0271-0749/02/2204-0347/0
Journal of Clinical Psychopharmacology
Vol. 22, No. 4

Printed in U.S.A.

Therapeutic Tolerance and Rebound Psychosis During Quetiapine Maintenance Monotherapy in Patients With Schizophrenia and Schizoaffective Disorder

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A 3-year open-label study was conducted to determine the long-term safety and efficacy of quetiapine monotherapy in schizophrenia and schizoaffective disorder.

Twenty-three male outpatients previously stable but with inter-episode residual symptoms on classical antipsychotics and/or risperidone and who had complained of side effects were selected. To initiate quetiapine, patients were hospitalized for 13 days and then treated as outpatients. Quetiapine dosage was adjusted according to therapeutic effects.

Only five patients (21.7%) completed 77 to 96 weeks of the study. Initial dose was 261 ± 65.6 mg/day (mean ± S.D.) administered in divided doses, with an ending dose of 487 ± 209.6 mg/day, corresponding with an 86.6% dose increase over the course of the study. For those completing 12 weeks or less (n = 11), mean ending dose was 362 ± 184.8 mg/day a 38.7% dose increase over baseline. For those completing 25 weeks or more (n = 12), mean ending dose was 592 ± 178.2 mg/day, a 126.8% dose increase over baseline. Six of the seven patients who relapsed after being stabilized on quetiapine for at least three months met criteria for supersensitivity psychosis (SSP).

Therapeutic tolerance and rebound psychosis were found to develop with quetiapine in male patients with a history of chronic treatment with classical antipsychotics. Seeman and Tallerico[3] have proposed pharmacologic explanations for quetiapine and clozapine drug-induced rebound phenomena. (J Clin Psychopharmacol 2002;22:347–352)

Quetiapine is a dibenzothiapine derivative that interacts with dopamine D_1 and D_2, serotonin $5HT_{1A}$, $5HT_{2A}$, $5HT_{2C}$ and $5HT_6$, histamine H_1 and α_1, α_{2A}, and α_{2C} adrenergic receptors.[1,2] Quetiapine was recently found to bind loosely and/or transiently to the D_2 receptor,[3,4] and it is easily displaced from the D_2 receptor, even by dopamine itself.[3] Relative to other atypical antipsychotics, including clozapine, risperidone and olanzapine, it occupies fewer serotonin receptors and does not saturate these receptors even at higher therapeutic doses.[5] However, quetiapine possesses a higher $5HT_{2A}$, $5HT_{2C}$, and α_{2C} relative to D_2 occupancy, which is believed to account for its unique antipsychotic properties and low extrapyramidal symptom liability.[1,3]

Six and eight-week clinical trials in schizophrenia have demonstrated quetiapine's efficacy for treatment of psychosis.[6–10] A meta-analysis found quetiapine to be more effective than placebo and equally effective to haloperidol on treatment of global schizophrenic symptomatology.[11] In contrast, others found that while quetiapine "appears to be effective in treating the positive symptoms of schizophrenia, the most robust effects were noted in a less ill population."[1] The longest trial fully published to date demonstrates the effectiveness of quetiapine in psychosis for 12 weeks in elderly subjects, who mostly had psychosis associated with dementia (59%) or Parkinson's disease (11%) while only 19% had schizophrenia.[12]

Several longer-term trials of quetiapine have been published as abstracts at scientific meetings. Kasper found sustained response for both positive and negative symptoms in 674 patients (66% male) followed for up to 130 weeks with a mean total quetiapine exposure of 325.2 days (46.5 weeks).[13] The actual total number of patients

Received February 1, 2001; accepted after revision October 1, 2001.
Presented in part at the American College of Neuropsychopharmacology (ACNP) Annual Meeting, Acapulco, Mexico, December 12–16, 1999 and the American Psychiatric Association (APA) Annual Meeting, Chicago, IL, May 15, 2000.
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DOI: 10.1097/01.jcp.0000024578.36017.2b

completing the study period, rate of dropouts, and survival analysis was not presented. Purdon et al. found equivocal outcome in 13 patients treated with quetiapine on the Positive and Negative Syndrome Scale (PANSS) positive cluster as compared to a comparison group of 12 treated with haloperidol in a 6-month trial.[14] These same patients did show greater improvement in the PANSS negative symptom cluster. Finally, a review of all published and unpublished data was conducted by Srisurapanont et al. for the Cochrane database of systematic reviews.[15] Their review of 42 studies found dropout rates between 36 and 64% and concluded that more trials of all duration are necessary regarding the use of quetiapine monotherapy in schizophrenia and similar illnesses.[15]

Maintenance studies in schizophrenia demonstrate clear advantages for treatment with antipsychotics compared with placebo. After one year, 26% of patients receiving classical antipsychotics relapse versus 69% on placebo.[16] The limited data available for the atypical antipsychotics clozapine, olanzapine, and risperidone indicates efficacy as maintenance pharmacotherapy in schizophrenia.[17] The current study was undertaken to explore long-term safety and efficacy of quetiapine.

Methods

Study design

Twenty-five stable male outpatients with schizophrenia or schizoaffective disorder were selected from 350 outpatients attending the specialized follow-up unit (SFU) of the Allan Memorial Institute, to enter a 13-day bioequivalence trial of quetiapine (5077IL/0072). The patients selected were stable but had inter-episode residual symptoms and expressed to have their antipsychotic medication changed because of side effects and discomfort associated with their current antipsychotic (classical antipsychotic and/or risperidone). All 25 subjects who completed this trial were candidates to enter a 3-year open-label extension study of quetiapine maintenance (5077IL/0051). Twenty-three out of 25 patients (92%) agreed to participate. The first patient entered the study (5077IL/0051) on February 25, 1997; the study terminated October 1, 1998; four patients were followed up to 12 additional weeks. The study was approved by the Research Ethics Board. Written informed consent was obtained from all patients on two occasions, first for the 13-day bioequivalence study (5077IL/ 0072) that originated from Zeneca U.S., and second for the 3-year open label extension (5077IL/0051). After the 13-day study, patients were seen as outpatients at weeks 1, 2, and 4, and monthly thereafter.

During the trial, the same research nurse and research assistant gave the hospital appointments, supported patients, assured compliance with appointments with the psychiatrist, and confirmed compliance with medication through the pill-count technique. Adverse events, drug dispensing, and pill count were recorded at each visit to determine compliance. During each visit, a psychiatric examination was performed by a psychiatrist (L.B. or G.C.), who had experience with clinical trials, and a quetiapine dose was determined in accordance with the patients' symptoms and administered in a BID regimen. PRN concomitant medications included chloral hydrate and procyclidine (an anticholinergic antiparkinsonian).

Inclusion and exclusion criteria

Inclusion criteria for study 5077IL/0072 included: male gender, age 18 to 60 inclusive, weight from 64 to 100 kg, history of favorable antipsychotic treatment during the past year, DSM-IV diagnosis of schizophrenia or schizoaffective disorder, and ability to give informed consent. Patients had to consent to hospitalization in a medical investigational unit for 13 days for the bioequivalence study. Exclusion criteria for 5077IL/0072 included: another DSM-IV axis I disorder; history of seizure, head trauma, or brain disease; positive drug urine screening test; positive blood test for HIV or HbsAg; evidence of chronic or severe disease (e.g. renal or hepatic impairment, or cancer); a WBC or neutrophil count below normal range; clinically significant deviations from normal on physical examination or ECG; any acute nonpsychiatric illness within 2 weeks of entering the trial; current (within 2 months) treatment with clozapine or history of clozapine nonresponsiveness; history of clozapine or drug-induced agranulocytosis; and significant history of asthma, allergic skin rash or other allergic conditions. Patients entering the open label extension (5077IL/0051), had to fully complete the 13-day bioequivalence trial and begin the open label extension within 5 days of its completion. A second written informed consent was also obtained at this time.

Patient characteristics

Of the 23 outpatients enrolled, 13 had a DSM-IV diagnosis of paranoid schizophrenia, 4 had residual schizophrenia, and 6 had schizoaffective disorder. Mean $\pm$ S.D. age was 40.1 $\pm$ 10.2 years (range 22–59 years). Patients had a mean 12.6 $\pm$ 8.1 years of treatment prior to study initiation (range 1–33 years). Mean age of first treatment received was 27.2 $\pm$ 5.6 years, while mean age of first hospitalization was 27.9 $\pm$ 5.8 years. Mean time elapsed since last hospitalization was 5.6 $\pm$ 7.3 years (Table 1). None of the patients had a trial of clozapine prior to study initiation and none were considered treatment resistant. At study entry, 14/23 (61%) met Schooler and Kane criteria for tardive dyskinesia,[18] a rate of TD consistent with the authors' previous studies in this long-term treated population.[19,20]

All patients were previously stable on an equivalence

TABLE 1. Patient characteristics (n = 23)

Characteristic	Mean	Standard Deviation	Range
Age (years)	40.1	10.2	22–59
Age first received treatment (years)	27.2	5.6	18–39
Years of antipsychotic drug treatment prior to study initiation[#]	12.6	8.1	1–33
Risperidone treatment only (n = 6)	2.2	0.8	0.58–2.8
Risperidone + classical antipsychotic (n = 4)	1.4	1.7	0.5–4
Classical antipsychotic only (n = 13)[‡]	9.6	6.6	1–23
Total classical antipsychotic (n = 23)[†]	12.0	8.0	1–30.2
Number of hospitalizations	3.3	2.9	0–9
Age of first hospitalization (years) (n = 21)*	27.9	5.8	18–39
Time since last hospitalized (years) (n = 21)*	5.6	7.3	0.67–31.1
Time stable on current medications (years)	2.2	2.2	0.5–12.1

[#]Only classical antipsychotics and/or risperidone were previously used in these patients; [‡]Never received risperidone; [†]Excludes time on risperidone treatment only and time on combination risperidone + classical antipsychotics; *The two patients who were never hospitalized were excluded from these two data sets.

of 9.2 ± 8.4 mg/day haloperidol units (where 1 mg of haloperidol = 50 mg of chlorpromazine)[21] of classical antipsychotics (n = 17), and/or 6.0 ± 4.0 mg/day of risperidone (n = 10). The mean duration of stability on current treatment (with only minor dose variations either upwards or downwards) was 2.1 ± 2.3 years. Nineteen patients were receiving procyclidine (mean dose ± SD 15.1 ± 8.2 mg/day, range 5–30 mg/day), which was reduced and discontinued over 2 weeks in patients (n = 10) who no longer needed it. Ten patients received other medications; 6 received sodium valproate (1062.5 ± 641.0 mg/day), 4 received clonazepam (0.81 ± 0.55 mg/day), and 4 received diazepam (11.9 ± 3.8 mg/day), all of which were tapered prior to study initiation. To evaluate for the presence of supersensitivity psychosis the Chouinard research diagnostic criteria were used.[22]

Results

Most patients did not remain on quetiapine after stabilization (Table 2). At 1 year, 30% remained on quetiapine with five (22%) completing 77 to 96 weeks of treatment. The study was terminated as planned by the sponsor after the approval of the medication by health authorities was obtained December 2, 1997. The daily dose of most patients initially stabilized had to be continually increased to control reemergent psychotic symptoms. The mean daily ending dose for all subjects was 487 ± 209.5 mg/day, corresponding to an 86.6% dose increase over the course of the study. For those completing 12 weeks or less, the mean ending dose was 362 ± 184.8 mg/day (n = 11), a 38.7% dose increase over baseline, while for those completing 25 weeks or more (n = 12), it was 592 ± 178.2 mg/day, a 126.8% dose increase over baseline. For subjects withdrawn after 25 weeks (n = 7), mean ending dose was 614 ± 167.6 mg/day, a 135.2% increase from baseline over the course of the study. As far as the metabolism of quetiapine is concerned, there is no evidence of hepatic enzyme induction of its own metabolism over its long-term use.

For two of the seven patients who were discontinued for protocol noncompliance, noncompliance was because of the inability of quetiapine to control psychosis at a dose which when increased led to intolerable side effects: feeling slowed down (n = 1) and increased heart rate (n = 1).

Patients with schizoaffective disorder who discontinued sodium valproate prior to study initiation had outcomes similar to the other subjects. Their mean ending

TABLE 2. Mean daily quetiapine dose requirements of patients remaining in the study by week

Week(s) of treatment	Number of patients remaining in study (%)	Quetiapine daily dose	
		Mean (mg/day)	Standard Deviation
0	23 (100)	261	65.6
2	19 (83)	395	112.9
8	15 (65)	433	117.5
12	14 (61)	471	132.6
16	12 (52)	542	144.3
30	11 (48)	591	164.0
52	7 (30)	571	205.8
77–96	5 (22)	560	207.4

quetiapine dose was 600 ± 209.8 mg/day. Two out of six (33%) completed the trial while the other four remained in the study for a mean of 41.5 ± 32.6 weeks. As a group, patients prescribed any prestudy medication other than antipsychotics or anticholinergics (n = 10) also had similar outcomes. They remained in the study for a mean of 36.3 ± 29.5 weeks and had a mean ending quetiapine dose of 530 ± 235.9 mg/day. Patients who had their central anticholinergic discontinued (n = 10) also did well. All five (50%) who completed the study were among this group, while the other 5 remained in the study a mean of 19.6 ± 24.7 weeks. Thus the discontinuation of anticholinergics, sodium valproate, and/or benzodiazepines did not predict a worse outcome and was not associated with evidence of cholinergic rebound or withdrawal anxiety upon gradual discontinuation, prior to study initiation.

Patients who relapsed were subsequently stabilized on other antipsychotics including risperidone (n = 7), haloperidol (n = 5), olanzapine (n = 3), fluspirilene (n = 3), and trifluoperazine (n = 1) (note that two patients were stabilized on two antipsychotics). Six patients required hospitalization due to psychotic relapse. Concomitant psychotropic medications required during the trial included procyclidine for nine patients (mean daily dose 11.1 ± 4.7 mg/day; mean length of treatment 86.8 ± 92.7 days, median 42 days), while five required chloral hydrate (mean daily dose 900.0 ± 223.6 mg/day; mean length of treatment 55.4 ± 120.0 days, median 2 days), and five received benzodiazepines including lorazepam, diazepam, and clonazepam (mean daily dose in diazepam equivalents 15 ± 14.1 mg/day; mean length of treatment 11.2 ± 17.7 days, median 1 day). Finally, one patient, who ultimately completed 14 months of the trial, received one dose of haloperidol 5 mg and diphenhydramine 50 mg during a minor relapse. To date, only 1/23 (4.3%) of the original cohort remains on quetiapine. This patient remains unstable, but refuses medication changes.

Another method to examine for therapeutic drug tolerance is through the concept of supersensitivity psychosis (SSP).[22] According to strict criteria for SSP, patients must be stabilized on medication for at least 12 weeks. Of the seven patients stabilized on quetiapine at least 12 weeks who later relapsed, six met criteria for SSP. The SSP criteria met by the patients included four who had 1) reappearance of psychotic symptoms upon decrease or discontinuation of medication (within 6 weeks) and 2) psychotic symptoms upon decrease of medication were of a greater severity; and two patients had 1) greater frequency of relapse (acute psychotic exacerbation) during continuous treatment with antipsychotics, and 2) tolerance to the antipsychotic effect of the medication (overall increase in dose by 20% or more).

Discussion

Monotherapy maintenance studies with atypical antipsychotics have demonstrated prevention of relapse and hospitalization. Clozapine has been shown to reduce 1-year hospitalization rates when compared with the year prior to clozapine treatment (mean of 1.3 versus 0.4 hospitalizations).[24] Clozapine also reduced hospitalization rates compared with usual care over a 1-year follow up (17% versus 41%).[25] Reduction in hospital days from a mean of 106 to 85 days was demonstrated for 27 patients treated with risperidone for 1 year as compared with the previous year of treatment with usual antipsychotics.[26] Similarly, hospital admissions were decreased by 60.3% in a retrospective cohort study of all patients in Saskatchewan when comparing a mean of 10 months prior and 10 months after risperidone initiation.[27] Olanzapine has also been shown to reduce hospitalization rates when compared to placebo (28.6% versus 69.9%),[28] haloperidol (19.7% versus 28.0%),[29] and risperidone (12.1% versus 32.3%).[30] In our study, 6 of the 23 patients (26.1%) who had a relapse required hospitalization, which is comparable with rates reported with olanzapine and risperidone but higher than rates with clozapine. To better characterize these six patients, the authors looked at time of relapse and prior hospitalizations and found that they had not been hospitalized for 8.7 ± 11.7 (range 0.9–31.1) years, which is greater than the mean of 5.6 ± 7.3 years for the entire sample. The data suggest that those patients who relapsed and required hospitalization had previously responded to classical antipsychotics and/or risperidone; this could be explained by the comparatively weak dopamine D_2 receptor antagonist activity of quetiapine.[3,4] The remaining patients who relapsed were managed with increased outpatient visits.

Megna and Dewan[31] demonstrated a 53% (10/19 patients) response rate over 14 months of follow-up, in a naturalistic study of risperidone maintenance treatment for outpatients with severe mental illness. They note that only four out of nine nonresponders relapsed due to psychotic exacerbation, but unlike our study, all drop outs occurred prior to 3 months of treatment. However, 30% (3/10) of the responders required augmentation of risperidone with typical antipsychotics to maintain treatment response. Tran et al.[30] demonstrated that among patients who responded at 8 weeks, 87.9% of olanzapine responders and 67.7% of risperidone responders maintained response at 28 weeks as defined by no worsening in PANSS total score of ≥20%. Brier et al.[24] noted a decrease in the number of relapses from 2.0 ± 1.6 in the year prior to clozapine treatment compared with 0.3 ± 0.7 in the first year of clozapine (n = 21). Similarly, days relapsed decreased from 42.6 ± 28.0 to 4.9 ± 11.0.[24] Finally, McElroy et al.[32]

conducted an open-label follow-up study with clozapine. Using primary treating clinician ratings, they demonstrated in patients with schizophrenia and schizoaffective disorder that 37.5% (24/64) had none or minimal improvement while 62.5% (40/64) had moderate or marked improvement. Mean length of follow-up was 23.3 ± 17.9 months for patients with schizophrenia (n = 39) and 34.7 ± 44.8 months for patients with schizoaffective disorder (n = 25).[32] In the present trial which included only male patients who had a mean 12.6 ± 8.1 years of prior antipsychotic treatment, only 5 of 23 patients (21.7%) completed 77 to 96 weeks of the study. Thus, response rate was lower than in previous maintenance studies with other atypical antipsychotics. Four explanations can be put forward: 1) men with schizophrenia are less likely to respond to antipsychotics than women,[33,34] in the present trial only men were included; 2) long history of classical antipsychotic drug treatment[35,36] (mean of 12.6 ± 8.1 years of previous drug treatment) which tends to increase TD and SSP; 3) receptor binding profile which tends to favor therapeutic drug tolerance or supersensitivity psychosis[3,4]; 4) small sample size of the present clinical trial without a comparator.

In this study, the high proportion of those with baseline TD who relapsed, as defined by an inability to complete the trial, suggests that a long history of previous classical antipsychotic exposure and TD itself may predispose to rebound psychosis. During the trial 11 out of 14 (78.6%) patients with baseline TD relapsed.

Data on weight changes at both the beginning and end of the study were available for 16 patients. Overall, there was no change in these 16 patients' mean Body Mass Index (BMI) from 25.4 ± 3.6 (range 20.9–30.8) at baseline, to 25.2 ± 3.8 at follow-up, (paired t-test(15) = .47, $p = 0.64$). However, six patients gained 4.4 ± 3.4 kg (range 0.8–9.0 kg; $t(5) = 3.25$, $p < 0.05$), nine patients lost 3.92 ± 2.82 kg (range 0.9–8.0 kg; $t(8) = 4.15$, $p < 0.05$), and one had no change in weight. Our BMI and weight change results are in agreement with those of other quetiapine clinical trials.[23] In this respect, our sample was not any different.

Therapeutic tolerance, rebound psychosis, or SSP was found to develop with quetiapine. This is understandable given Seeman and Tallerico's[3] finding that quetiapine binds loosely to the D_2 receptor. Multiple daily doses of quetiapine may initially enhance D_2 receptor downregulation but then cause increased receptor density as the cell tries to compensate for this loose and short D_2 occupancy. Giving the drug only once daily may reduce this phenomenon as the cell would then likely produce less dopamine receptors due to a reduced number of peak levels in antipsychotic concentration, and thus it would be less prone to tolerance and rebound; however, one would still expect clinical relapse earlier for medications that bind loosely.[37] The short half-life of quetiapine is also an intrinsic drug risk factor for rebound psychosis with quetiapine treatment.[35,36] However, as it blocks receptors other than D_2,including D_1, $5HT_{1A}$, $5HT_{2A}$, $5HT_{2C}$, $5HT_6$, α_1, and α_{2C}, all of which are currently believed to play a role in schizophrenia treatment, quetiapine remains a promising option for combination antipsychotic polytherapy in monotherapy resistant psychotic patients.[38]

Clozapine also has this loose binding property at the D_2 receptor, which may explain why rebound psychosis is seen upon abrupt discontinuation of clozapine.[39–43] The short half-life of clozapine and greater affinity for mesolimbic than striatal dopamine receptors make rebound psychosis more likely upon clozapine withdrawal.[35,44] Rebound psychosis and SSP has also been observed in three patients upon sudden withdrawal of olanzapine.[45] Clozapine and olanzapine differ from quetiapine in binding to a higher percentage of $5HT_{2A}$ receptors than quetiapine.[5] According to Kapur et al.,[46] serotonin may modulate D_2 occupancy to protect against dopamine surges, which would displace loosely bound dopamine molecules. This protection would not occur with quetiapine because of its lower $5HT_{2A}$ occupancy, making it particularly vulnerable to displacement from the D_2 receptor. Rebound and therapeutic tolerance would therefore occur with quetiapine. As discussed earlier, these phenomena would be easier to observe with quetiapine and clozapine than with other atypical and classical antipsychotics.

Limitations of this study include that it is an open-label noncomparative trial involving only male patients most of whom had been chronically treated with classical antipsychotics. Thus, it is possible that our population was particularly vulnerable to rebound psychosis, and therapeutic tolerance. Long-term antipsychotic studies in monotherapy conditions (without antiepileptics or continuous benzodiazepine therapy) are necessary to assess the potential therapeutic drug tolerance of the new antipsychotics.

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