# Quetiapine: An Effective Antipsychotic in First-Episode Schizophrenia Despite Only Transiently High Dopamine-2 Receptor Blockade

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***Background:*** It has been suggested that transiently high dopamine-2 ($D_2$) receptor occupancy by antipsychotic medication may be sufficient for inducing an antipsychotic response. We treated patients experiencing their first episode of schizophrenia with a single daily dose of quetiapine to achieve a transient daily peak of $D_2$ receptor blockade, to determine if this would lead to an antipsychotic response.

***Method:*** Fourteen patients with a DSM-IV diagnosis of schizophrenia or schizophreniform or schizoaffective disorder were treated with quetiapine titrated to a single daily dose (mean ± SD dose at the time of the positron emission tomography [PET] scan = 427 ± 69 mg) for 12 weeks. Peak $D_2$ occupancy approximately 2 hours postdose and trough $D_2$ occupancy approximately 20 hours postdose were determined using PET and [$^{11}$C]raclopride. Clinical symptoms and side effects were measured at baseline and every 2 weeks during the treatment phase.

***Results:*** Quetiapine administration led to a mean peak $D_2$ occupancy of 62% ± 10% 2 hours postdose, which declined to 14% ± 8% approximately 20 hours postdose. Ten (71%) of 14 patients responded to treatment with quetiapine, scoring "much improved" or greater on the Clinical Global Impressions-Improvement scale. Plasma drug levels and peak $D_2$ occupancy were highly correlated ($r = 0.84$; $p = .003$), as were prolactin and plasma drug levels when measured 2.5 hours after drug administration ($r = 0.60$; $p < .05$). Mean weight gain for the 10 subjects who completed the 12-week study was 4.2 ± 4.6 kg (9.3 ± 10.2 lb). No clinically relevant motor side effects occurred during the trial.

***Conclusion:*** Patients with a first episode of schizophrenia responded to treatment with a single daily dose of quetiapine despite only transiently high $D_2$ receptor occupancy. Our findings raise the question of whether continuously high $D_2$ blockade is necessary for obtaining an antipsychotic response. Future studies aimed at evaluating the relative merits of "transiently high" versus "continuously high" $D_2$ occupancy are warranted.

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In vitro studies consistently show that all antipsychotics bind to dopamine-2 ($D_2$) receptors and that the affinity for the $D_2$ receptor is inversely correlated with the clinical dosage.[1,2] Using positron emission tomography (PET) and radioactive labeled ligands such as [$^{11}$C]raclopride, the proportion of $D_2$ receptors occupied by an antipsychotic can be quantitatively determined. Quetiapine and clozapine show a much lower $D_2$ receptor occupancy in vivo than other antipsychotics; in the case of quetiapine, neuroimaging studies with PET and single photon emission computed tomography have revealed that, 12 hours after intake of the last dose, $D_2$ receptor occupancy ranged from 0% to 40%.[3–6] This low $D_2$ occupancy probably reflects a more rapid dissociation from the receptors than with other antipsychotics rather than an actual low peak occupancy.[7]

Previous clinical trials have shown that quetiapine given in 2 or 3 doses per day is clinically effective in acutely psychotic patients[8–10] and in those with only partial response to conventional antipsychotic treatment.[11] A 6-week, double-blind, randomized, multicenter, parallel-group clinical trial in 618 schizophrenic patients showed that twice-daily administration was equally effective and equally well tolerated as quetiapine 3 times daily.[12]

It is possible that transiently high $D_2$ occupancy, achieved once a day, may be sufficient to induce an anti-

psychotic response. We recently reported 2 cases in which quetiapine gave rise to transiently high (58%–64%) $D_2$ occupancy 2 to 3 hours after a single dose, which then decreased to minimal levels within 12 hours.[5] Another study[4] showed that clearance of quetiapine from plasma (elimination half-life of approximately 5 hours) was even more rapid than from the $D_2$ receptors in the brain, where an occupancy half-life of 10 hours was found. On the basis of these reports, it may be questioned whether continuous (i.e., 24-hour) blockade of $D_2$ receptors is necessary for achieving antipsychotic response.[13] Thus, a primary purpose of this study was to determine if once-daily administration of quetiapine, leading to only a transient peak of $D_2$ occupancy, would be sufficient to induce an antipsychotic response.

Quetiapine may be of particular importance in the treatment of patients experiencing a first episode of schizophrenia. First-episode patients are expected to respond favorably to antipsychotic treatment and, in the case of conventional antipsychotics, to relatively low doses.[14] There is increasing evidence that quetiapine has a very low propensity to induce extrapyramidal symptoms (EPS) and carries a low risk of tardive dyskinesia, perhaps as a result of its transient $D_2$ occupancy.[7,8,15] Because of the chronic nature of schizophrenia, current treatment guidelines stress the importance of antipsychotic maintenance treatment for years.[16,17] Thus, a medication that is used to treat a condition occurring in adolescents or relatively young adults and that needs to be taken over a relatively long period of time should combine a low propensity to induce motor and/or other side effects with good clinical efficacy to increase compliance and optimize clinical outcome.

We conducted a prospective 12-week study that involved treating patients experiencing a first episode of psychosis with quetiapine given once daily to evaluate the efficacy of the treatment and to examine the relationship between peak/trough $D_2$ occupancy and clinical response. We expected to achieve an antipsychotic response with a transiently high $D_2$ occupancy, which would then decline to a very low trough level before the next dose.

## METHOD

### Subjects and Study Design

Subjects were recruited from consecutive referrals to the inpatient and outpatient services of the First Episode Psychosis Program at the Centre for Addiction and Mental Health in Toronto, Canada. Subjects were enrolled if they were aged 16 to 45 years and able and willing to provide informed consent to participate. To be asked to participate, patients had to meet DSM-IV criteria for a first episode of schizophrenia or schizoaffective or schizophreniform disorder and be rated as at least "moderately ill" on the Clinical Global Impressions scale (CGI).[18] Patients were excluded if they (1) received prior antipsychotic treatment for more than 16 cumulative weeks during their lifetime, (2) had a history of poor response to any previous trial of antipsychotic medication of sufficient dose and duration, (3) were pregnant or nursing, (4) were inpatients who were hospitalized on an involuntary basis, (5) had an unstable medical illness, (6) had a history of allergic reactions to quetiapine, (7) met DSM-IV criteria for substance dependence within 1 month prior to initiation of the study, (8) had treatment with long-acting depot medication within 1 year of the study, or (9) had concurrent treatment with antidepressant or mood-stabilizing medications. The study was approved by the Human Subjects Review Committee of the University of Toronto.

Nineteen patients were enrolled originally. Five withdrew within the first week (because of medication noncompliance) and therefore were excluded from all analyses. Of the 14 patients who continued in the study, 2 withdrew after 4 weeks (did not want to take medication on a regular basis), 1 withdrew after 6 weeks (poor response), and 1 discontinued the study after 8 weeks because of discomfort with side effects. The data of all 14 patients were included for further analysis of their clinical status. After providing informed consent, all subjects were interviewed using the Structured Clinical Interview for DSM-IV.[19] All 14 patients (11 male and 3 female) were experiencing a first episode of psychosis and met DSM-IV diagnostic criteria for schizophrenia (10 paranoid and 1 disorganized type), schizoaffective disorder (N = 1), or schizophreniform disorder (N = 2). Mean ± SD age at baseline was 22.6 ± 3.7 years. Mean duration of untreated psychosis was 14.9 ± 17.8 months. Four subjects were inpatients and 10 were outpatients at the time they entered the study. Clinical evaluations including weight, blood pressure, and heart rate assessment were performed at baseline and every other week. At baseline and after 12 weeks, blood was drawn for a complete blood cell count, prolactin level, liver function tests, fasting blood glucose, and lipid profile. Clinical ratings were performed using the Positive and Negative Syndrome Scale (PANSS),[20] CGI,[18] Barnes Akathisia Scale (BAS),[21] Simpson-Angus Scale (SAS)[22] for extrapyramidal symptoms, UKU Side Effect Rating Scale,[23] and Abnormal Involuntary Movement Scale (AIMS).[24] Patients were regarded as clinical responders if they were rated as "much improved" or "very much improved" on the Clinical Global Impressions-Improvement scale (CGI-I). The overall determination of response was made at study endpoint after 12 weeks. However, to assess clinical correlates of the PET receptor occupancy data, we also determined responder/nonresponder status at the time of the PET scans after 4 weeks of quetiapine treatment.

### Quetiapine Dosage

Patients were started on quetiapine at a dose of 50 mg twice a day. Doses were increased by 50 or 100 mg per day, if tolerated, to a target dose of 400 mg/day. Once patients were titrated to this dose, they were shifted to a single nighttime dose, and patients were maintained at this dose until the end of the fourth week of the study. Two patients could not tolerate their medication as a single dose and were given the larger dose of 250 or 300 mg in the evening and the smaller dose of 150 or 100 mg in the morning. Twelve patients were able to take medication once daily at night. Mean daily dose at the time of the PET scans was 427 ± 69 mg. After completion of 4 weeks, the dose was adjusted individually up to 750 mg/day. The mean dose for the 10 patients completing 12 weeks was 494 ± 129 mg. Twelve of the 14 study participants were neuroleptic naive at baseline, and 2 had previously received risperidone but discontinued it 6 months before entering the present study. Additional psychotropic medication was restricted to lorazepam, which was used in 3 patients for insomnia or agitation.

### PET Scanning Procedures

Two [$^{11}$C]raclopride PET scans were performed after 4 weeks of quetiapine treatment to estimate $D_2$ receptor occupancy. The first PET scan was performed 19 to 20 hours after last medication intake (trough). The patients then received their daily quetiapine dose, and the second (peak) scan was carried out between 1 and 2.5 hours postdose. This time was chosen in order to coincide with peak plasma levels. Thirteen patients were scanned twice using PET and [$^{11}$C]raclopride to determine "peak" and "trough" $D_2$ occupancy. One of those patients was unable to complete the PET scan at the time of peak plasma levels, and this scan was excluded from further analysis.

The PET scans were obtained immediately after the injection of 10 mCi of high-specific activity [$^{11}$C]raclopride (300–1600 Ci/mmol) through the use of a bolus plus infusion protocol with a head-dedicated PET camera (GEMS 2048–15B, General Electric Medical Systems, Milwaukee, Wis.). The methods employed here are identical to those described in previous studies of various antipsychotics and have been explained in detail before.[25] An estimate of the $D_2$ binding potential of [$^{11}$C]raclopride was obtained from a ratio of the striatal to cerebellar activity minus 1, at a time when tracer equilibrium was reached, i.e., 35 to 75 minutes after injection. In our laboratory, this method yields a within-subject scan-rescan standard deviation of 6% and is operationalized to yield a high interrater and intrarater reliability of greater than 0.95 as measured using intraclass correlation coefficients. As a pretreatment estimate of available $D_2$ receptors, we used an age-corrected baseline derived from a separate sample of 12 antipsychotic-naive patients with schizophrenia and 15 age-matched normal controls.[25,26]

At the time of the PET scans, blood was drawn for plasma quetiapine and prolactin level analysis 20 hours postdose and 1 and 2.5 hours following the next dose. The levels of quetiapine were determined by Keystone Analytical Laboratories (North Wales, Pa.) in heparinized plasma using a liquid chromatography/mass spectroscopy method. Prolactin levels were determined using a 2-site chemoluminometric immunoassay with a minimum detectable limit of 0.3 ng/mL and a coefficient of variance of 3.6% to 4.4% (ACS, Ciba-Corning Diagnostics, Corning, N.Y.).

### Statistical Analysis

Mean peak and trough occupancy values were assessed, and 2 outliers of the peak occupancy values were removed from further analyses. Outliers were defined as values differing more than 2 standard deviations from the mean. Peak and trough occupancy values were compared using a paired t test. To test whether $D_2$ occupancy at 4 weeks predicted treatment response at 4 weeks, we compared peak and trough occupancies of responders and nonresponders by means of an unpaired Student t test. To assess improvement in PANSS total scores and CGI scores, we used repeated-measures analysis of variance (ANOVA). Analyses were done using the last observation carried forward (LOCF) and separately with those who completed the 12-week protocol. To test whether quetiapine affected the outcome with regard to motor side effects, weight, and heart rate, we used repeated-measures ANOVA and paired-sample t tests for post hoc analyses. All tests were 2-tailed, with $p < .05$ as a threshold for statistical significance. Statistical analyses were implemented using SPSS, version 10.0 (SPSS, Inc., Chicago, Ill.).

## RESULTS

### $D_2$ Receptor Occupancy

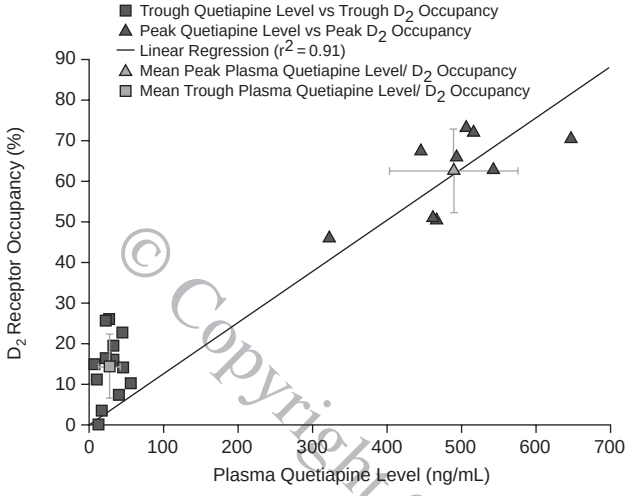
After removing 2 outliers, the peak striatal $D_2$ receptor occupancy ranged from 46.5% to 73.7%, with a mean of 62.0% ± 9.8%. At trough levels 18 to 20 hours later, the mean $D_2$ occupancy declined to 14.3% ± 7.9%. The difference between peak and trough brain $D_2$ occupancy levels was statistically significant ($t = –21.824$, $df = 9$, $p < .001$).

Nonresponders at week 4 had a mean peak $D_2$ occupancy of 60.3% ± 10.7%, and responders at week 4 had a mean peak $D_2$ occupancy of 65.9% ± 7.9%. This difference was not statistically significant ($t = –0.801$, $df = 8$, $p = .446$).

### Plasma Quetiapine and Prolactin Levels

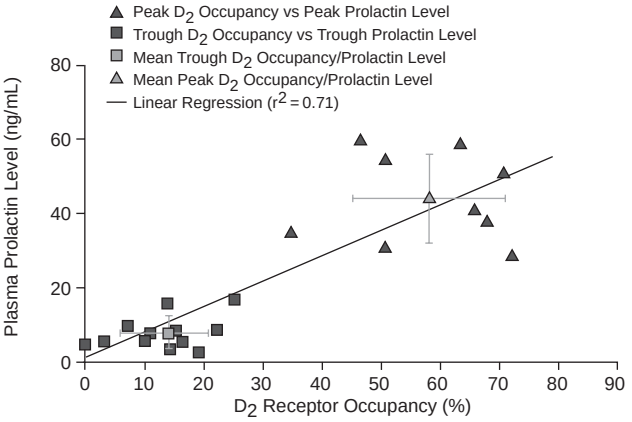
In parallel to the cyclic variation of brain receptor occupancy, plasma levels of quetiapine declined from a mean of 589 ± 530 ng/mL (range, 17–1454 ng/mL) 1 hour postdose and 493 ± 163 ng/mL (range, 184–827 ng/mL)

**Figure 1. $D_2$ Receptor Occupancy and Plasma Quetiapine Levels: Peak and Trough Values[a]**




[a]Nine data points are shown for peak drug level vs. peak $D_2$ occupancy. Of the 13 patients with 2 positron emission tomography (PET) scans, 2 outliers (peak $D_2$ occupancy value > 2 standard deviations from the mean) were excluded, 1 did not complete the PET scan at the time of peak plasma drug levels, and 1 had missing plasma level data. Peak drug levels were measured 2.5 hours after quetiapine administration.

**Figure 2. $D_2$ Receptor Occupancy and Plasma Prolactin Levels: Peak and Trough Values[a]**




[a]Nine data points are shown for peak $D_2$ occupancy vs. peak prolactin level. Of the 13 patients with 2 positron emission tomography (PET) scans, 2 outliers (peak $D_2$ occupancy value > 2 standard deviations from the mean) were excluded, 1 did not complete the PET scan at the time of peak plasma drug levels, and 1 had missing peak and trough plasma prolactin level data. Peak prolactin levels were measured 2.5 hours after quetiapine administration.

2.5 hours postdose to a mean trough level of 29 ± 15 ng/mL (range, 9–56 ng/mL) 20 hours postdose.

Prolactin levels showed the same cyclic variation and declined from a mean of 33.1 ± 27.6 µg/L 1 hour postdose and 48.5 ± 16.9 µg/L 2.5 hours postdose to 8.4 ± 4.2 µg/L 20 hours postdose. The difference between peak and trough values of plasma quetiapine and prolactin levels was highly significant ($p < .001$). At the time of peak plasma concentration, quetiapine and prolactin levels were significantly correlated ($r = 0.60$, $p < .05$).

All prolactin levels at baseline and after 12 weeks of quetiapine treatment were in the normal range, with the exception of a slightly elevated level in a neuroleptic-naive patient at baseline, which resolved at follow-up. All of these prolactin levels were obtained 12 hours after the previous dose. These levels did not significantly change after 12 weeks of treatment ($F = 1.636$, $df = 1$, $p = .242$).

We found a strong correlation between plasma drug levels and peak $D_2$ occupancy ($r = 0.84$, $p = .003$). This correlation was more pronounced when the entire range of data, i.e., peak and trough plasma quetiapine levels, as well as peak and trough $D_2$ occupancy, was considered ($r = 0.96$, $p < .001$; Figure 1). In addition, there was a pronounced correlation between prolactin levels (peak and trough) and $D_2$ occupancy (peak and trough) ($r = 0.86$, $p < .001$; Figure 2).

## Clinical Response

Table 1 summarizes the clinical response data with and without LOCF. Ten of the 14 patients completed the 12-week trial. Of the 10 completers, 5 were rated as "much improved" and 5, as "very much improved" on the CGI-I. Mean Clinical Global Impressions-Severity of Illness score declined from 4.6 ± 0.7 to 3.1 ± 0.9 ($F = 25.138$, $df = 6$, $p < .001$) in the LOCF population. On average, patients went from being "markedly ill" at baseline to "mildly ill" at the end of the study. The reduction in schizophrenic symptoms as measured by PANSS total score at baseline and at weeks 4 ($t = 4.026$, $df = 13$, $p < .001$) and 12 ($F = 22.527$, $df = 2$, $p < .001$) was statistically significant. Furthermore, the observed reductions in PANSS positive ($F = 41.629$, $df = 2$, $p < .001$), negative ($F = 19.973$, $df = 2$, $p < .001$), and general ($F = 24.577$, $df = 2$, $p < .001$) scores were statistically significant.

## Side Effects

All SAS, BAS, and AIMS scores (Table 1) showed negligible differences before and after treatment. There was no significant increase in scores on any of these scales as assessed by either the intent-to-treat or completer analysis.

At baseline, patients weighed a mean of 68.2 ± 11.7 kg (151.6 ± 26.0 lb) and had a mean body mass index (BMI) of 23.0 ± 2.7. During the study, the mean weight change among completers was 1.9 ± 1.9 kg (4.2 ± 4.2 lb) (median = 1.8 kg [4.0 lb]; range, –0.9 to 6.8 kg [–2.0 to 15.1 lb]) after 4 weeks ($t = –3.786$, $df = 13$, $p = .002$) and 4.2 ± 4.6 kg (9.3 ± 10.2 lb) (median = 4.6 kg [10.2 lb]; range, –3.7 to 13.6 kg [–8.2 to 30.2 lb]) after 12 weeks of treatment with quetiapine. This weight gain over 12 weeks was statistically significant ($F = 7.423$, $df = 2$,

Table 1. Psychopathology and Adverse Events During a 12-Week Open Trial With Quetiapine in First-Episode Schizophrenia[a]

| | Baseline | 4 Weeks | 12 Weeks | |
|---|---|---|---|---|
| Variable[b] | (N = 14) | (N = 14) | (N = 10)[c] | (N = 14)[d] |
| CGI-S | 4.6 ± 0.7 | 4.1 ± 0.7 | 2.7 ± 0.7 | 3.1 ± 0.9 |
| PANSS | | | | |
| Total | 82.6 ± 7.9 | 70.5 ± 13.2 | 54.5 ± 9.9 | 61.9 ± 16.4 |
| Positive | 22.5 ± 2.9 | 18.1 ± 4.0 | 13.1 ± 3.0 | 13.7 ± 3.6 |
| Negative | 22.1 ± 6.3 | 19.9 ± 7.5 | 14.6 ± 4.3 | 16.4 ± 7.1 |
| General | 37.9 ± 4.6 | 32.5 ± 5.0 | 26.8 ± 5.5 | 28.3 ± 7.1 |
| Parkinsonism | 1.9 ± 2.4 | 1.5 ± 2.0 | 1.7 ± 1.6 | 1.7 ± 1.4 |
| Akathisia | 1.0 ± 1.6 | 0.9 ± 1.5 | 0.7 ± 0.9 | 1.3 ± 2.5 |
| Tardive dyskinesia | 1.3 ± 1.6 | 1.4 ± 1.4 | 1.4 ± 2.8 | 1.9 ± 2.5 |
| Sedation | 0.1 ± 0.5 | 1.0 ± 1.0 | 0.4 ± 0.5 | 0.6 ± 0.8 |
| Supine heart rate/min | 86.0 ± 14.3 | 87.7 ± 17.2 | 91.2 ± 19.4 | 88.3 ± 19.9 |
| Weight (kg) | 68.2 ± 11.7 | 70.1 ± 12.3 | 74.7 ± 13.7 | 71.7 ± 12.9 |
| Body mass index | 23.0 ± 2.7 | 23.7 ± 2.6 | 25.0 ± 2.4 | 24.2 ± 2.4 |

[a]Values expressed as mean ± SD. Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale.
[b]Parkinsonism was measured with the Simpson-Angus Scale; akathisia, with the Barnes Akathisia Scale; tardive dyskinesia, with the Abnormal Involuntary Movement Scale; and sedation, with the UKU Side Effects Rating Scale.
[c]Includes only completers of 12 weeks.
[d]Includes all patients, with last observation carried forward.

p = .004). Mean BMI at 12 weeks increased significantly to 25.0 ± 2.4 (F = 6.842, df = 6, p < .001).

After 4 weeks of quetiapine treatment, 9 (64%) of 14 patients experienced mild-to-moderate sedation, and at endpoint, 4 (40%) of 10 patients reported mild sedation.

Mean supine heart rate at baseline was 86 beats per minute, and at endpoint, 91 beats per minute. We observed no significant change in resting heart rate during the trial (F = 0.545, df = 2, p = .589). Blood pressure and routine blood work, including complete blood cell count, liver function tests, fasting blood glucose, lipid profile, and thyroid-stimulating hormone, were within normal range at baseline and at follow-up.

## DISCUSSION

Our main finding was that 71% of our patients experiencing a first episode of psychosis responded to a 12-week open trial with the novel antipsychotic quetiapine despite only transiently high $D_2$ receptor blockade. We found that a transient peak $D_2$ receptor occupancy of 62% observed with [$^{11}$C]raclopride and PET shortly after the previous quetiapine dose was associated with substantial clinical improvement. These PET findings are consistent with recent in vivo neuroimaging reports which demonstrated that $D_2$ occupancy peaked with quetiapine administration in the range of 50% to 58% approximately 2 hours postdose.[4,5] After 12 to 14 hours, $D_2$ receptor occupancy had declined to 20% to 30%,[3,4] and it decreased to negligible occupancy 20 to 24 hours postdose. In parallel with the occupancy values observed in the brain, plasma quetiapine and prolactin levels also showed a relatively brief peak and declined to significantly lower trough levels. Both plasma prolactin and quetiapine levels were significantly correlated with $D_2$ occupancy in the entire range of peak and trough values.

Quetiapine was very well tolerated by most patients in our study, and the observed reductions in psychopathology as measured with PANSS total, positive, negative, and general symptom scores were statistically and clinically significant. It is well documented that quetiapine leads to minimal motor side effects, comparable to the rate seen with placebo.[8,9] In our 12-week study, we found no relevant EPS or other motor side effects. Our PET results provide a possible explanation for the low propensity of quetiapine to induce motor side effects: in contrast to the constant high $D_2$ blockade seen with most typical and some atypical neuroleptics,[27] the transient $D_2$ occupancy associated with quetiapine may translate into a more favorable motor side effect profile. This favorable profile may be due to the fact that the physiologic dopamine transmission in the striatum is left unimpaired for a substantial proportion of time each day.

We had hypothesized that a relationship would be detected between peak $D_2$ occupancy and clinical response. Our inability to predict clinical response on the basis of peak or trough $D_2$ receptor occupancy levels was most likely limited by the following factors: (1) a very small sample size, (2) restriction in range of peak $D_2$ occupancy, (3) restriction in range of clinical response, and (4) variability in time to response, which may be greater than 4 weeks in some individuals. It is also possible that the sample included a number of poor responders, as well as some individuals who may have improved for reasons unrelated to drug treatment. The inadvertent inclusion of such subjects would make it more difficult to detect such a relationship. Larger scale studies using a range of doses over a longer response interval would be necessary to determine if there is a minimum level of peak $D_2$ occupancy that is required to induce a response.

The exact timing of blood draws in relation to medication intake may have also influenced the results. When we compared prolactin levels at baseline (obtained in the morning 12–14 hours after the last dose) with those after 12 weeks of treatment with quetiapine, we found no significant elevation of prolactin. This finding is in line with earlier published analyses of plasma prolactin concentrations which revealed that quetiapine did not differ from placebo in its effect on plasma prolactin after up to 6 weeks of treatment.[8,10,28,29] A meta-analysis of plasma prolactin levels obtained during phase 2 trials with quetiapine confirmed that quetiapine did not cause sustained elevation of prolactin.[30] However, when we obtained blood samples after 4 weeks of treatment with quetiapine at the time of peak drug concentration in the blood, prolactin

levels were significantly higher than baseline values and clearly outside normal range. This finding confirms the transient nature of dopamine receptor blockade by quetiapine and is consistent with the view that prolactin elevation mirrors antagonism by quetiapine at extracerebral, tuberoinfundibular $D_2$ receptors.[31]

In summary, our findings suggest that quetiapine is an effective antipsychotic in patients with a first episode of schizophrenia and that its efficacy is probably due to its significant but only transiently high blockade of dopamine $D_2$ receptors. The transient nature of the $D_2$ receptor blockade may help to explain why quetiapine shows a very low propensity to induce motor side effects. It is not known whether there might be other clinical advantages (e.g., on cognition or negative symptoms) for antipsychotic medications that cause only transient $D_2$ blockade. Our findings lead us to question whether continuously high $D_2$ blockade is necessary for antipsychotic response in schizophrenia therapy. Future studies aimed at comparing the effects of "transiently high" versus "continuously high" $D_2$ occupancy are warranted.

*Drug names:* clozapine (Clozaril and others), lorazepam (Ativan and others), quetiapine (Seroquel), risperidone (Risperdal).



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