

A Prospective, Open-Label, Flexible-Dose Study of Quetiapine in the Treatment of Delirium

Yukiya Sasaki, M.D.; Tetsuaki Matsuyama, M.D.; Seishiro Inoue, M.D.;
Tomoko Sunami, M.D.; Takeshi Inoue, Ph.D.; Kenzo Denda, Ph.D.;
and Tsukasa Koyama, Ph.D.

Background: Delirium is an organic psychiatric syndrome characterized by fluctuating consciousness and impaired cognitive functioning. High-potency typical neuroleptics have traditionally been used as first-line drugs in the treatment of delirium. However, these drugs are frequently associated with undesirable adverse events including extrapyramidal symptoms (EPS). The purpose of the present open-label, flexible-dose study was to provide preliminary data on the usefulness and safety of quetiapine for patients with delirium.

Method: Twelve patients with DSM-IV delirium were treated with flexible doses of open-label quetiapine (mean \pm SD dosage = 44.9 ± 31.0 mg/day). To evaluate the usefulness and safety of quetiapine, scores from the Delirium Rating Scale, Japanese version, were assessed every day (for 1 outpatient, at least twice per week), and scores from the Mini-Mental State Examination, Japanese version, and the Drug-Induced Extrapyramidal Symptom Scale were assessed at baseline and after remission of delirium. Data were gathered from April to October 2001.

Results: All patients achieved remission of delirium several days after starting quetiapine (mean \pm SD duration until remission = 4.8 ± 3.5 days). Quetiapine treatment was well tolerated, and no clinically relevant change in EPS was detected.

Conclusion: Quetiapine may be a useful alternative to conventional neuroleptics in the treatment of delirium due to its rapid onset and relative lack of adverse events. Further double-blind, placebo-controlled studies are warranted.

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The authors report no financial affiliation or other relationship relevant to the subject matter of this article.

Corresponding author and reprints: Yukiya Sasaki, M.D., Department of Psychiatry, Hokkaido University School of Medicine, North 15, West 7, Sapporo 060-8638, Japan (e-mail: yukiya@seagreen.ocn.ne.jp).

Delirium is an organic psychiatric syndrome characterized by acute onset, an altered level of consciousness, a fluctuating course, and global impairment of cognitive functioning. Abnormalities of mood, perception, and behavior are frequently seen.¹ Delirium occurs in up to 51% of hospitalized medical and surgical patients and appears to be associated with significant increases in functional disability, length of hospital stay, rate of admission to long-term care institutions, mortality, and health care costs.^{2–4} The management and treatment of delirious patients are essential aspects of the psychiatrist's work.

High-potency typical antipsychotics such as haloperidol have traditionally been used as first-line therapy in the treatment of delirium.⁵ Surprisingly, they are even recommended by authoritative guidelines.⁶ Haloperidol is often used for clinical treatment of delirium, but its usefulness has not been proven; the only study that has been reported so far is that of Breitbart et al.,⁷ which enrolled patients with delirium complicated by acquired immunodeficiency syndrome. No other study has been carried out in patients with delirium diagnosed on the basis of operational diagnostic criteria that used control groups and standardized scales to clarify the efficacy and side effects of high-potency typical neuroleptics such as haloperidol. High-potency typical antipsychotics are frequently associated with adverse events, including extrapyramidal symptoms (EPS), which are more frequent in elderly patients, who are more likely to develop delirium. As a result of taking selective dopamine D₂ receptor antagonists, elderly patients often develop complications such as pneumonia, bedsores, bone fractures, and falls. Adding an anticholinergic agent to reduce EPS is not a satisfactory solution because this may exacerbate delirium.

Some recent studies have discussed the efficacy and safety of several "atypical" antipsychotics in the treatment of delirium, but these studies have been quite limited from the viewpoint of methodology. Because atypical antipsychotics are less likely to cause EPS than typical antipsychotics,⁸ they may be more useful in the management of delirium than high-potency typical antipsychotics. According to the published data we found on atypical antipsychotics, delirium is currently treated with risperidone, olanzapine, and quetiapine.

There have been 4 case reports⁹⁻¹² suggesting that risperidone in relatively low doses is effective and well tolerated in the treatment of delirium. These cases, however, were open-label and involved at most 11 patients. The latest case reports were by Horikawa et al.,¹² who carried out an open, prospective trial in which risperidone was given to 10 patients with delirium. Risperidone (1.7 mg/day, on average) proved effective in 80% of the patients, and efficacy became evident within a few days. Moreover, there were no serious adverse effects except for sleepiness (30%) and mild EPS (10%).

Sipahimalani and Masand¹ compared the responses of 11 delirious patients treated with olanzapine (5–15 mg/day) and those of 11 delirious patients treated with haloperidol (0.5–5 mg/day). Olanzapine showed efficacy almost equal to that of haloperidol in the treatment of delirium. Moreover, none of the patients treated with olanzapine developed adverse events, while 3 patients treated with haloperidol developed EPS. On the basis of these results, the authors concluded that olanzapine might be a useful alternative to haloperidol in the treatment of delirium. The severity of patients' delirium was evaluated retrospectively using the Delirium Rating Scale (DRS).

Breitbart et al.¹³ conducted an open, prospective trial of olanzapine for the treatment of DSM-IV delirium in 79 hospitalized cancer patients. Using the Memorial Delirium Assessment Scale, they showed that 57 patients had complete resolution of delirium over the course of a 7-day period. Moreover, no patients experienced EPS. On the basis of these results, the authors suggested that olanzapine was a clinically efficacious and safe drug for the treatment of the symptoms of delirium in the medically ill.

Schwartz and Masand¹⁴ compared the responses of 11 delirious patients treated with quetiapine (25–750 mg/day) and those of 11 delirious patients treated with haloperidol (1.5–10 mg/day). They showed that quetiapine had efficacy almost equal to that of haloperidol in the treatment of delirium. None of the patients treated with quetiapine developed EPS, while 2 patients treated with haloperidol developed EPS. On the basis of these results, Schwartz and Masand concluded that quetiapine appeared to be an efficacious and well tolerated treatment for delirium. In this study, the efficacy of each treatment was evaluated retrospectively using the DRS.

Torres et al.¹⁵ reported on 2 cases of delirium in which patients were successfully treated with low doses of quetiapine (25 mg/day) and did not experience adverse events such as EPS.

One concern in the reports cited above is that adverse events, in particular EPS, are seldom assessed using standardized scales. Therefore, it is difficult to say that the usefulness and safety of atypical antipsychotics for the treatment of delirium have been demonstrated objectively. In this study, we examined the usefulness and

safety of quetiapine in the treatment of delirium, utilizing a prospective, open-label, flexible-dose trial design to systematically assess responsiveness to quetiapine therapy for delirium (using the Delirium Rating Scale-Japanese version [DRS-J]¹⁶), as well as EPS (using the Drug-Induced Extrapyramidal Symptom Scale [DIEPSS]¹⁷).

METHOD

Patients

We examined patients during the period from April through October 2001. Those able to satisfy the following requirements were enrolled as subjects in the study. (1) They were able to meet the diagnostic criteria for delirium in DSM-IV. (2) They were able to take quetiapine orally. (3) They could be assessed for observed symptoms of delirium according to the DRS-J.¹⁶ (4) They could be thoroughly followed by the authors through the course of their delirium (from first visit to remission). A total of 12 patients met the inclusion criteria for this study.

The mean \pm SD age of the patients was 67.3 ± 14.8 years. The patients comprised 10 men and 2 women; 11 were inpatients, and 1 was an outpatient.

The etiologies of their delirium were diverse and included postsurgical delirium (esophageal cancer, DeBakey type I aortic dissection, thoracoabdominal aortic aneurysm, abdominal aortic aneurysm, Bowen's disease, ossification of the posterior longitudinal ligament), severe burns, facial fracture/subarachnoid hemorrhage, leukemia, malignant melanoma, laryngeal cancer, and lung cancer.

Prior to the study, 8 patients had undergone drug therapy for delirium but had experienced no beneficial effect. One patient had taken an antipsychotic, 4 had taken benzodiazepine hypnotics, and 3 had taken antipsychotics and benzodiazepine hypnotics.

Written informed consent was obtained from all patients and/or family members responsible for the patients before starting quetiapine therapy. Because the procedures were undertaken without deviating from standardized clinical practice, institutional review board approval for the study was not obtained.

Medication

In this clinical, open-label, flexible-dose prospective trial, quetiapine treatment was usually started at 25 or 50 mg/day. Subsequent titration of dosage was based on clinical judgment. Quetiapine was titrated, in principle, upward until maximum clinical benefit was obtained or until intolerable adverse events necessitated cessation. After remission of delirium, quetiapine treatment was continued, reduced, or stopped, according to the conditions of each case. Quetiapine was orally administered once daily before bedtime, and a further 25 to 50 mg of quetiapine was added for agitation or insomnia. No concomitant psychotropic medications were permitted during the study

Table 1. Demographics and Baseline Characteristics of 12 Delirium Patients

Patient	Age (y)	Gender	Etiology of Delirium	Duration of Delirium (d)	Prior Drug Therapy for Delirium
1	63	M	Postsurgical (esophageal cancer)	22	Flunitrazepam, zopiclone, tiapride
2	40	M	Postsurgical (type I aortic dissection)	7	...
3	77	F	Severe burns	12	Triazolam, zopiclone, diazepam
4	73	M	Postsurgical (OPLL)	98	...
5	37	M	Facial fracture/subarachnoid hemorrhage	3	...
6	73	M	Leukemia	2	Triazolam, quazepam
7	82	M	Malignant melanoma	3	...
8	65	M	Laryngeal cancer	3	Zopiclone, flunitrazepam, haloperidol
9	75	M	Lung cancer	1	Diazepam
10	69	M	Postsurgical (thoracoabdominal aortic aneurysm)	Unidentified	Haloperidol
11	84	F	Postsurgical (Bowen's disease)	1	Diazepam
12	70	M	Postsurgical (abdominal aortic aneurysm)	6	Etizolam, quazepam, haloperidol

Abbreviations: F = female, M = male, OPLL = ossification of the posterior longitudinal ligament. Symbol: ... = none received.

except for flunitrazepam, diazepam, or haloperidol injections, which were given for severe agitation or insomnia when oral administration was impossible.

Clinical Measures and Safety Assessment

Changes in the severity of delirium were assessed using the DRS-J. DRS-J scores were assessed every day for the 11 inpatients and at least twice per week for the outpatient until remission of delirium. Remission was defined as a DRS-J score of less than 12 points, which is the cutoff point on the DRS-J for delirium, and the authors' assessment that the patient's symptoms of delirium had remitted clinically.

As a secondary efficacy variable, we used the Mini-Mental State Examination, Japanese version (MMSE-J),¹⁸ when scores were available, to evaluate the patients' cognitive functions at baseline and after remission of delirium.

In addition to evaluating the safety of quetiapine, we assessed EPS at baseline and after remission of delirium using the DIEPSS¹⁷ when scores were available. The DIEPSS, which was established in Japan, is a clinician-rated scale designed to evaluate the severity of drug-induced EPS that occur during antipsychotic drug treatment. The DIEPSS consists of 8 individual items (gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, dyskinesia) and 1 global item constructed to measure EPS based on 5-point scales (total range, 0–36).

During the first visit, medical and psychiatric histories were recorded. Patients underwent an electrocardiogram and an electroencephalogram, and laboratory studies were performed. Blood pressure, heart rate, use of other medications, and any medical problems were assessed. We retrospectively identified the day on which patients' delirium began by reviewing charts and nursing records and/or by collecting information from their families.

Statistical Methods

A 2-tailed paired *t* test was used to analyze changes from baseline on the MMSE-J and DIEPSS. All *p* values less than .05 were considered significant.

RESULTS

Quetiapine was generally well tolerated. No patient withdrew from the study due to adverse events, and all patients continued to use quetiapine until remission of their delirium. The mean \pm SD dose of quetiapine was 44.9 ± 31.0 mg/day, and the mean \pm SD maximum dose was 63.5 ± 44.4 mg/day (4 patients: 25 mg; 4 patients: 50 mg; 1 patient: 62.5 mg; 2 patients: 125 mg; 1 patient: 150 mg). Concomitant medication to treat agitation or insomnia was necessary for only 2 patients. Table 1 summarizes the patients' demographics and clinical characteristics during the study.

Primary Efficacy Variables

Mean \pm SD duration of treatment until remission of delirium was 4.8 ± 3.5 days. Mean DRS-J score was 18.1 ± 4.2 at baseline and 9.3 ± 1.6 after remission. The change in the mean DRS-J score (from day 0 to day 7) is illustrated in Figure 1.

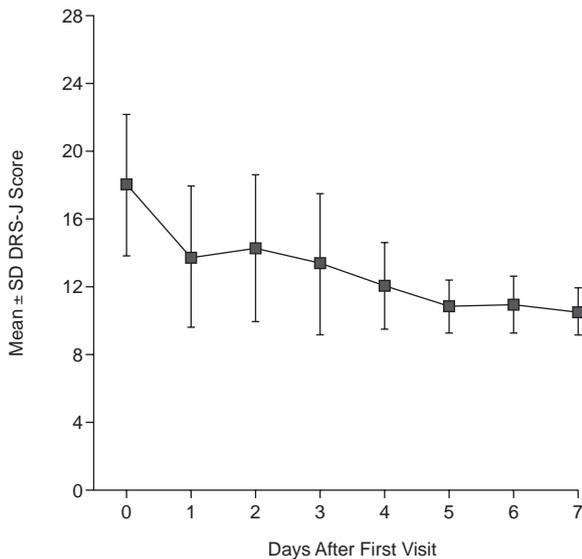
Secondary Efficacy Variable

MMSE-J scores were assessed in 8 of the 12 patients at baseline and after remission of delirium (Table 2). The mean \pm SD MMSE-J score was 19.6 ± 3.8 at baseline and 24.0 ± 3.0 after remission; the change from baseline indicated a statistically significant improvement ($p = .0256$).

Adverse Events

None of the patients experienced excessive sedation or somnolence in the daytime. DIEPSS scores were assessed for 10 of the 12 patients at baseline and after remission of delirium. The mean \pm SD DIEPSS score was 1.5 ± 1.7 at baseline and 0.7 ± 1.3 after remission; the change from baseline was not statistically significant. Anticholinergic adverse events such as constipation and dry mouth were not reported. There were no consistent changes or clinically relevant abnormalities in vital signs (blood pressure and heart rate) or laboratory safety parameters.

Figure 1. Change in DRS-J Score During Week 1 of Quetiapine Treatment in 12 Patients With Delirium^a



^aRemission was defined as a DRS-J score of <12. When patients underwent remission before day 7, data from their day of remission was included with data from the following day (last observation carried forward)

Abbreviation: DRS-J = Delirium Rating Scale-Japanese version.

DISCUSSION

The period until remission was relatively short in this study, and EPS were not detected using the DIEPSS. Cognitive functions as measured by the MMSE-J also improved, which suggests that the impact of quetiapine on delirium does not derive from a nonspecific sedative action that may exert an undesirable influence on the cognitive functions.

Our study is the first to use operational diagnostic criteria and standardized scales to show that quetiapine brings about remission in patients with delirium without exerting an adverse influence on cognitive functions or causing EPS.

Pharmacologic Profile of Quetiapine

Quetiapine is a dibenzothiazepine derivative that has a novel and unique pharmacologic profile. It has a higher affinity for serotonin 5-HT_{2A} receptors (IC₅₀ = 148 nM) than for dopamine D₂ receptors (IC₅₀ = 329 nM)^{19,20} and has high affinity for histamine H₁ receptors (IC₅₀ = 30 nM) and α_1 -adrenergic receptors (IC₅₀ = 94 nM). Quetiapine's blockade of muscarinic M₁ receptors (IC₅₀ = 5000 nM) is very low.¹⁹ D₂ receptor occupancy by quetiapine is not only much lower than that of conventional neuroleptics, but also transient.²¹ After chronic administration, quetiapine demonstrated selectivity for the limbic system by producing depolarization blockade of the A10 meso-

limbic but not the A9 nigrostriatal dopamine-containing neurons.²²

A variety of physiologic and structural abnormalities can cause delirium.²³ As quetiapine has a broad neurotransmitter receptor profile, it is difficult to determine how quetiapine generally improved delirium.

Mechanisms of Action on Delirium

Hyperactivity of the limbic system is believed to be one of the pathophysiologies of delirium.²⁴ Quetiapine might control the hyperactivity of this area by selectively blocking the mesolimbic D₂ receptors. However, we found that 4 patients who were administered antipsychotics (haloperidol, tiapride) prior to quetiapine with no beneficial effect did benefit from quetiapine, which has a lower affinity for D₂ receptors than do haloperidol and tiapride. This finding suggests that the improvement of delirium symptoms by quetiapine might be due to more than just the blocking of the mesolimbic D₂ receptors. Because the sedative action resulting from the H₁ receptor-blocking property is considered to be more desirable for delirious patients than that of benzodiazepine hypnotics, the high affinity for histamine H₁ receptors might be one of the mechanisms of action of quetiapine in the treatment of delirium.²⁵

Studies in both humans and animals indicate that selective 5-HT₂ receptor antagonists increase slow-wave sleep.²⁶ Sharpley et al.²⁷ reported that olanzapine produced substantial and highly significant dose-related increases in slow-wave sleep and improved measures of sleep continuity in healthy volunteers, probably by blocking the brain 5-HT_{2C} receptors. They suggested that the beneficial effect of olanzapine on subjective sleep quality is attributable to a combination of improved sleep continuity and an increase in slow-wave sleep. In patients with delirium, disturbed sleep is one of the most frequent symptoms,²⁸ and adjustment of the sleep-wake rhythms of delirious patients has been reported to improve the other symptoms of delirium.²⁹ Because quetiapine also has a relatively high affinity for 5-HT_{2A/2C} receptors,³⁰ it is possible that quetiapine, much like olanzapine, has a beneficial effect on sleep quality and ameliorates delirium by reducing sleep-wake rhythm disturbances.

The low affinity of quetiapine for the M₁ receptors may be an advantage in the treatment of delirium, because its action as an M₁ receptor antagonist could theoretically exacerbate delirium by influencing cognitive function.

Not only the pharmacologic properties of quetiapine but also its pharmacodynamic properties may have beneficial effects in the treatment of delirium. Quetiapine shows rapid absorption and a short half-life,³¹ although it is reported that quetiapine clearance was 30% to 50% lower in the elderly than in young adults.³² This characteristic of quetiapine might be important in preventing difficulty in waking the next morning and in maintaining the sleep-wake rhythm.

Table 2. Efficacy and Safety Assessments in 12 Delirium Patients Treated With Quetiapine

Patient	Duration of Treatment Until Remission (d)	Mean Dose of Quetiapine (mg/d)	Concomitant Drug Therapy for Delirium	DRS-J Score		DIEPSS Score		MMSE-J Score	
				Before Treatment	After Remission	Before Treatment	After Remission	Before Treatment	After Remission
1	5	85.0	...	21	11	2	0	N/A	26
2	7	100.0	...	14	11	0	0	13	29
3	3	25.0	Diazepam (day 2)	25	11	0	0	N/A	N/A
4	12	25.0	...	19	8	2	1	22	23
5	7	100.0	...	18	10	N/A	N/A	N/A	25
6	1	25.0	...	15	10	0	0	25	28
7	8	34.375	...	21	8	4	2	19	23
8	5	45.0	...	25	10	0	0	N/A	23
9	6	25.0	...	16	6	3	4	22	23
10	1	25.0	Haloperidol (day 1)	13	10	N/A	N/A	16	22
11	1	25.0	...	16	8	0	0	20	20
12	1	25.0	...	14	9	4	0	21	24

Abbreviations: DIEPSS = Drug-Induced Extrapyramidal Symptom Scale; DRS-J = Delirium Rating Scale, Japanese version; MMSE-J = Mini-Mental State Examination, Japanese version; N/A = scale could not be administered. Symbol: ... = none received.

Safety

From the standpoint of safety, quetiapine may be superior to conventional antipsychotics in the treatment of delirium. According to a report by McManus et al.,³³ who examined the safety and efficacy of quetiapine in elderly patients with psychotic disorders, the most common adverse events were somnolence (32% of patients), dizziness (14%), postural hypotension (13%), agitation (11%), and EPS (6%). In this trial, no adverse events were observed or reported by the patients, their families, or the medical staff. The primary reason might be that the quetiapine doses given to the patients in this trial were much lower than the doses given to patients with schizophrenia, who receive between 150 and 750 mg/day.³⁴

Mean DIEPSS scores obtained from 10 of the 12 patients in the study were unchanged even after remission of delirium. This finding suggests that patients with delirium may run little risk of experiencing EPS when taking relatively low doses of quetiapine. We were not able to administer the DIEPSS to all subjects in our study, however, so our evaluation of the safety of quetiapine may be limited.

Although it may be argued that the relief of symptoms was a result of the natural course of delirium and treatment of the underlying cause, it is our impression that quetiapine played an integral part in the remission of delirium in these patients.

This study has several limitations. One is that the study was an uncontrolled trial without a comparison or control group. The trial was open, and investigators were not blind to treatment conditions or DRS-J scores. Additionally, the sample size was small, and the samples were not randomized. Nevertheless, our study is regarded as an important first step that showed the clinical usefulness and safety of quetiapine in the management of delirium. Further research, particularly larger, double-blind, randomized, controlled trials in patients with delirium, will be needed to confirm our findings and to determine recommended dosing and titration schedules.

CONCLUSION

As we stated, many open studies suggest that, in the treatment of delirium, some atypical antipsychotics are not only as effective as but also safer than high-potency typical antipsychotics. "Atypical antipsychotic" is, however, a rather vague categorization, and the atypical antipsychotics differ pharmacologically. The atypical antipsychotics also differ from each other with regard to the risk of EPS.⁸ Moreover, they influence anticholinergic adverse events in ways different from each other,⁸ which may lead to exacerbation of delirium. On comparing these pharmacologic differences among atypical antipsychotics, we concluded that quetiapine might be the ideal option in the treatment of delirium because it has a relatively low risk of causing EPS or anticholinergic adverse events.

Quetiapine may be a useful alternative to high-potency conventional antipsychotics such as haloperidol in the treatment of delirium due to its rapid onset and rare incidence of adverse events. Larger, controlled studies are warranted to further explore these preliminary findings and conclusions.

Drug names: diazepam (Valium and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quazepam (Doral), quetiapine (Seroquel), risperidone (Risperdal), triazolam (Halcion and others).

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