Rapid Versus Conventional Initiation of Quetiapine in the Treatment of Schizophrenia: A Randomized, Parallel-Group Trial

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Objectives: The primary objective of this study was to compare the safety and tolerability of a rapid initiation of quetiapine with the conventional initiation approved by the U.S. Food and Drug Administration (FDA). The secondary objectives included assessment of the efficacy of a rapid initiation of quetiapine compared with a conventional initiation approved by the FDA.

Method: Patients with acute schizophrenia were randomly assigned in a 3:1 ratio to the rapid-initiation group (200 mg on day 1, 400 mg on day 2, 600 mg on day 3, and 800 mg on day 4) or to the conventional-initiation group (50 mg on day 1, 100 mg on day 2, and increased in 100 mg/day increments to reach 400 mg on day 5). The tolerability measures were Barnes Akathisia Scale (BAS) and Simpson-Angus Scale (SAS) as well as all adverse events at day 1, 2, 3, 4, 5, 6, and 7 and at day 14. Standard efficacy measures were administered at baseline, day 1, day 4, day 5, day 7, and day 14. These measures consisted of the Positive and Negative Syndrome Scale (PANSS), PANSS-Excited Component (EC), and Clinical Global Impressions-Severity of Illness (CGI-S) scale.

Results: Forty patients were randomly assigned to treatment. The mean (SD) dose of quetiapine at study end point was 763.3 (106.6) and 600.0 (249.4) mg/day in the rapid-initiation group and conventional-initiation group, respectively. The most common side effects were sedation and dizziness, with no significant differences in frequency between groups. Only 2/30 patients from the rapid-initiation group discontinued treatment due to an adverse event (both for sedation), and 1/10 patients from the conventional-initiation group discontinued before receiving quetiapine. Neither serious adverse events nor differences between groups in vital signs, laboratory assessments, ECG measures, or weight changes were reported. Rapid initiation of quetiapine was generally well-tolerated and was associated with a faster onset of action than conventional initiation as measured by improvement in psychotic symptoms at days 4 and 5.

Conclusion: This study may offer preliminary evidence for tolerability and effectiveness in rapid dose initiation of quetiapine in the treatment of schizophrenia.

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Patients with acute schizophrenia would benefit from rapid and effective initiation of their antipsychotic medication.[1] However, the challenge facing clinicians is to ultimately achieve a balance between an effective dose and minimizing associated side effects. The atypical antipsychotics risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole are recommended as first-line treatment in schizophrenia.[2]

Quetiapine fumarate is a dibenzothiazapine derivative that has demonstrated first-line efficacy in a broad symptom range. Three large, placebo-controlled, 6-week, randomized trials in patients with acute schizophrenia found that quetiapine consistently improved scores on the Brief Psychiatric Rating Scale (BPRS)[3] and the Clinical Global Impressions (CGI)[4] scale and offered improved response

to therapy.[5–7] Importantly, meta-analysis of these trials showed that quetiapine improved scores in the BPRS and Scale for Assessment of Negative Symptoms (SANS) within 1 week versus placebo.[8]

The onset of improved efficacy during the first week of treatment was demonstrated in a 6-week, randomized, double-blind trial that found that quetiapine was associated with a significantly higher response rate than chlorpromazine (65% vs. 52%; p = .04) in patients with schizophrenia or schizophreniform disorder.[9] After 1 week, approximately 60% of patients in each group were rated as being "much improved" or "very much improved" on the CGI scale. More recently, a naturalistic, noncomparative study demonstrated that, in patients with acute aggressive psychosis, quetiapine treatment can lead to a significant reduction in the severity of aggressive symptoms against others within 24 hours ($p < .05$ vs. baseline).[10]

Quetiapine has a distinctive safety and tolerability profile that features an incidence of extrapyramidal symptoms (EPS) similar to placebo (7.3% vs. 11.7%, respectively) across the recommended dose range.[11] Importantly, there is no evidence of cumulative EPS.[5] A large, open-label, long-term extension trial showed that the incidence of EPS in patients receiving quetiapine was 7.1%, similar to the level reported in placebo-controlled trials in patients with schizophrenia.[12] These data contrast with the EPS profile of other atypical antipsychotics, such as olanzapine, risperidone, and ziprasidone, that are associated with dose-related increases in EPS.[13–15] Furthermore, quetiapine does not increase prolactin levels in patients with schizophrenia, a side effect that can lead to distressing hormonal side effects such as amenorrhoea, galactorrhoea, and sexual dysfunction.[5,16] Weight gain with quetiapine is generally limited to the early weeks of treatment, and mean weight gain at 6 weeks has been estimated at 2.18 kg.[17,18] In patients receiving quetiapine for ≥ 6 months, quetiapine demonstrated a favorable weight profile across all body mass index categories.[18]

Current prescribing information states that quetiapine can be initiated up to 300 to 400 mg by day 4, with subsequent dose adjustment up to 800 mg/day.[19] However, as hospitalized patients with an acute exacerbation of schizophrenia may require more rapid resolution of their symptoms, the accelerated initiation of quetiapine may prove beneficial. Indeed, because of the relatively low binding potency of quetiapine to dopamine D_2 receptors[20] (a characteristic that probably results in low incidence of EPS or prolactin elevation), the attainment of a therapeutically active dose of quetiapine in the acute setting could take longer than is required with the current initiation regimen.

The primary objective of this study was to compare the safety and tolerability of a rapid initiation of quetiapine with the conventional initiation approved by the U.S. Food and Drug Administration (FDA). The secondary objectives included assessment of the efficacy of a rapid initiation of quetiapine compared with a conventional initiation approved by the FDA.

METHOD

Patients

All patients were screened according to the Structured Clinical Interview, DSM-IV Axis I Disorders-Clinician Version (SCID-I-CV).[21] Patients were eligible for inclusion if they had a documented clinical diagnosis of schizophrenia or schizoaffective disorder according to the DSM-IV criteria.[22] All patients were hospitalized, had a CGI score ≥ 4, were 18 to 65 years old, and provided written informed consent before participating in the study.

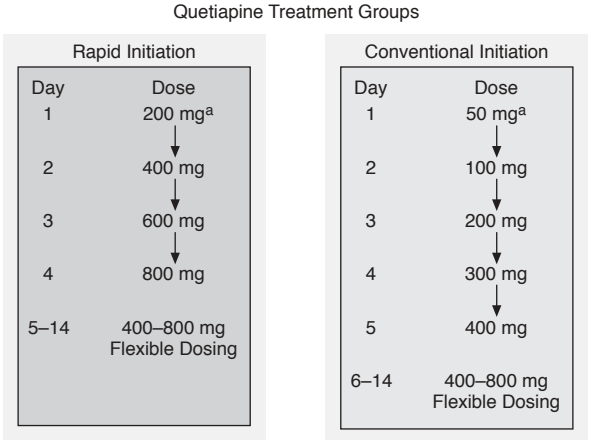
Exclusion criteria were treatment with depot antipsychotic medications within 1 dosing interval before day 1, pregnancy or breastfeeding (any women of childbearing potential were required to use reliable contraceptives), any Axis I disorder other than schizophrenia or schizoaffective disorder, any medical condition that precluded treatment with an investigational drug, prior treatment with quetiapine that was discontinued due to adverse events or lack of efficacy, treatment with clozapine within 28 days of random assignment, or known arrhythmia or QTc > 450 msec. Patients could be discontinued at any time and the reason(s) for discontinuation recorded. The study protocol was approved by an institutional review board of Kangnam St. Mary's Hospital. The study was conducted from February 2, 2004, through August 4, 2004.

Study Medication

All eligible patients were randomly assigned in a 3:1 ratio to the quetiapine rapid- or conventional-initiation groups. In the quetiapine rapid-initiation group, patients received 200 mg on day 1, 400 mg on day 2, 600 mg on day 3, and 800 mg on day 4. In the quetiapine conventional-initiation group, patients received 50 mg on day 1, 100 mg on day 2, 200 mg on day 3, 300 mg on day 4, and 400 mg on day 5. (See Figure 1.) In each group, quetiapine was administered as a single dose on day 1 and then as equal twice-daily doses thereafter. In each group, the dose of quetiapine could be adjusted, at the discretion of the investigator, according to the patient's clinical response. This flexible dosing (400–800 mg/day) started on day 5 for patients in the rapid-initiation group and day 6 in the conventional-initiation group.

The use of any antipsychotic drug other than quetiapine was not permitted during the study, and prior oral antipsychotics were withdrawn 3 days before initiating quetiapine. Antidepressants, benzodiazepines, and mood stabilizers taken at stable doses for > 4 weeks before study entry were permitted at the discretion of the investigator. Rescue benzodiazepine (≤ 4 mg/day) and antiparkinso-

Figure 1. Quetiapine Initiation Schedules



[a]Single dose on day 1 only.

Table 1. Baseline Characteristics in the Quetiapine Rapid-Initiation Group and in the Conventional-Initiation Group

Characteristic	Rapid (N = 30)	Conventional (N = 10)
Gender, N (%)		
Male	14 (46.7)	5 (50.0)
Female	16 (53.3)	5 (50.0)
Age, y		
Mean (SD)	36.7 (11.9)	35.8 (9.8)
Range	18–62	21–48
Ethnicity, N (%)		
Asian (Korean only)	30 (100)	10 (100)
Family history of schizophrenia, N (%)	4 (13.3)	1 (10.0)
Duration of schizophrenia, mean, y	6.0	5.8
Number of hospitalizations, mean	1.9	2.5
Duration of previous antipsychotic treatment, mean, y	5.9	4.9
Psychopathologic score, mean (SD)		
PANSS total	103.2 (23.2)	104.6 (10.6)
PANSS-EC	19.8 (6.0)	18.3 (3.7)
CGI-S	5.3 (1.0)	4.9 (0.8)
Weight, mean (SD), kg	60.1 (12.8)	64.1 (7.9)

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS-EC = Positive and Negative Syndrome Scale-Excitatory Component.

nian medication were permitted for acute EPS but not for prophylactic use.

Assessments

Primary end points (tolerability). Recording of adverse events began after the first dose of quetiapine was administered. Extrapyramidal symptoms were assessed using the Simpson-Angus Scale (SAS)[23] and the Barnes Akathisia Scale (BAS)[24] on days 1 through 7, and at day 14. Vital signs, including blood pressure (sitting and standing), body temperature, and heart rate were collected at screening and during each study visit. Weight, electrocardiogram (ECG) and assessments of hematology and clinical chemistry were performed at screening and at day 14.

Secondary end points (efficacy). The primary efficacy measure was total score of the Positive and Negative Syndrome Scale (PANSS)[25] recorded at days 1 (baseline), 4, 5, 7, and 14. In order to assess the efficacy of rapid-initiation quetiapine on the excitation of psychopathology, mean changes in PANSS-Excitatory Component (EC) score from baseline at each period were also assessed at these study visits.[26] The CGI[4] score was recorded at screening and on days 1, 4, 5, 7, and 14.

Statistical Analysis

The target population size for this trial was 40 patients. Descriptive statistics and χ^2 tests were performed for between-group differences in the frequencies of side effects. Analysis of covariance (ANCOVA) was used to compare mean changes in the laboratory measures between initiation groups. The safety population included patients who had taken at least 1 dose of study medication and had undergone at least 1 postdosing assessment. Relative risk and 95% CIs were calculated where appropriate.

Repeated-measures analysis of variance (ANOVA) was performed on PANSS and CGI-Severity of Illness (CGI-S) scores to test for treatment effects throughout the study. ANCOVA was performed on change from baseline PANSS-EC scores at each postbaseline assessment using baseline characteristics as covariates. For PANSS total, PANSS-EC, and CGI-S scores, each patient's percentage change from baseline was also analyzed. The intent-to-treat population was analyzed using last-observation-carried-forward data.

All statistical tests were 2-tailed, and a p value of $< .05$ was considered proof of statistical significance. Statistical analysis was performed using the SPSS software version 10.0 for Windows (SPSS, Inc., Chicago, Ill.) program.

RESULTS

Baseline Characteristics

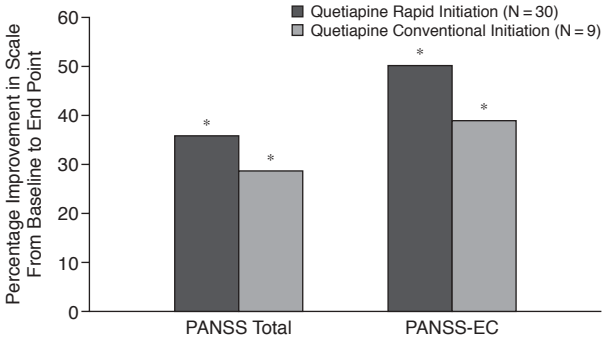
A total of 40 Asian patients were enrolled into the study (30 to the rapid-initiation group and 10 to the conventional-initiation group). All the patients were diagnosed with schizophrenia, and the 2 populations were well-balanced in terms of baseline characteristics (Table 1). Prior to study entry, patients were taking risperidone (N = 4), olanzapine (N = 4), quetiapine (N = 2), or haloperidol (N = 2). The remaining patients were not receiving any antipsychotic treatment when they entered the study. In the rapid-initiation group, 28 (93.3%) completed the study compared with 9 (90%) in the conventional-initiation group. One patient in the conventional-initiation group withdrew consent on day 1 and did not receive any study medication.

Table 2. Mean (SD) SAS and BAS Scores for Patients Receiving Quetiapine in the Rapid-Initiation Group and in the Conventional-Initiation Group[a]

	SAS Score, Mean (SD)		BAS Score, Mean (SD)	
Day	Rapid (N = 30)	Conventional (N = 9)	Rapid (N = 30)	Conventional (N = 9)
1	0.17 (0.91)	0.78 (1.72)	0.50 (2.24)	0 (…)
2	0.10 (0.55)	0.67 (1.32)	0.33 (1.49)	0 (…)
3	0 (…)	0.22 (0.67)	0.40 (1.52)	0 (…)
4	0.30 (1.64)	0.22 (0.67)	0.47 (1.63)	0 (…)
5	0.28[b] (1.49)	0.22 (0.67)	0.62 (1.52)	0 (…)
6	0.24[b] (1.12)	0.11 (0.33)	0.76 (2.05)	0 (…)
7	0.17[b] (0.76)	0.11 (0.33)	0.79 (1.63)	0 (…)
14	0.14[c] (0.76)	0.11 (0.33)	0.29 (1.05)	0 (…)

[a]No significant differences between treatment groups.
[b]N = 29.
[c]N = 28.
Abbreviations: BAS = Barnes Akathisia Scale, SAS = Simpson-Angus Scale.
Symbol: … = not applicable.

Figure 2. Percentage Improvement From Baseline to End Point PANSS Total and PANSS-EC Scores in Quetiapine Initiation Groups



*p < .001 vs. baseline.
Abbreviation: PANSS-EC = Positive and Negative Syndrome Scale-Excitatory Component.

Table 3. Frequencies of Adverse Events in the Study[a]

Adverse event, N (%)	Rapid (N = 30)	Conventional (N = 9)	Relative Risk	95% Confidence Intervals
Sedation	11 (36.7)	2 (22.2)	1.158	0.789 to 1.410
Dizziness	6 (20.0)	0 (0.0)	1.375	0.837 to 1.375
Restlessness	5 (16.7)	1 (11.1)	1.100	0.589 to 1.323
Dry mouth	5 (16.7)	0 (0.0)	1.360	0.772 to 1.360
Constipation	4 (13.3)	1 (11.1)	1.046	0.503 to 1.300
Postural hypotension	2 (6.7)	1 (11.1)	0.857	0.269 to 1.241
Tremor	2 (6.7)	0 (0.0)	1.321	0.454 to 1.321
Fatigue	1 (3.3)	0 (0.0)	1.310	0.269 to 1.310
Headache	0 (0.0)	1 (11.1)	0.000	0.000 to 1.027

[a]No significant differences between treatment groups.

Dosing

The mean (SD) dose of quetiapine at study end point was 763.3 (106.6) mg/day in the rapid-initiation group and 600.0 (249.4) mg/day in the conventional-initiation group. The mean (SD) dose of lorazepam administered during the study was similar in each group: 2.8 (0.7) mg/day and 2.2 (1.0) mg/day in the rapid-initiation group and conventional-initiation group, respectively.

Tolerability

Quetiapine was well-tolerated, with no statistically significant differences between the initiation groups in SAS or BAS scores. Patients were assessed with both tools on days 1 through 7 and day 14, and no significant differences in either SAS or BAS scores were observed at any time point (Table 2).

In the overall study population, the most common side effects were sedation (33.3%), dizziness (15.4%), restlessness (15.4%), and dry mouth (12.8%). Although rapid escalation of quetiapine was associated with a numerically higher rate of sedation, dizziness, and restlessness than in the conventional-initiation group, there were no significant differences in the incidences of any adverse event between the initiation groups (Table 3). In the rapid-initiation group, 6 patients experienced dizziness, but only 1 of these patients also experienced a drop in blood pressure. Although the difference was not statistically significant, more patients in the rapid-initiation group experienced restlessness than in the conventional-initiation group (16.7% vs. 11.1%, respectively). A total of 57.5% of patients in both groups received rescue lorazepam. In the rapid-initiation group, 15 patients received rescue lorazepam compared with 8 patients in the conventional-initiation group. In addition, 3 patients in the rapid-initiation group received 1 mg/day benztropine compared with 2 in the conventional-initiation group.

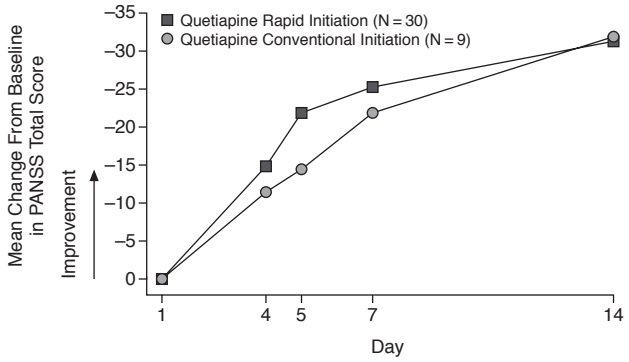
Only 2 patients were discontinued from treatment due to an adverse event, with 1 patient withdrawing in the first week. (Withdrawals occurred on day 5 and day 8.) Both patients were in the rapid-initiation group, and each experienced sedation that completely resolved within 2 and 3 days of treatment discontinuation. No serious adverse event was reported in either initiation group.

There was a lower incidence of postural hypotension in the rapid-initiation group compared with the conventional-initiation group, although this difference did not reach statistical significance. There was no statistically significant difference between the rapid- and conventional-initiation groups in weight change from baseline (+0.7 kg and +1.2 kg, respectively). Vital signs, ECG measures, and laboratory assessments were not significantly different between the initiation groups.

Efficacy

Positive and Negative Syndrome Scale. There was a significant improvement from baseline to end point in PANSS total and PANSS-EC scores in both the rapid- and conventional-initiation groups ($p < .001$, both; Figure 2).

Figure 3. Mean Change From Baseline in PANSS Total Scores in the Quetiapine Initiation Groups[a]



[a]Mean score at baseline (day 1): rapid-initiation group = 103.2; conventional-initiation group = 104.6.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Longitudinal improvements from baseline in PANSS total scores were similar in each of the quetiapine initiation groups (Figure 3). The overall improvement in the PANSS total scores for the whole group over the study period was 33.1% ($p < .001$).

Across the 14-day study, the PANSS-EC score showed a significant decrease over time ($p < .001$), but no significant differences were observed between the 2 treatment groups at the end of the study. However, rapid initiation achieved a faster onset of action than conventional initiation, as shown by significantly greater improvements in PANSS-EC scores at day 4 (36.4% vs. 13.1%) and day 5 (39.9% vs. 15.3%) ($p < .05$, both). Mean change from baseline in PANSS-EC scores is shown in Table 4.

Clinical Global Impressions-Severity of Illness scale. Both treatment groups achieved significant improvements from baseline to end point in CGI-S scores (24.5% and 14.4%, respectively; $p < .001$, both). No significant differences were recorded between the 2 treatment groups or for interaction between treatment group and time.

DISCUSSION

The present study further supports the widely reported favorable efficacy and safety profile of quetiapine for the treatment of schizophrenia, as demonstrated by the overall improvement in the PANSS and CGI-S scores, few patient discontinuations, and no serious adverse events in the overall study population.

Our findings are the first to demonstrate that rapid initiation of quetiapine in patients with acute schizophrenia is both efficacious and well-tolerated in the Asian population. Importantly, rapid initiation of quetiapine was associated with a faster onset of action than conventional initiation, as measured by significantly superior improvements in PANSS-EC scores at days 4 and 5.

Table 4. Mean Change From Baseline in PANSS-EC Scores in the Quetiapine Initiation Groups

	Rapid		Conventional	
Day	PANSS-EC, Mean ± SD	Change, Mean ± SD	PANSS-EC, Mean ± SD	Change, Mean ± SD
0	19.8 ± 6.0	0	18.3 ± 3.7	0
4	12.8 ± 3.8	–7.2 ± 6.5	15.7 ± 4.1	–2.4 ± 2.3
5	12.0 ± 4.2	–7.9 ± 6.9	15.2 ± 1.5	–2.8 ± 2.6
7	11.2 ± 4.5	–8.7 ± 8.0	12.6 ± 3.1	–5.2 ± 3.0
14	10.0 ± 4.0	–9.9 ± 7.7	10.4 ± 2.0	–7.1 ± 4.3

Abbreviation: PANSS-EC = Positive and Negative Syndrome Scale Excitatory Component.

These data are consistent with findings from a double-blind pilot study[27] that compared 3 quetiapine initiation schedules: 400 mg by day 5, 400 mg by day 3, and 400 mg by day 2. Three of 69 hospitalized patients with schizophrenia discontinued treatment due to adverse events during the study, and there were no differences in the overall frequency of adverse events among the groups. Data from a path analysis indicated that quetiapine appears to have direct effects on agitation that are independent of improvements in psychoses or overall psychopathology.[28] Results from our study would appear to corroborate this finding, i.e., that quetiapine showed effectiveness on the improvement of Behavioral Agitation Score derived from subitems of the BPRS.[28] A pooled analysis that included 426 patients also revealed the beneficial effect of quetiapine on the excitement component.[29] Small et al.[8] suggested that the improvements in each item of excitement and tension were significantly greater in patients treated with quetiapine than with placebo, within 1 week of initiating treatment. This result is similar to that in the present study, in that the rapid-initiation group significantly improved mean PANSS-EC scores compared with the conventional-initiation group on days 4 and 5, although the difference was not maintained at subsequent visits. Taking differences in study design into consideration, we believe the effectiveness and tolerability of rapid initiation of quetiapine for the control of acute agitation in schizophrenia to be demonstrated in our study population.

Rapid and conventional initiation of olanzapine in patients with acute agitation was investigated using a design similar to that used in our study.[30] Investigators reported that PANSS-EC scores decreased significantly in both groups, with a significant difference from day 2 onward. Improvements in PANSS-EC scores from baseline to day 4 (42.6%) were comparable with the levels of improvement achieved in our study (50%). A pooled analysis of the first-line atypical antipsychotics in published, short-term, randomized, controlled trials demonstrated that, beyond the finding that quetiapine significantly improves positive symptoms compared with olanzapine ($p < .05$), these drugs have similar efficacy in patients with schizophrenia.[31]

The overall frequencies of adverse events observed in our study were consistent with that observed in previous trials of quetiapine in patients with schizophrenia.[5,7,32] There were no significant differences in adverse events, EPS ratings, ECG, vital signs, or laboratory assessments between the rapid-initiation group and the conventional-initiation group in the present study. However, though the difference was not significant, patients in the rapid-initiation group experienced more frequent sedation, restlessness, and dizziness compared with those in the conventional-initiation group. Restlessness has been related to akathisia during rapid initiation of other atypical antipsychotics. However, there were no differences in akathisia as assessed using BAS between the rapid-initiation group and conventional-initiation group in our study. Further study of the rapid-initiation–related adverse events will be required before this strategy can be recommended in wider clinical practice or in a less acutely ill patient group.

This study has several inherent limitations. Although patients derived some tentative benefits from the rapid initiation of quetiapine in controlling their excitatory symptoms, the primary focus of our study was not excitement, and future studies should use more excitatory-specific end points in order to build upon these preliminary findings. The study design is also limited by the absence of a control arm, by the small sample size, and by the potential for observed bias associated with open-label studies. The 3:1 random assignment of patients to the rapid-initiation group and conventional-initiation group, respectively, further reduced the sample size in the conventional-initiation group. The 3:1 size was not based on a statistical consideration but chosen because of the small nature of the study and the primary objective of evaluating rapid initiation quetiapine, rather than standard initiation, as this schedule is approved for use and has been extensively studied.

CONCLUSION

This study confirms the established clinical efficacy and favorable tolerability of quetiapine in the treatment of acute schizophrenia. Our findings suggest that a novel approach to initiation of quetiapine using daily increments of 200 mg up to a target dose of 800 mg by day 4 is a potentially valid option for the treatment of acute schizophrenia but warrants further investigation.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), clozapine (Clozaril), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

REFERENCES

1. Arango C, Bobes J. Managing acute exacerbations of schizophrenia: focus on quetiapine. Curr Med Res Opin 2004;20:619–626
2. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia, revised 2004. Available at: www.psych.org. Accessed August 15, 2005
3. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychological Report 1962;10:799-812
4. CGI Clinical Global Impressions. In: Guy W, Bonato RR, eds. Manual for the ECDEU Assessment Battery, 2. Rev Ed. Chevy Chase, Md: National Institute of Mental Health; 1962:217–222
5. Arvanitis LA, Miller BG, the Seroquel Trial 13 study group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997;42:233–246
6. Borison RL, Arvanitis LA, Miller BG, et al. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J Clin Psychopharmacol 1996;16: 158–169
7. Small JG, Hirsch SR, Arvanitis LA, et al. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. Arch Gen Psychiatry 1997;54:549–557
8. Small JG, Kolar MC, Kellams JJ. Quetiapine in schizophrenia: onset of action within the first week of treatment. Curr Med Res Opin 2004;20: 1017–1023
9. Peuskens J, Link CGG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. Acta Psychiatr Scand 1997;96: 265–273
10. Ganesan S, Levy M, Bilsker D, et al. Effectiveness of quetiapine for the management of aggressive psychosis in the emergency psychiatric setting: a naturalistic uncontrolled trial. Int J Psychiatr Clin Pract 2005;9: 199–203
11. Meats P. Quetiapine ('Seroquel'): an effective and well-tolerated atypical antipsychotic. Int J Psychiatry Clin Pract 1997;1:231–239
12. Arvanitis LA, Rak IW. The long-term efficacy and safety of 'Seroquel' (Quetiapine) [poster]. Presented at the International Congress on Schizophrenia Research; April 12–16, 1997; Colorado Springs, Co
13. Zhong X, Sweitzer D, Hamer RM, et al. Comparison of quetiapine and risperidone in the treatment of schizophrenia: a randomized, double-blind, flexible-dose, 8-week study. J Clin Psychiatry 2006;67:1093–1103
14. Eli Lilly and Company. Zyprexa olanzapine tablets/US prescribing information, revised 2005. Available at: http://pi.lilly.com/us/zyprexa-pi.pdf. Accessibility verified November 15, 2006
15. Daniel DG, Zimbroff DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Neuropsychopharmacology 1999;20:491–505
16. Finn SE, Bailey JM, Schultz RT, et al. Subjective utility ratings of neuroleptics in treating schizophrenia. Psychol Med 1990;20:843–848
17. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156: 1686–1696
18. Brecher M, Zukin S, Leong R, et al. Long-term weight change with quetiapine treatment in schizophrenia: a comprehensive data review. Neuropsychopharmacology 2004;29:S109
19. AstraZeneca. Seroquel (quetiapine fumarate) tablets/US prescribing information, revised 2005. Available at: http://www.astrazeneca-us.com/pi/Seroquel.pdf. Accessibility verified November 15, 2006
20. Goldstein JM. Mechanism of action of quetiapine: modulation of dopamine at the D2 receptor [poster]. Presented at the 12th Congress of the Association of European Psychiatrists; April 14–18, 2004; Geneva, Switzerland
21. First MB, Williams JB, Spitzer RL, et al. Structured Clinical Interview for DSM-IV Axis I Disorders-Clinical Version (SCID-IV). Washington, DC: American Psychiatric Press; 1997
22. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Washington, DC: American Psychiatric Association; 1994
23. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
24. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
25. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
26. Lindenmayer JP, Brown E, Baker RW, et al. An excitement subscale of the Positive and Negative Syndrome Scale. Schizophr Res 2004;68: 331–337

27. Smith MA, McCoy R, Hamer-Maansson J, et al. Rapid dose escalation with quetiapine: a pilot study. J Clin Psychopharmacol 2005;25:331–335
28. Chengappa KNR, Goldstein JM, Greenwood M, et al. A post hoc analysis of the impact on hostility and agitation of quetiapine and haloperidol among patients with schizophrenia. Clin Ther 2003;25:530–541
29. Buckley PF. Efficacy of quetiapine for the treatment of schizophrenia: a combined analysis of three placebo-controlled trials. Curr Med Res Opin 2004;20:1357–1363
30. Baker RW, Kinon BJ, Maguire GA, et al. Effectiveness of rapid initial dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation. J Clin Psychopharmacol 2003;23:342–348
31. Tandon R, Jibson MD. Comparing efficacy of first-line atypical antipsychotics: no evidence of differential efficacy between risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. Int J Psychiatry Clin Pract 2005;7:204–212
32. De Nayer A, Windhager E, Irmansyah, et al. Efficacy and tolerability of quetiapine in patients with schizophrenia switched from other antipsychotics. Int J Psychiatry Clin Pract 2003;7:59–66