberg et al,[2] 2007
TDM study of hospital inpatients Thrice daily dosing Trough plasma analyzed at steady state	LC-MS-MS	N = 94 Age, mean ± SD (range), y: male, 44.9 ± 20 (17–85); female, 79.6 ± 15.4 (33–107) 36 male 58 female Diagnoses: dementia, schizophrenia, affective disorders, and others	Exclusion: Abnormal renal or hepatic function Comedication permitted other than CYP3A4-inducing comedication	Male: 381 ± 53 (25–1,200)[a] Female: 392 ± 43 (25–1,800)[a]	Male: 54.8 ± 9.3 (3–491)[a] Weight corrected: 56.2 ± 10.0[b] Female: 76.2 ± 10.2 (5–446)[a] Weight corrected: 71.0 ± 9.8[b]	Concentration-dose ratio, mean ± SD, (ng/mL)/(mg/d) Male: 0.144 ± 0.016 Female: 0.195 ± 0.017 ($P = .035$) No significant difference in weight-corrected concentration-dose ratios Male: 0.148 ± 0.017 Female: 0.181 ± 0.016	Aichhorn et al,[3] 2006
TDM study Steady-state trough serum analyzed Dosing frequency not stated	HPLC- UV	N = 59 Diagnoses: schizophrenia/ schizoaffective disorder Other details not available	All other medication permitted Other details not reported	Total sample: 591 (50–1,200) Male: 603 ± 284[b] Female: 582 ± 275[b]	Total sample: 120[c] Male: 131[c] Female: 91[c]	Significant weak correlation between dose and serum concentration ($r_s = 0.34$, $P < .0005$) Higher male than female serum concentration ($P = .0005$) Clinical improvement greater when concentration > 77 ng/mL	Dragicevic et al,[4,5] 2003, 2005
TDM study Steady-state serum concentration analyzed Dosing frequency and time of sample not available	HPLC	N = 75 Age, mean ± SD, y: 36 ± 14 28 male 47 female Diagnoses: schizophrenia/ schizoaffective disorder	Inclusion: Quetiapine monotherapy Other details not reported	Male: 606 ± 284[b] Female: 600 ± 283[b]	Male: 145 ± 120[b] Female: 137 ± 119[b]	No difference in male/female doses or serum concentration Good clinical response more frequent in those with serum concentration of 50–100 ng/ mL ($P = .05$)	Dragicevic et al,[8] 2005
TDM study in adolescents 2-y inpatient study Twice daily dosing Trough serum concentration analyzed at steady state	HPLC-UV	N = 21 Age, mean ± SD (range), y: 15.9 ± 1.5 (13.3–17.9) 12 male 9 female Diagnosis: schizophrenia	Inclusion: First-episode illness Exclusion: Medical illness, drug misuse, suicide risk, pregnancy Other medication permitted	560.0 ± 150.7 (100–800)[a]	139.4 ± 172.3 (19–877)[a]	Weak correlation between dose and serum concentration ($r = 0.273$, $P = .048$) and no gender dependency Variability of concentrations (19–877 ng/mL) No threshold concentration found in relation to clinical response	Gerlach et al,[9] 2007
TDM study of hospital inpatients over 2 wk Doses titrated according to clinical judgment over 4 to 6 d Dose frequency unknown Trough plasma samples analyzed at steady state	HPLC	N = 41 Age, mean ± SD, y: 37.7 ± 12.9 36 male 5 female Diagnoses: schizophrenia, drug-induced psychosis, personality disorder	Inclusion: Exacerbation of illness, medication-free for 3 previous weeks Exclusion: Previous depot	555.13 ± 162.54 (250–1,000)[a]	Actual concentration not reported	Linear relationship between plasma concentration and dose/kg ($r = 0.31$, $P < .05$) Higher mean ± SD plasma concentrations and doses/kg found in females (reported as 83.9 ± 19.5 mg, presumably 8.39 ± 1.95 mg/ kg) than males (reported as 46.3 ± 32.2 mg, presumably 4.63 ± 3.22 mg/kg) ($P < .01$)[d] No differences between responders and nonresponders (reported as 58.8 ± 12.2 and 57.4 ± 11.4 mg, presumably 5.88 ± 1.22 and 5.74 ± 1.14 mg/kg, respectively)[d]	Mauri et al,[11] 2007

(continued)

Table 3 (continued). Quetiapine Therapeutic Drug Monitoring (TDM) Studies

Design	Method	Participants	Inclusion/Exclusion Criteria and Other Medication	Dose, Mean (range), mg/d	Plasma Level, Mean (range), ng/mL	Main Outcomes	Study
TDM study of hospital patients 2-wk washout followed by quetiapine for 2 wk Plasma concentration analyzed at steady state Time of sample and frequency of dosing not reported	HPLC	N = 37 Age, mean ± SD, y: 37.7 ± 13.2 31 male 6 female Diagnoses: schizophrenia, personality disorder	Inclusion and exclusion details not reported	570.7 ± 154.4[b]	387.6 ± 239.5 (45.3–898.0)[a]	No correlations between plasma concentration and age, clinical improvement, or side effects	Mauri et al,[14] 2004
Naturalistic TDM study carried out over 2 y Bed status not available Steady-state, trough serum concentration analyzed Twice daily dosing	HPLC	N = 62 Age, mean (range), y: male, 34 (20–62); female, 33.5 (15–64) 26 male 36 female Diagnosis not stated	Other medication was permitted Grouped according to comedication: Monotherapy, n = 8 Carbamazepine, n = 2 CYP3A4-interacting drugs, n = 38 CYP2D6-interacting drug, n = 10 Drugs with no known interactions, n = 4	500 (37.5–1,200)[e]	All: 66.4 (0–383.2) (173 [0–999] nmol/L)[e,f] Male: 63.7 (0–314.2) (166 [0–819] nmol/L)[e,f] Female: 71.0 (0–383.2) (185 [0–999] nmol/L)[e,f]	No correlation between dose and concentration ($r^2 = 0.0417$), and median plasma concentrations of quetiapine in males and females were not significantly different. Concentration-dose ratio, median (range), (nmol/L)/(mg/24 h) All: 0.41 (0.01–2.38) Female: 0.47 (0.01–2.38) Male: 0.35 (0.02–1.89) Concentration-dose ratio of those taking interacting drugs: Monotherapy, 0.28 (0.15–1.25) CYP3A4 drugs, 0.48 (0.01–2.38) CYP2D6 drugs, 0.23 (0.02–0.68)	Hasselstrøm and Linnet,[15] 2004
Six-year TDM study of 27 psychiatric drugs in a high-security unit Serum trough routine TDM samples compared to a hospital TDM database as a control frequency of dosing not stated	LC-MS	Study group, n = 10 Control group, n = 50 Details not available	Other medication permitted Samples excluded if known interacting drugs were also taken	Study group: 700 (150–1,600)[e] Control group: 600 (150–2,000)[e]	Study group: 218.3 (16.5–551.6) (569 [43–1,438] nmol/mL)[e,f] Control group: 132 (8.8–348) (344 [23–907] nmol/mL)[e,f]	Concentration-dose ratio, median (range), (nmol/L)/(mg/d): Study group: 0.86 (0.29–1.45) Control group: 0.54 (0.04–1.86)	Castberg and Spigset,[16] 2008

[a]Mean ± SD (range).
[b]Mean ± SD.
[c]Range unavailable.
[d]Figures described as "doses/kg" were reported as "mg" doses, which we have considered to be too high to be the true daily dose when applied to an average 70-kg man. We have therefore interpreted the doses as "mg/kg" and reduced the reported figures by a factor of 10.
[e]Median (range).
[f]Values converted to ng/mL from nmol/L (nmol/L divided by a conversion factor of 2.607).
Abbreviations: CYP2D6 = cytochrome P450 2D6, CYP3A4 = cytochrome P450 3A4, HPLC = high performance liquid chromatography, HPLC-UV = high performance liquid chromatography with ultraviolet detection, LC-MS = liquid chromatography with mass spectroscopy, LC-MS-MS = liquid chromatography with tandem mass spectroscopy.

including sedation and extrapyramidal symptoms (EPS), were recorded for 35% of the study population, with no gender differences. In female participants, EPS were significantly associated with higher quetiapine concentrations (median concentration of 210 ng/mL, $P < .05$). Seventy-nine percent of the group made a moderate or greater clinical response. Older age was significantly associated with weaker clinical response ($P = .012$) and increased occurrence of adverse effects ($P = .029$). A serum quetiapine concentration above 50 ng/mL to 100 ng/mL was associated with an increased frequency of good clinical response ($P = .05$).

Gerlach and colleagues[9] reported a TDM study of quetiapine in adolescents. Hospitalized inpatients were monitored over 2 years according to the Arbeitsgemeinschaft fur Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) interdisciplinary TDM expert group guidelines.[1] Details are shown in Table 3. There was a large variability in serum concentration measured and a weak correlation between dose and serum concentration ($r = 0.273$, $P = .048$). Gender and coprescription of additional psychoactive drugs had no effect on the concentration of quetiapine in this population. This study also investigated the relationship between serum concentration and clinical response. *Response* was defined as a 40% or more reduction in Brief Psychiatric Rating Scale (BPRS)[10] score between the first and last observation. Fifty-seven percent of all patients were classed as responders. On the basis of the plasma concentration range of 70–170 ng/mL suggested by the AGNP-TDM expert group, 40.8% of the patients were below this range, 24.5% were above this range, and 34.7% of the patients fell within the guideline range. No threshold concentration was related to response and there was not a correlation evident between serum concentration and any adverse effect assessed, including sedation, weight gain, cardiovascular effects, and EPS.

Plasma concentration of quetiapine was also monitored by Mauri and coauthors[11] in a study of patients diagnosed with schizophrenia, drug-induced psychosis, or borderline personality disorder. Clinical assessments were carried out at the end of the 2-week period by BPRS, Positive and Negative Syndrome Scale (PANSS),[12] and the Hamilton Depression Rating Scale (HDRS).[13] Other details of the study are shown in Table 3. There was a linear relationship between plasma concentration and dose/kg. Higher concentration and doses/kg were measured for female than male subjects, although there were no differences between responders and nonresponders as classed by a 30% or more reduction in BPRS or PANSS scores. The relationship between clinical response and plasma concentration was assessed by analysis of the percentage improvement in PANSS scores. Those patients with a diagnosis of schizophrenia and personality disorders were assessed separately to those with drug-induced psychosis. A significant correlation was found between the concentration/(dose/kg) and the percentage improvement in PANSS for all diagnoses (Spearman coefficient, 0.75 [$P < .01$] for schizophrenia/borderline personality disorder and 0.68 [$P < .05$] for drug-induced psychosis).

A similar study by Mauri and colleagues[14] reported the plasma quetiapine concentrations of 37 inpatients diagnosed with schizophrenia and personality disorder. At day 15, plasma concentrations and clinical improvement were assessed using the BPRS, PANSS, and HDRS. There were no correlations between plasma concentrations and age, clinical improvement, or side effects.

A Danish study carried out by Hasselstrøm and colleagues[15] failed to find a correlation between dose and serum concentration. There was no gender difference in the median serum concentration of quetiapine in male and female participants and no relationship between age and concentration/dose ratio. Many patients were taking medication in addition to quetiapine. Those taking carbamazepine had small concentration/dose ratios compared with those taking quetiapine alone. A 70% higher median concentration/dose was measured for patients also taking drugs known to interact with CYP3A4 enzymes than the monotherapy group, although this was not a significant difference. Details are shown in Table 3.

Over a 6-year period, Castberg and colleagues[16] monitored the plasma concentration of all psychotropic drugs taken by patients hospitalized in a psychiatric high-security unit. Ten patients were included in the quetiapine sample and were compared with a hospital (non–high security) TDM database of quetiapine concentrations from 50 patients. Although several samples were collected from each patient, just 1 sample from each patient was analyzed to enable comparison with the control group. Results are shown in Table 3. Although there was no significant difference in dose, median concentrations were higher in the study group than in the control group: 569 (range, 43–1,438) nmol/L (218.3 [range, 16.5–551.6] ng/mL) versus 344 (range, 23–907) nmol/L (132.0 [range, 8.8–348.0] ng/mL); $P = .028$. Authors could offer no explanation for the higher concentrations found in the study group than the control despite similarly prescribed doses ($P = .028$). Increased adherence to the prescribed dose by the high security patients may have been responsible for their higher concentrations.

Efficacy Studies and Pharmacokinetic Data

Six studies included in this analysis provide pharmacokinetic data on 410 participants aged 10 to 85 years old.

A 6-week, randomized controlled trial was conducted by Small and colleagues[17] to compare the efficacy and tolerability of low-dose and high-dose quetiapine with placebo (details shown in Table 4).[17] Psychiatric assessment was carried out using the BPRS, CGI, the modified Scale for the Assessment of Negative Symptoms (SANS),[18] and the negative scale of the PANSS. At 6 weeks, a significantly greater improvement was measured in the high-dose group than in the placebo-treated group on all scales other than the negative scale of the PANSS. There were no significant relationships between plasma concentration and change in baseline scores as measured at end point on any of the various efficacy scales.

Li and colleagues[19] reported a pharmacokinetic study of quetiapine in 21 Chinese hospital inpatients. There were no

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Table 4. Quetiapine Efficacy and Pharmacokinetic Studies

Design	Analytic Method	Participants[a]	Inclusion/Exclusion Criteria and Other Medication	Dose, mg/d	Plasma Level, Mean, ng/mL	Main Outcomes	Study
6-wk efficacy study of inpatients comparing 2 dose ranges of quetiapine and placebo over 42 d Steady-state trough plasma drawn Frequency of dosing not reported	GC-MS	N = 286 Age, y (low dose): 37 ± 9 (19–63) Age, y (high dose): 36 ± 9 (20–61) 203 male 83 female Diagnosis: schizophrenia	Exclusion: Other Axis I *DSM-III-R* diagnoses, suicidal behavior, mental retardation, convulsive disorders, head trauma, brain disorder, risk of pregnancy, and use of depot antipsychotic within 4 wk of trial Limited use of drugs for minor complaints permitted	Low dose: n = 94; 209 (50–267)[b] High dose: n = 96; 360 (50–566)[b] Placebo: n = 96	41.5 (range, 17.3–90.4) 67.8 (range, 21.5–169.0)	No significant relationship found between the efficacy variables tested and plasma concentrations	Small et al,[17] 1997
8-d pharmacokinetic study in Chinese inpatients Patients titrated from 25 mg BD to 200 mg BD by day 4 On day 8, trough plasma concentration drawn before morning dose and then at frequent intervals until 24 h after the last dose	HPLC-MS	N = 21 Age, y: 18–45 11 male 10 female Diagnoses: schizophrenia, schizophreniform disorder	Exclusion: Any drugs in 2 wk prior to trial, other medical illness Alprazolam, inosine, and propranolol permitted during the trial	400	147 ± 142[c]	No statistical differences between males and females in any pharmacokinetic parameter	Li et al,[19] 2004
23-d pharmacokinetic study of inpatient adolescents 2 age groups (12 to14 y and 15 to17 y) Doses in both groups were titrated from 25 mg BD on day 1 to 400 mg BD by day 21 Steady-state plasma samples drawn at trough on days 11 and 23 and then subsequently throughout the day	HPLC	N = 10 Age, mean (range), y: 13.6 (12.3–15.9) 5 male 5 female Diagnoses: schizoaffective disorder, bipolar disorder	Exclusion: Depot in previous dosing interval, clozapine or interacting drugs within previous 6 wk, substance/alcohol misuse, medical condition, pregnancy Antipsychotics discontinued on day 1 of trial Chloral hydrate, benztropine, lithium, and paracetamol permitted during the trial	Day 11: 100 mg BD Day 23: 400 mg BD	35.8 122.4	No pharmacokinetic differences between the 2 dose groups No significant differences between the 2 age groups or between the 2 doses in terms of the drug's pharmacokinetic profile	McConville et al,[20] 2000
27-d pharmacokinetic study of elderly inpatients, doses titrated throughout study period TDS dosing, trough plasma concentration drawn at steady state Patients required to fast for 8 h before and 3 h after the morning dose on these days	HPLC-UV	N = 9 Age, mean (range), y: 70.9 (63–85) 8 male 1 female Diagnoses: schizophrenia, schizoaffective disorder, bipolar disorder	Exclusion: MMSE score < 12, drug misuse, hepatitis B, any significant medical conditions, interacting drugs within 6 wk of trial entry Antipsychotics discontinued on day 1, quetiapine started on day 3 Choral hydrate and paracetamol permitted	Day 15: 100 mg TDS Day 23: 250 mg TDS	146 (SE = 30.1) 355 (SE = 45.3)	Correlation coefficient between dose and trough level: $r = 0.72$ ($P < .0001$)	Jaskiw et al,[21] 2004
13-d pharmacokinetic study Children, adolescents, and adults were titrated to 400 mg BD over 13 d according to tolerance Once reached steady state at 200 mg BD, blood samples drawn post morning dose until 12 hours' postdose Repeated at steady state at 400 mg BD and continued until 24 h	RP-HPLC	N = 56 Children, n = 13 Age, y: 11.0 ± 0.9 (10–12) 6 female, 7 male Adolescents, n = 14 Age, y: 13.9 ± 1.3 (13–17) 7 female, 7 male Adult n = 29 Age, y: 37.2 ± 7.4 (18–45) 9 female, 20 male Diagnoses: schizophrenia, schizoaffective disorder, bipolar affective disorder	Inclusion: Children, 32–84 kg; adults, 45–114 kg Exclusion: Other *DSM-IV* Axis I disorder, clinical disorder, contraindication to quetiapine, use of depot in last dosing interval, daily use of benzodiazepines, treatment with clozapine in last 28 days, positive urine drug test Psychotropic drugs withdrawn 3 d before quetiapine initiation Conventional mood stabilizers, lorazepam, paracetamol, methylphenidate, atomoxetine, and dexamphetamine permitted	200 mg BD Child (n = 9) Adolescent (n = 12) Adult (n = 25) 400 mg BD Child (n = 9) Adolescent (n = 12) Adult (n = 25)	 33.1 (113.6)[d] 27.2 (99.9)[d] 47.8 (72.1)[d] 66.7 (74.4)[e] 54.9 (66.9)[e] 86.8 (65.9)[e]	Mean plasma concentration of quetiapine and all metabolites increased with dose for all age groups	Winter et al,[24] 2008

(continued)

Table 4 (continued). Quetiapine Efficacy and Pharmacokinetic Studies

Design	Analytic Method	Participants[a]	Inclusion/Exclusion Criteria and Other Medication	Dose, mg/d	Plasma Level, Mean, ng/mL	Main Outcomes	Study
10-d crossover study to compare IR and XR quetiapine in hospitalized patients. Trough plasma concentration drawn before morning dose and for next 24 h Group 1: 300 mg XR OD on days 1 and 2, then 150 mg IR BD on days 3–6. Days 7–10: 300 mg XR OD Group 2: 300 mg XR OD on days 1 and 2, then 300 mg XR OD on days 3–6. Days 7–10: 150 mg IR BD	LC-MS-MS	N = 28 Age, mean (range), y: 43.7 (18–62) n = 18 male n = 10 female Diagnoses: schizophrenia, schizoaffective disorder, and bipolar disorder	Inclusion: Remission from acute exacerbation of illness, tolerant to antipsychotic for at least a year and not be at risk of pregnancy Exclusion: Other Axis I disorders, substance misuse, depot within 1 dosing interval of the study, intolerance to quetiapine, significant medical disease, pregnancy, treatment with clozapine in prior 2 months, history of nonresponse to clozapine Other medication prohibited throughout study, other than lithium	Group 1 150 mg IR BD 300 mg XR OD Group 2 300 mg XR OD 150 mg IR BD	113.2 (SEM = 24.2) 92.5 (SEM = 17.3) 126.3 (SEM = 23.3) 196.1 (SEM = 31.0)	No difference in pharmacokinetic data between each group; therefore, treatment sequence had no effect Mean C_{max} was 13% lower for XR than IR formulation	Figueroa et al,[25] 2009

[a]All are mean values ± SD (range) when available from the original study, unless otherwise stated.
[b]Value shown is mean (range).
[c]Converted to ng/ml from µg/L; value shown is mean ± SD.
[d]Geometric mean (CV%) for 12 hours' postdose.
[e]Geometric mean (CV%) for 24 hours' postdose.
Abbreviations: BD = twice daily, C_{max} = maximum plasma concentration, CV = coefficient of variation, GC-MS = gas chromatography-mass spectroscopy, HPLC = high performance liquid chromatography, HPLC-MS = high performance liquid chromatography with mass spectroscopy, HPLC-UV = high performance liquid chromatography with ultraviolet detection, IR = immediate release, LC-MS-MS = liquid chromatography with tandem mass spectroscopy, MMSE = Mini-Mental State Examination, OD = once daily, RP-HPLC = reverse phase high performance liquid chromatography, SE = standard error, SEM = standard error of the mean, TDS = 3 times a day, XR = extended release.

differences between male and female patients for any of the pharmacokinetic parameters studied including plasma concentration (trough concentration not reported individually for gender).

A study of the pharmacokinetic profile of quetiapine in 2 age groups of adolescents with psychotic disorders was conducted by McConville and colleagues.[20] During the study, both age groups were dosed with 100 mg twice daily and 400 mg twice daily to reach steady state. Details of the study are shown in Table 4. There were no significant differences between the 2 age groups or between the 2 doses in terms of the drugs pharmacokinetic profile. Psychotic and negative symptoms improved as illustrated by a significant decrease from baseline in mean BPRS and Clinical Global Impressions-Severity of Illness (CGI-S) scale scores at day 20 ($P \leq .001$) and a significant decrease in mean SANS summary score by day 20 ($P = .0006$).

In a 27-day rising-dose study, Jaskiw and colleagues[21] investigated the pharmacokinetics of quetiapine in elderly patients. Pharmacokinetic analysis revealed no difference between 2 doses (100 mg 3 times a day and 250 mg 3 times a day) for time to peak concentration, dose-normalized minimum plasma concentration, and the area under plasma concentration–time curve. Apparent oral clearance values were approximately 30%–50% lower than those found in studies of younger adults taking similar quetiapine doses.[22,23] Trough plasma concentration of quetiapine increased linearly with dose; the correlation coefficient for the relationship was 0.72 ($P < .0001$).

A further pharmacokinetic study of quetiapine in different age groups was carried out by Winter and colleagues.[24] Details are shown in Table 4. Mean plasma concentration of quetiapine and all metabolites increased with dose for all age groups. Children had a 71% greater mean peak quetiapine plasma concentration than adolescents on day 7 and 54% greater by day 13. Comparison of pediatric and adult data revealed no consistent age-related differences in pharmacokinetic data (peak concentration, area under the dose-normalized curve, half-life) of quetiapine or 7-hydroxy quetiapine. However, a greater exposure to quetiapine sulfoxide and norquetiapine was measured in the children and adolescents than in the adult population, ranging from 27%–45% increases. After body-weight adjustment, a significant age-related decrease in peak concentration of quetiapine and 7-hydroxy quetiapine (but not of norquetiapine or quetiapine sulfoxide) was measured.

Figueroa and colleagues[25] have compared the pharmacokinetic profile of extended-release (XR) quetiapine with immediate-release (IR) quetiapine. As there were no significant differences in pharmacokinetic data between each group (suggesting no effect for treatment sequence), the pharmacokinetic data were combined for analysis. Mean maximum concentration (C_{max}) at

steady state was approximately 13% lower for quetiapine XR than for quetiapine IR (495.3 ng/mL and 568.1 ng/mL, respectively).

Positron Emission Tomography Studies

Many studies have evaluated the relationship between dopamine receptor occupancy by quetiapine and dose; 4 were found in which plasma concentration was also reported. Several research groups have debated whether striatal or extrastriatal occupancy best predicts antipsychotic response[26–28] and the importance of 5-HT_{2A} occupancy in the treatment of schizophrenia.[29,30] Striatal dopamine occupancy was measured in all 4[29,31–33] of the studies discussed here, with just 1 article[29] also reporting 5-HT_{2A} receptor occupancy. This last study demonstrated that 5-HT_{2A} occupancy was higher than D_2 occupancy, but the authors of the study argued that neither the high 5-HT_{2A} receptor occupancy nor the 5-HT_{2A}/D_2 ratio of receptor occupancy is likely to be responsible for quetiapine's antipsychotic effect (5-HT_{2A}/D_2 ratio was broadly the same at all doses). Here we report only the D_2 receptor results.

Gefvert and colleagues[31] were the first study group to investigate striatal dopamine D_2 occupancy of quetiapine while monitoring blood plasma concentrations. Method and results are shown in Table 5. Mean plasma concentration fell from 402.8 ng/mL at 2 hours' postdose to 47 ng/mL by 12 hours' postdose. Twenty-six hours after the last dose, dopamine occupancy had dropped from 44% at 2 hours' postdose to the same level as that in untreated healthy volunteers. Systematic rating scales were not used to assess clinical progress, although all patients were reported to have improved throughout the trial and there were no reports of any notable adverse effects.

Striatal dopamine occupancy and plasma concentration of quetiapine were investigated by Kapur and colleagues[29] across a range of quetiapine doses. Plasma concentration increased in a dose-dependant manner across the range ($r = 0.71$, $P = .008$). Further details are shown in Table 5. At week 4, a significant clinical improvement was reported as a score of "much improved" or "very much improved" as rated on the CGI-Improvement scale. However, the relationships between clinical response, dopamine occupancy and plasma concentration were not investigated.

Tauscher-Wisniewski and coworkers[33] investigated striatal dopamine occupancy and plasma concentration in relation to clinical response. Further details of the study design and results are shown in Table 5. At the end of week 4, those patients who did not respond to treatment (as measured by CGI-S and PANSS rating scales) had a mean ± SD peak dopamine D_2 occupancy of 60.3% ± 10.7%. Those deemed to have made a response had a peak dopamine occupancy of 65.9% ± 7.9%, although the difference between the 2 groups was not statistically significant ($P = .446$).

Mamo and colleagues[32] compared the striatal D_2 receptor binding of the XR formulation of quetiapine with the IR preparation in patients already taking quetiapine. At steady state, each patient was scanned and plasma samples taken at peak and trough times. Patients were then switched to XR quetiapine and the process repeated. Comparison of the XR and IR preparations did not reveal any differences in plasma concentration or D_2 receptor occupancy at any dose at any time. Plasma concentrations at trough were significantly lower than at peak for all doses and preparations other than the 300 mg IR and 800 mg IR doses. Similarly, mean D_2 receptor occupancy was significantly lower at trough than at peak for IR and XR formulations at all doses except IR 800 mg/d, while mean peak binding potential was significantly lower than at trough for all formulations and doses except IR 800 mg/d. There was a negative correlation between plasma concentration and D_2 receptor binding potential ($r = -0.63$, $P < .001$), with no difference between XR and IR at any dose.

CONCLUSIONS

This review suggests that there is a weak interindividual correlation between quetiapine dose and measured plasma concentration (from trough samples). Quetiapine dose is correlated with central dopamine D_2 occupancy, although the relationship between plasma level and D_2 occupancy is less clear. Data on plasma level response relations are not sufficiently robust to allow the determination of a therapeutic plasma level range for quetiapine.

Concentration-Dose Relationship

A strong, positive correlation was found between quetiapine dose and plasma concentration in 2 controlled fixed-dose studies.[21,29] In TDM studies, a weaker correlation[4,5,9,11] or a lack of correlation[15] was suggested by different studies. Combined, pooled data from all reviewed studies suggest a weak interindividual correlation between dose and plasma level (Figure 1).

Clinical Response Relationships

Although not assessed in this review, the dose-response relationship of quetiapine IR has been the subject of much debate, with some reports suggesting that higher than licensed dosages may be necessary for full therapeutic effect,[34–36] although a review of all available data found little robust evidence for prescribing above the licensed dose range.[37] In fixed-dose studies, clinical response appears optimal at a dose of around 300 to 400 mg/d. No additional benefit is observed above this threshold.[38] Clinical response and its relationship with plasma quetiapine concentration were assessed by few of the studies reviewed here. Dragicevic and colleagues[4,5] reported trough quetiapine concentrations above 77 ng/mL were associated with increased clinical improvement. The same study group later reported a weak association between good clinical response and the trough plasma level range 50–100 ng/mL.[8] Mauri and colleagues[11] reported a significant relationship between trough concentration/(dose/kg) and the percentage improvement in PANSS score ($r = 0.68$ to 0.75, depending on diagnosis; $P < .05$) although a threshold for response was not suggested and

Table 5. Quetiapine Dopamine Occupancy Studies

Design	Participants[a]	Inclusion/Exclusion Criteria	Mean Dose, mg/d[b]	Quetiapine Plasma Concentration, ng/mL[b]	Striatal D_2 Receptor Occupancy, Mean (%)	Major Outcomes	Study
1-wk study Dosed to 150 mg TDS then fixed for 29 d with 4 PET scans over 26 h after last dose Plasma drawn at trough steady state and until 26 hours' postdose Plasma analyzed by HPLC Ligand: [^{11}C]raclopride	N = 8 8 male Age, y: 33.9 (20–43) Diagnosis: schizophrenia	Inclusion: PANSS score < 120, CGI score ≤ 4 Exclusion: Other psychotropic medication in previous 2 mo, previous diagnosis of clozapine-induced agranulocytosis	150 TDS	2 hours' postdose: 402.8 8 hours' postdose: 102.2 12 hours' postdose: 47	2 hours' postdose: 44 (21–68) 8 hours' postdose: 30 (16–60) 12 hours' postdose: 27 (6–54)	No systematic ratings/clinical measures used—all participants clinically improved throughout study period	Gefvert et al,[31] 1998
28-d PET study BD dosing to target randomized dose, maintained for at least 14 d Scan and plasma concentration 12 h after last dose on days 21 and 28 Plasma analyzed by LC-MS-MS Ligand: [^{11}C]raclopride	N = 12 9 male 3 female Age, y: 29.6 ± 6 (21–40) Diagnosis: schizophrenia	Exclusion: Major illness or substance misuse, depot antipsychotic in last 12 mo Benzodiazepines permitted	75 BD 150 BD 225 BD 300 BD	12 hours' postdose: 29 ± 4 50 ± 28 172 ± 111 201 ± 113	12 hours' postdose: −2 ± 2 5 ± 7 14 ± 11 19 ± 1	Dose-dependent increase in concentration (r = 0.71, P = .008)	Kapur et al,[29] 2000
4-wk PET study Titration to 200 mg BD then 400 mg once daily until end of week 4, then adjusted to 750 mg/d PET scans at 4 weeks' treatment, 19 to 20 h after the once daily dose, then scan between 1 and 2.5 hours' postdose (peak) Plasma drawn at time of scans, analyzed by LC-MS Ligand: [^{11}C]raclopride	N = 14 11 male 3 female Age, y: 22.6 ± 3.7 Diagnosis: first-episode psychosis	Exclusion: Prior antipsychotic for more than 16 cumulative wk, prior poor response to medication, unstable medical illness, substance misuse, pregnancy/nursing, treatment with antidepressant, or mood stabilizers	427 ± 69	1 hour postdose: 589 ± 530 (17–1,454) 2.5 hours' postdose: 493 ± 163 (184–827) 20 hours' postdose: 29 ± 15 (9–56)	Peak (1–2.5 hours' postdose): 62.0 ± 9.8 (46.5–73.7) 18–20 hours' postdose: 14.3 ± 7.9 (range not reported)	Strong correlation between plasma concentration and peak D_2 occupancy (r = 0.84, P = .003) Stronger correlation when both peak and trough (18–20 hours' postdose) concentration and occupancies were considered (r = 0.96, P < .001) Significant reduction in dopamine D_2 occupancy and plasma concentration from peak to trough (P < .001)	Tauscher-Wisniewski et al,[33] 2002
18-d study comparing XR with IR. Assigned to IR at dose according to prestudy dose then switched to XR at same dose PET scan and plasma concentration taken at peak and trough for each preparation at steady state BD dosing for IR and once daily for XR Plasma drawn at same time as scans, analyzed by HPLC Ligand: [^{11}C]raclopride	N = 12 10 male 2 female Age, y: 32 ± 8 Diagnoses: Schizophrenia/schizoaffective disorder	Inclusion: Monotherapy of quetiapine IR at time of enrollment Exclusion: Depot within 12 mo, substance misuse in previous 3 mo, serious medical condition	300 IR 600 IR 800 IR 300 XL 600 XL 800 XL	37.0 ± 1.8 121.0 ± 27.0 111.0 ± 47.2 55.5 ± 9.3 172.5 ± 21.0 120.8 ± 93.3	−4.5 ± 8.7 8.0 ± 12.2 24.0 ± 8.8 −5.5 12.4 ± 6.8 17.9 ± 15.2[c]	No difference in concentration of XR and IR at any dose or time No difference in D_2 occupancy between IR and XR at trough and peak for all dose groups	Mamo et al,[32] 2008

[a]Age is mean ± SD (range) years of age.
[b]All values are mean ± SD (range) unless otherwise stated.
[c]Occupancy at time of trough plasma concentration.
Abbreviations: BD = twice daily, CGI = Clinical Global Impressions scale, HPLC = high performance liquid chromatography, IR = immediate release, LC-MS = liquid chromatography with mass spectroscopy, LC-MS-MS = liquid chromatography with tandem mass spectroscopy, PANSS = Positive and Negative Symptom Scale, PET = positron emission tomography, TDS = 3 times a day, XR = extended release.

there was no difference in the plasma concentration of patients who did or did not respond to treatment. Three of the reviewed studies failed to find a correlation between plasma concentration and clinical response.[9,14,17] The AGNP-TDM expert group[1] proposed a therapeutic plasma concentration range of 70–170 ng/mL based on the results of the study by Small et al[17] discussed earlier in this review. (This study reported a high-dose quetiapine group in which a significantly greater clinical improvement was seen compared with placebo. Mean plasma level in this group was 67.8 ng/mL, and the range was 21.5–169 ng/mL. The mean and the upper limit of the range appear to be the basis of the recommended AGNP-TDM range.) However, this study did not find a relationship between plasma concentration and change in score of any of the efficacy scales. The studies here have found a possible relationship with efficacy at concentrations above 77 ng/mL and the range between 50 and 100 ng/mL, although there is insufficient evidence to support the therapeutic range suggested by the AGNP-TDM group.

Clinical response was measured by the use of various rating scales in each of the reviewed studies, including the BPRS,[10] CGI,[6] and PANSS[12] scales (although there is close correlation between these measures[39]). Patients' diagnoses also differed and symptom levels were of varying severity at baseline. All of these factors must be considered when appraising the putative relationship between plasma concentration and clinical response.

Dopamine Occupancy Relationships

The relationship between quetiapine dose and dopamine D_2 receptor occupancy is somewhat complicated by quetiapine's loose in vivo binding to D_2 receptors.[40] Studies here show that therapeutic doses (even at peak quetiapine concentration) afford striatal dopamine occupancies that are below the 65% D_2 occupancy threshold generally accepted as necessary for drugs to exert an antipsychotic response.[41] By 12 hours' postdose (ie, trough concentration in many of these studies), dopamine occupancy was around 20%–30%.[29,31–33] This rapid reduction in D_2 occupancy has been noted previously[42] and is in all likelihood related to 2 qualities of quetiapine—its fast dissociation, or k_{off}, from the receptor (also labeled "loose binding") and its rapid plasma- and brain-level kinetics. Further, there is a question whether the measure of occupancy itself is influenced by the affinity and kinetics of the ligand and there is a possibility that quetiapine's dopamine receptor occupancy may be higher than suggested by brain-imaging conditions in studies such as those presented here.[40] Nonetheless, in contrast to other agents, D_2 receptor occupancy did not reach the proposed 78% threshold for extrapyramidal effects[41] at any point in the studies reviewed.

There is a positive correlation between dose and dopamine occupancy (scans at predose trough) when the results from all studies are pooled (Figure 2; $r^2 = 0.5247$, $P = .0273$). Although Tauscher-Wisniewski and colleagues[33] found a strong relationship between plasma concentration and occupancy (peak and trough occupancies and plasma concentration assessed), the relationship is less clear when results from all studies are pooled (Figure 3; $r^2 = 0.1626$, $P = .2819$). High variability in D_2 occupancy was recorded at each plasma level, making any relationship difficult to define.

Adverse Effects

The majority of the included studies did not assess adverse events. Dragicevic and colleagues[4,5] found no correlation between side effects (measured by the UKU scale) and quetiapine concentration. The same study group later reported that 35% of their naturalistic sample experienced side effects, with no difference between genders.[8] However, in female participants only, EPS were significantly associated with increased quetiapine concentration, with a median trough concentration of 210 ng/mL ($P < .05$). Older age was also associated with increased adverse effects. Two further study groups[9,14] found no correlation between concentration and adverse effects, including sedation, weight gain, EPS, and cardiovascular events.

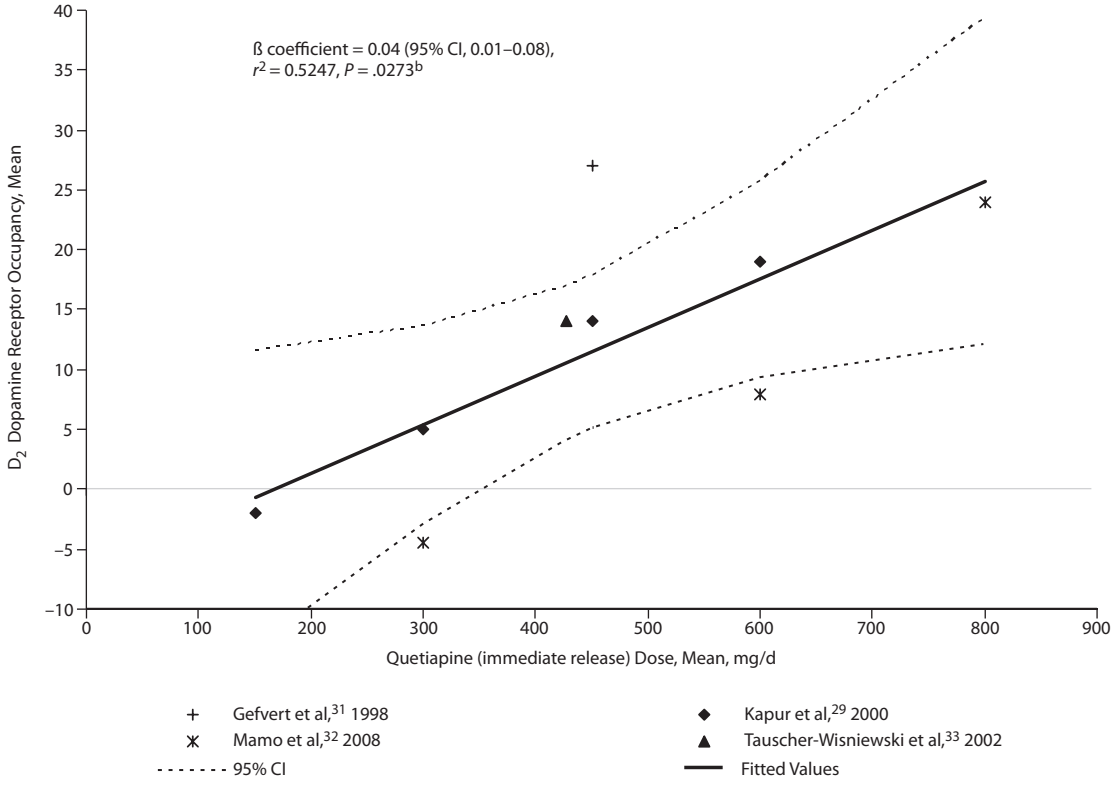
Other Potential Predictors of Variance

Several of the included studies investigated other potential predictors of variance. Gender had no significant effect on plasma concentration in 5 of the 8 studies to investigate it,[2,8,9,15,19] while 2 studies found female participants had non-significantly higher concentrations than male participants[3,11] and another found that female participants had significantly lower concentrations than male participants despite similar doses.[4,5] Increased age was associated with increased concentration in 2 studies[2,3] but not in another.[14] Although older age and female gender might be expected to cause higher quetiapine concentrations due to differences in renal function, weight, volume of distribution, and expression of metabolizing enzymes,[43,44] there is insufficient evidence from the existing data to support the use of TDM for monitoring for variation due to gender or age.

Quetiapine is metabolized to 11 identified metabolites, 2 of which are known to be active; 7 hydroxy-quetiapine and 7-hydroxy-*N*-desalkyl-quetiapine. Present in the plasma at 2%–12% of the parent, both are generally believed to have negligible pharmacologic effects.[22,45] However a recent rodent study has suggested that 7-hydroxy-*N*-desalkyl-quetiapine may, at least in part, contribute to quetiapine's antidepressant-like activity.[46] Further studies into the activity of quetiapine's metabolites are required to assess their possible importance on individual antipsychotic response to quetiapine.

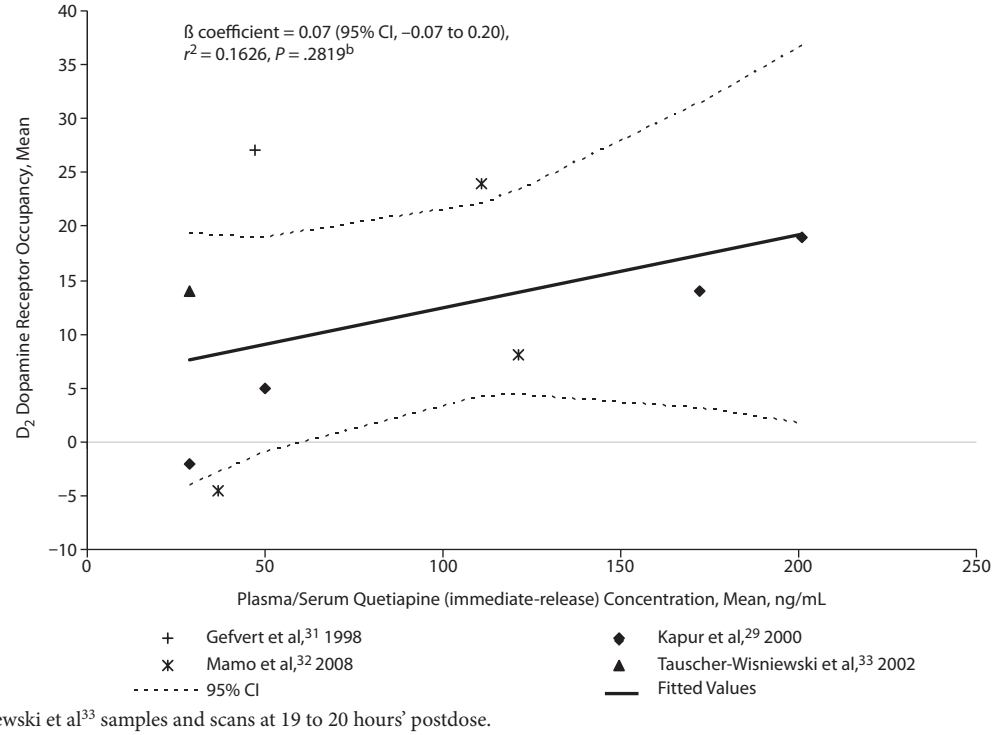
Interindividual variability in the metabolism of quetiapine may merit further investigation. We have found there is a weak interindividual relationship between trough plasma/serum concentration and quetiapine dose, which alone may support the argument for conducting routine TDM of quetiapine. However, in the absence of a therapeutic range as a reference for either efficacy or adverse effects, routine TDM of quetiapine cannot be recommended. Studies of several drugs have suggested that inherited variants in drug-metabolizing enzymes, transporters, and receptors may play a major role in clinical response to drugs.[47–49] It may be that,

Figure 2. Mean Quetiapine (immediate release) Dose Versus Mean Striatal D_2 Dopamine Receptor Occupancy (scan at trough[a])



[a]Tauscher-Wisniewski et al[33] scan at 19 to 20 hours' postdose.
[b]Nonweighted meta-regression.

Figure 3. Mean Trough Quetiapine (immediate release) Plasma/Serum Concentration Versus Mean Striatal D_2 Dopamine Receptor Occupancy (trough samples and scans[a])



[a]Tauscher-Wisniewski et al[33] samples and scans at 19 to 20 hours' postdose.
[b]Nonweighted meta-regression.

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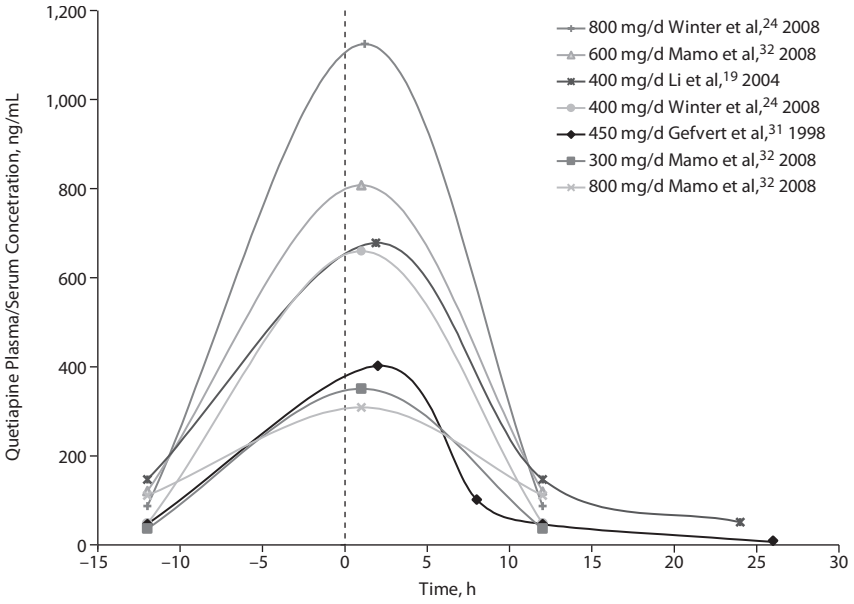
for some drugs, identification of genetic polymorphisms and individual activity of the relevant metabolizing enzymes could be crucial in making appropriate adjustments to drug doses when trying to reach a desired drug concentration and optimize drug therapy. Current studies into genetic polymorphisms in the treatment of depression have produced equivocal results. A naturalistic study[50] of 44 subjects taking various antidepressants reported that the CYP2D6 genotype is associated with adverse effects and clinical nonresponse. However, investigation into a large cohort of subjects prescribed citalopram during the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial[51] found no significant association between the studied genetic polymorphisms and clinical response or tolerance. There are no available studies of quetiapine and the genetic polymorphisms of its metabolizing enzymes, although a recent study[52] has suggested that functional single-nucleotide polymorphisms in genes encoding neuroreceptor drug targets could explain interindividual differences in response and tolerability to atypical antipsychotic drugs including quetiapine. Pharmacogenetic gene studies may be an area for future investigation in the optimization of quetiapine therapy.

Figure 4. Change in Quetiapine (immediate release) Plasma/Serum Concentration Over Time: Comparison of Peak and Trough Plasma Concentrations



Drug interactions were investigated by several of the TDM studies,[2,3,15] and several drugs were found to affect quetiapine concentration. Drugs known to induce or inhibit CYP3A4 (the enzyme mainly responsible for the metabolism of quetiapine) may be expected to effect the plasma concentration of quetiapine. The reviewed studies did not quantify the clinical effects of any such interaction in any way, and, in most studies, subjects were also taking other medication; thus it is difficult to evaluate the implications of these interactions in any meaningful way. In the absence of a target therapeutic range in terms of efficacy or safety, it is unhelpful to make any recommendation for plasma level monitoring in patients prescribed potentially interacting medications.

Plasma Concentration-Time Relationship

In view of the lack of relationship between trough concentration and either dose or dopamine occupancy, we plotted quetiapine plasma concentration (data from the IR preparation) over time, using measured peak and trough concentrations at times stated, assuming prior trough concentrations were the same as those measured afterward (as would be the case at steady state) (Figure 4). Figure 4 displays very clearly that, in these studies, peak concentration ranged between approximately 300 and 1,100 ng/mL, while trough plasma concentrations were measured only within a relatively small range (approximately 50–150 ng/mL) regardless of the dose or magnitude of the corresponding peak level. This limited variability is likely to be an important factor in our failure to find a relationship between dose and *trough* plasma concentration (as all trough concentrations are broadly similar regardless of dose) and between trough plasma level and D_2 occupancy (as trough concentrations do not differ markedly with dose or reflect prior peak concentrations of quetiapine). When considering quetiapine's extensive metabolism, short half-life, and fast dissociation from D_2 receptors, it might be predicted that trough samples or scans (at 12 hours' postdose for twice daily dosing) would show low concentrations or occupancies, regardless of the dose administered. As shown in Figure 4, plasma concentrations from all doses are indistinguishable, making any relationship difficult to identify. However, when measuring peak concentrations (taken prior to the extensive metabolism of the drug), there is a clear difference in concentrations at different doses. Although peak samples are not always convenient to measure in practice, they may be more useful in determining a relationship with quetiapine dose, dopamine occupancy, or even response. Further analysis of quetiapine peak plasma concentration is required to clarify this further.

Clinical Implications

Drugs with high plasma concentration intervariability and plasma concentrations that are not reliably predicted from dose are often suitable for the use of therapeutic drug monitoring, particularly those drugs with a narrow

therapeutic index. However, plasma level monitoring is only valuable when there is an established target range, whether it be for safety or efficacy, and when there is lack of an established dose-response relationship. In the case of quetiapine, we have found a weak interindividual relationship between dose and plasma concentration, and we know a broad dose range within which it is efficacious and tolerated, but we do not have sufficient evidence to recommend a plasma level range in which the drug is likely to be both optimally safe and efficacious. In the currently existing data, for the most part, trough plasma concentrations have been utilized, which have a weak correlation with dose. The wide range in plasma concentrations that has been found for peak but not trough concentration suggests that peak plasma sampling may be of more value when searching for a dose-level correlation, or for a therapeutic range. This review does, however, supply a range of plasma concentrations that have been found within the licensed dose range without reported toxicity. Mean doses in this review ranged from 200 mg/d to 800 mg/d, and mean trough plasma concentration ranged from 27 ng/mL to 387 ng/mL. These ranges may provide some broad guidance, but, as the highest and lowest concentrations were not necessarily found at the highest and lowest doses, there is little value in the use of TDM to assess patient adherence or the degree of a suspected drug interaction.

Limitations

The broad range in plasma quetiapine concentration that has been found for peak (but not trough) concentrations across the dose range has prompted us to suggest that peak plasma sampling may be of more value than trough sampling for TDM purposes. However, the fixed-dose controlled studies reviewed here each found a strong significant correlation between dose and trough plasma level,[21,29] while the TDM studies did not. This finding raises the question of reliability of data from TDM studies. This concern was also highlighted in the study by Castberg and colleagues,[16] who found that patients in a high-secure forensic unit had higher concentrations than those prescribed similar doses in the TDM sample, suggesting relatively poor compliance in the nonforensic TDM arm. Although naturalistic studies may more accurately reflect prescribing in a clinical population than under controlled conditions, data from such studies are vulnerable to collecting less accurate data due to uncontrolled sampling times, variable dosing times, patient adherence, and coprescribed medication. Although all but 2 studies represented in Figure 1 reported sampling at trough (ie, just before the next dose is due), in practice blood samples are often taken at a time convenient to the phlebotomist or clinician rather than at the precise, true trough. Also, not all patients in these studies were dosed twice a day, and additional medications were not always prohibited in all studies. Therefore, results may not truly reflect what is happening at a prescribed dose and may account for some of the lack of relationships found in this review.

Studies reviewed here also used different analytic methods to measure plasma concentrations of the drug, which may be considered a limitation as we have pooled results measured by different methods. However, although the liquid chromatography coupled with mass spectroscopy methods may be more sensitive, the value of these methods over high performance liquid chromatography and gas chromatography methods is still to be proven for routine drug concentration analysis such as that carried out in the studies here.[1]

A further limitation of using naturalistic studies, such as those reviewed here, is that they were not designed to determine whether plasma levels of quetiapine correlate with efficacy, safety, or tolerability. Also, some of the smaller studies, such as the pharmacokinetic and dopamine occupancy studies, do not have sample sizes large enough, or study duration long enough, to determine such relationships. When pooling results such as we have in this review, the limitations of the individual studies are minimized but must be considered.

Other than the positron emission tomography scan studies, most studies included patients with a variety of psychiatric diagnoses, did not exclude those with a diagnosis of substance misuse, and many permitted other medication to be taken during the study period. In addition, only published reports were sought and reviewed. All these factors may have had significant influence on the results of the studies, from measuring clinical response to the plasma concentrations themselves. These limitations should be considered when applying any of the information learned to clinical practice. Further controlled, fixed-dose studies would enable clarification of whether or not there actually is a relationship with trough concentration and dose, which we were unable to replicate when pooling the results from our largely naturalistic data set.

The dose-response relationship for quetiapine IR is established, with optimal efficacy seen at doses around 300 to 400 mg/d. Although the reviewed studies provide a range of plausible plasma concentrations to be expected within the current licensed dose range, there is currently insufficient evidence to suggest a recommended plasma level range for optimal clinical response or avoidance of adverse effects. Therapeutic drug monitoring is thus probably not routinely useful in optimizing quetiapine dose. Examination of the relationship between peak quetiapine plasma concentration and clinical response may bear more fruit.

Drug names: alprazolam (Xanax, Niravam, and others), atomoxetine (Strattera and others), benztropine (Cogentin and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clozapine (FazaClo, Clozaril, and others), lithium (Lithobid and others), methylphenidate (Daytrana, Ritalin, and others), propranolol (Inderal, InnoPran, and others), quetiapine (Seroquel).

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REFERENCES

1. Baumann P, Hiemke C, Ulrich S, et al; Arbeitsge-meinschaft fur neuropsychopharmakologie und pharmakopsychiatrie. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. *Pharmacopsychiatry*. 2004;37(6):243–265.
2. Castberg I, Skogvoll E, Spigset O. Quetiapine and drug interactions: evidence from a routine therapeutic drug monitoring service. *J Clin Psychiatry*. 2007;68(10):1540–1545.
3. Aichhorn W, Marksteiner J, Walch T, et al. Influence of age, gender, body weight and valproate comedication on quetiapine plasma concentrations. *Int Clin Psychopharmacol*. 2006;21(2):81–85.
4. Dragicevic A, Muller MJ, Sachse J, et al. Therapeutic drug monitoring (TDM) of quetiapine. Lecture presented at the Symposium of the AGNP; October 8–10, 2003; Munich, Germany.
5. Dragicevic A, Sachse J, Hartter S, et al. Serum concentrations of quetiapine and clinical effects. International Meeting on Pharmacovigilance in Psychiatry, Therapeutic Drug Monitoring and Pharmacogenetics of Psychotropic Drugs; September 1–3, 2005; Lausanne, Switzerland.
6. Guy W. The Clinical Global Impressions Scale. In: Guy W, ed. *ECDEU Assessment Manual for Psychopharmacology*. *Rev Ed*. Rockville, MD: National Institute of Mental Health; 1976:157–169.
7. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: A New Comprehensive Rating Scale for Psychotropic Drugs and a Cross-Sectional Study of Side Effects in Neuroleptic-Treated Patients. *Acta Psychiatr Scand suppl*. 1987;76(s334):1–100.
8. Dragicevic A, Trotzauer D, Hiemke C, et al. Gender and age effects on quetiapine serum concentrations in patients with schizophrenia or schizoaffective disorders. Lecture presented at the 24th Symposium of the AGNP; October, 5–8; 2005. Munich, Germany.
9. Gerlach M, Hünnerkopf R, Rothenhöfer S, et al. Therapeutic drug monitoring of quetiapine in adolescents with psychotic disorders. *Pharmacopsychiatry*. 2007;40(2):72–76.
10. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10(3):799–812.
11. Mauri MC, Volonteri LS, Fiorentini A, et al. Two weeks' quetiapine treatment for schizophrenia, drug-induced psychosis and borderline personality disorder: a naturalistic study with drug plasma levels. *Expert Opin Pharmacother*. 2007;8(14):2207–2213.
12. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
13. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
14. Mauri MC, Fiorentini A, Volonteri FS, et al. Quetiapine in acute psychosis and personality disorders during hospitalisation: assessment of therapeutic range. Poster presented at the World Psychiatric Association International Congress; November 10–13, 2004; Florence, Italy.
15. Hasselstrøm J, Linnet K. Quetiapine serum concentrations in psychiatric patients: the influence of comedication. *Ther Drug Monit*. 2004;26(5):486–491.
16. Castberg I, Spigset O. Prescribing patterns and the use of therapeutic drug monitoring of psychotropic medication in a psychiatric high-security unit. *Ther Drug Monit*. 2008;30(5):597–603.
17. Small JG, Hirsch SR, Arvanitis LA, et al; Seroquel Study Group. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry*. 1997;54(6):549–557.
18. Andreasen N. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. *Br J Psychiatry suppl*. 1989;155(suppl 7):49–58.
19. Li KY, Li X, Cheng ZN, et al. Multiple dose pharmacokinetics of quetiapine and some of its metabolites in Chinese suffering from schizophrenia. *Acta Pharmacol Sin*. 2004;25(3):390–394.
20. McConville BJ, Arvanitis LA, Thyrum PT, et al. Pharmacokinetics, tolerability, and clinical effectiveness of quetiapine fumarate: an open-label trial in adolescents with psychotic disorders. *J Clin Psychiatry*. 2000;61(4):252–260.
21. Jaskiw GE, Thyrum PT, Fuller MA, et al. Pharmacokinetics of quetiapine in elderly patients with selected psychotic disorders. *Clin Pharmacokinet*. 2004;43(14):1025–1035.
22. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. *Clin Pharmacokinet*. 2001;40(7):509–522.
23. Gunasekara NS, Spencer CM. Quetiapine: a review of its use in schizophrenia. *CNS Drugs*. 1998;9(4):325–340.
24. Winter HR, Earley WR, Hamer-Maansson JE, et al. Steady-state pharmacokinetic, safety, and tolerability profiles of quetiapine, norquetiapine, and other quetiapine metabolites in pediatric and adult patients with psychotic disorders. *J Child Adolesc Psychopharmacol*. 2008;18(1):81–98.
25. Figueroa C, Brecher M, Hamer-Maansson JE, et al. Pharmacokinetic profiles of extended release quetiapine fumarate compared with quetiapine immediate release. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(2):199–204.
26. Xiberas X, Martinot JL, Mallet L, et al. In vivo extrastriatal and striatal D2 dopamine receptor blockade by amisulpride in schizophrenia. *J Clin Psychopharmacol*. 2001;21(2):207–214.
27. Xiberas X, Martinot JL, Mallet L, et al. Extrastriatal and striatal D(2) dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia. *Br J Psychiatry*. 2001;179(6):503–508.
28. Agid O, Mamo D, Ginovart N, et al. Striatal vs extrastriatal dopamine D2 receptors in antipsychotic response—a double-blind PET study in schizophrenia. *Neuropsychopharmacology*. 2007;32(6):1209–1215.
29. Kapur S, Zipursky R, Jones C, et al. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. *Arch Gen Psychiatry*. 2000;57(6):553–559.
30. Gefvert O, Lundberg T, Wieselgren IM, et al. D(2) and 5HT(2A) receptor occupancy of different doses of quetiapine in schizophrenia: a PET study. *Eur Neuropsychopharmacol*. 2001;11(2):105–110.
31. Gefvert O, Bergström M, Långström B, et al. Time course of central nervous dopamine-D2 and 5-HT2 receptor blockade and plasma drug concentrations after discontinuation of quetiapine (Seroquel) in patients with schizophrenia. *Psychopharmacology (Berl)*. 1998;135(2):119–126.
32. Mamo DC, Uchida H, Vitcu I, et al. Quetiapine extended-release versus immediate-release formulation: a positron emission tomography study. *J Clin Psychiatry*. 2008;69(1):81–86.
33. Tauscher-Wisniewski S, Kapur S, Tauscher J, et al. Quetiapine: an effective antipsychotic in first-episode schizophrenia despite only transiently high dopamine-2 receptor blockade. *J Clin Psychiatry*. 2002;63(11):992–997.
34. Citrome L, Jaffe A, Levine J, et al. Dosing of quetiapine in schizophrenia: how clinical practice differs from registration studies. *J Clin Psychiatry*. 2005;66(12):1512–1516.
35. Pierre JM, Wirshing DA, Wirshing WC, et al. High-dose quetiapine in treatment refractory schizophrenia. *Schizophr Res*. 2005;73(2–3):373–375.
36. Bobes J, Garcia-Portilla MP, Saiz PA, et al. High degree of tolerability for monotherapy with high doses of quetiapine: a case report. *J Clin Psychiatry*. 2002;63(11):1048–1049.
37. Sparshatt A, Jones S, Taylor D. Quetiapine: dose-response relationship in schizophrenia. *CNS Drugs*. 2008;22(1):49–68, discussion 69–72.
38. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. *Biol Psychiatry*. 1997;42(4):233–246.
39. Leucht S, Kane JM, Etschel E, et al. Linking the PANSS, BPRS, and CGI: clinical implications. *Neuropsychopharmacology*. 2006;31(10):2318–2325.
40. Seeman P, Tallerico T. Rapid release of antipsychotic drugs from dopamine D2 receptors: an explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine or quetiapine. *Am J Psychiatry*. 1999;156(6):876–884.
41. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry*. 2000;157(4):514–520.
42. Kapur S, Seeman P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics? a new hypothesis. *Am J Psychiatry*. 2001;158(3):360–369.
43. Schwartz JB. The influence of sex on pharmacokinetics. *Clin Pharmacokinet*. 2003;42(2):107–121.
44. Beierle I, Meibohm B, Derendorf H. Gender differences in pharmacokinetics and pharmacodynamics. *Int J Clin Pharmacol Ther*. 1999;37(11):529–547.
45. Mauri MC, Volonteri LS, Colasanti A, et al. Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. *Clin Pharmacokinet*. 2007;46(5):359–388.
46. Jensen NH, Rodriguiz RM, Caron MG, et al. N-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT1A

agonist, as a putative mediator of quetiapine's antidepressant activity. *Neuropsychopharmacology*. 2008;33(10):2303–2312.
47. Tomalik-Scharte D, Lazar A, Fuhr U, et al. The clinical role of genetic polymorphisms in drug-metabolizing enzymes. *Pharmacogenomics J*. 2008;8(1):4–15.
48. Weinshilboum R. Inheritance and drug response. *N Engl J Med*. 2003; 348(6):529–537.
49. Goldstein DB. Pharmacogenetics in the laboratory and the clinic. *N Engl J Med*. 2003;348(6):553–556.
50. Rau T, Wohlleben G, Wuttke H, et al. CYP2D6 genotype: impact on adverse effects and nonresponse during treatment with antidepressants—a pilot study. *Clin Pharmacol Ther*. 2004;75(5):386–393.
51. Peters EJ, Slager SL, Kraft JB, et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. *PLoS ONE*. 2008;3(4):e1872.
52. Davies MA, Conley Y, Roth BL. Functional SNPs in Genes encoding the 5-ht2a receptor modify the affinity and potency of several atypical antipsychotic drugs. *Biol Res Nurs*. 2010.
53. Summary of Product Characteristics. Seroquel. eMC (the electronic Medicines Compendium) Web site. http://www.medicines.org.uk/EMC/medicine/2295/SPC/SEROQUEL+25+mg%2c+100+mg%2c+150+mg%2c+200+mg%2c+300+mg+film-coated+tablets/. Accessed November 29, 2010.
54. Nemeroff CB, Kinkead B, Goldstein J. Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. *J Clin Psychiatry*. 2002; 63(suppl 13):5–11.
55. Fabre LF Jr, Arvanitis L, Pultz J, et al. ICI 204,636, a novel, atypical antipsychotic: early indication of safety and efficacy in patients with chronic and subchronic schizophrenia. *Clin Ther*. 1995;17(3):366–378.
56. Wong JYM, Ewing BJ, Jaskiw G, et al. Multiple-dose pharmacokinetics of 'Seroquel' (ICI 204,636) in elderly schizophrenic patients. *Eur Psychiatry*. 1996;11(suppl 4):430s.
57. Wong JYW, Ewing BJ, Fabre LF, et al. Multiple-dose pharmacokinetics of "Seroquel" (ICI 204,636) in schizophrenic men and women. *Eur Psychiatry*. 1996;11:429s–430s.
58. Wong JYM, Ewing BJ, Thyrum PT, et al. Multiple-dose pharmacokinetics of 'Seroquel' (quetiapine) in schizophrenic men and women. *Schizophr Res*. 1997;24(1–2):200.
59. Küfferle B, Tauscher J, Asenbaum S, et al. IBZM SPECT imaging of striatal dopamine-2 receptors in psychotic patients treated with the novel antipsychotic substance quetiapine in comparison to clozapine and haloperidol. *Psychopharmacology (Berl)*. 1997;133(4):323–328.
60. Davis PC, Wong J, Gefvert O. Analysis and pharmacokinetics of quetiapine and two metabolites in human plasma using reversed-phase HPLC with ultraviolet and electrochemical detection. *J Pharm Biomed Anal*. 1999;20(1–2):271–282.
61. Kimko HC, Reele SS, Holford NH, et al. Prediction of the outcome of a phase 3 clinical trial of an antischizophrenic agent (quetiapine fumarate) by simulation with a population pharmacokinetic and pharmacodynamic model. *Clin Pharmacol Ther*. 2000;68(5):568–577.
62. Stephenson CM, Bigliani V, Jones HM, et al. Striatal and extra-striatal D(2)/D(3) dopamine receptor occupancy by quetiapine in vivo. [(123) I]-epidepride single photon emission tomography(SPET) study. *Br J Psychiatry*. 2000;177(5):408–415.
63. Sachse J, Hartter S, Muller MJ, et al. Therapeutic drug monitoring of quetiapine. *Psychopharmakotherapie*. 2003;10:19–22.
64. Savasi I, Millson RC, Owen JA. Quetiapine blood level variability. *Can J Psychiatry*. 2002;47(1):94.
65. Rothenhofer S, Mehler-Wex C, Schupp U, et al. Therapeutic drug monitoring of quetiapine in child and adolescents. *Pharmacopsychiatry*. 2005;38:75.
66. Strakowski SM, Keck PE Jr, Wong YW, et al. The effect of multiple doses of cimetidine on the steady-state pharmacokinetics of quetiapine in men with selected psychotic disorders. *J Clin Psychopharmacol*. 2002;22(2):201–205.
67. Potkin SG, Thyrum PT, Alva G, et al; Pharmacokinetic Study Group. Effect of fluoxetine and imipramine on the pharmacokinetics and tolerability of the antipsychotic quetiapine. *J Clin Psychopharmacol*. 2002; 22(2):174–182.
68. Li KY, Li X, Cheng ZN, et al. Effect of erythromycin on metabolism of quetiapine in Chinese suffering from schizophrenia. *Eur J Clin Pharmacol*. 2005;60(11):791–795.
69. Härtter S, Connemann B, Schönfeldt-Lecuona C, et al. Elevated quetiapine serum concentrations in a patient treated concomitantly with doxepin, lorazepam, and pantoprazole. *J Clin Psychopharmacol*. 2004; 24(5):568–571.
70. Köhnlein O, Lutz R, Schmauss M, et al. [Determining serum concentrations of the modern antipsychotic quetiapin: clinical relevance in therapeutic drug monitoring]. [Article in German] *Psychiatr Prax*. 2004;31(suppl 1):S175–S177.
71. Sachse J, Köller J, Härtter S, et al. Automated analysis of quetiapine and other antipsychotic drugs in human blood by high performance-liquid chromatography with column-switching and spectrophotometric detection. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2006;830(2): 342–348.
72. Winter HR, DeVane CL, Figueroa C, et al. Open-label steady-state pharmacokinetic drug interaction study on co-administered quetiapine fumarate and divalproex sodium in patients with schizophrenia, schizoaffective disorder, or bipolar disorder. *Hum Psychopharmacol*. 2007;22(7): 469–476.
73. Schulz-Du Bois C, Schulz-Du Bois AC, Bewig B, et al. Major increase of quetiapine steady-state plasma concentration following co-administration of clarithromycin: confirmation of the pharmacokinetic interaction potential of quetiapine. *Pharmacopsychiatry*. 2008;41(6):258–259.
74. Catafau AM, Penengo MM, Nucci G, et al; Barcelona Clinical Imaging in Psychiatry Group. Pharmacokinetics and time-course of D(2) receptor occupancy induced by atypical antipsychotics in stabilized schizophrenic patients. *J Psychopharmacol*. 2008;22(8):882–894.

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