

# Is quetiapine suitable for treatment of acute schizophrenia with catatonic stupor? A case series of 39 patients

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**Purpose:** We aimed to determine which antipsychotic is most effective for the treatment of acute schizophrenia with catatonic stupor.

**Patients and methods:** Data were obtained from the medical records of 450 patients with the diagnosis of schizophrenia, who had received acute psychiatric inpatient treatment between January 2008 and December 2010 at our hospital. Among them, 39 patients (8.7%) met the definition of catatonic stupor during hospitalization. The diagnoses of schizophrenia in all 39 patients were reconfirmed during the maintenance phase. We retrospectively reviewed the medical records of these 39 patients to investigate which antipsychotics were chosen for treatment during the period from admission to recovery from catatonia, at the time of discharge, and 12 and 30 months after discharge.

**Results:** As compared to other antipsychotics, it was found out that use of quetiapine had better outcomes and hence was used more often. A total of 61.5% of patients were on quetiapine at the time of recovery from catatonia and 51.3% of patients were on quetiapine at the time of discharge as compared to only 17.9% of patients on quetiapine on admission. However, at 12 and 30 months after discharge, the rates had decreased to 38.4% and 25.6%. Similarly, of 29 patients who were not administered electroconvulsive therapy, quetiapine was used at significantly higher rates at the time of recovery from catatonia (48.3%) than at the time of admission (17.2%). All 39 patients had received an antipsychotic as the first-line treatment and some antipsychotics might have contributed to the development of catatonia.

**Conclusion:** This study suggests that quetiapine is a promising agent for the treatment of schizophrenia with catatonic stupor during the acute phase.

**Keywords:** catatonia, electroconvulsive therapy, quetiapine, schizophrenia, stupor

## Introduction

Catatonia is a syndrome characterized by marked psychomotor abnormalities associated with schizophrenia, mood disorders, general medical conditions, drug withdrawal, and toxic drug states.<sup>1</sup> The clinical symptoms of catatonia are stupor, catalepsy, excessive and purposeless motor activity, extreme negativism, mutism, peculiarities of voluntary movement, echolalia, and echopraxia.<sup>2,3</sup> Catatonia is observed in 5%–15% of psychiatric patients who require acute psychiatric hospital treatment. The predilection of psychiatrists to diagnose catatonic patients with schizophrenia appears to be based on historical reasons.<sup>4</sup> However, previous studies show that most cases of catatonia are caused by mood disorders, irrespective of the age group, while 10%–20% of them are caused by schizophrenia.<sup>5–7</sup>

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Malignant catatonia is a condition in which psychomotor symptoms of catatonia are accompanied by autonomic instability or hyperthermia.<sup>8</sup> This frequently fatal condition cannot be distinguished from neuroleptic malignant syndrome (NMS) either clinically or by laboratory tests, which leads to the conclusion that NMS is a variant form of malignant catatonia, and that treating catatonia with antipsychotics is recognized as a risk factor for the development of NMS.<sup>9–11</sup>

Benzodiazepines (BZP) and electroconvulsive therapy (ECT) are the only recognized treatments of catatonia.<sup>5,12–16</sup> Numerous articles indicate that BZP are rapidly effective, safe, and easily administered and are therefore regarded as suitable for first-line treatment for catatonia. If catatonic symptoms do not resolve rapidly with BZP, ECT is indicated. It may be necessary in some cases to treat with antipsychotics, but some authors recommend that antipsychotics should be avoided altogether in patients with catatonia because their use may be harmful.<sup>6,17</sup>

The number of cases of catatonia due to schizophrenia is minor, but the treatment of acute schizophrenia with catatonia is very complex, and the use of antipsychotics in patients with catatonia is controversial.<sup>6</sup> Catatonic symptoms of patients with schizophrenia are somewhat less likely to respond to BZP.<sup>12,18</sup> Even if catatonic symptoms are resolved rapidly with BZP, they may recur without adequate treatment of the underlying cause.<sup>5</sup> However, which antipsychotic is most effective for the treatment of acute schizophrenia with catatonia has not been determined. To our knowledge, there is no more suggestive indication for treating schizophrenia with catatonia than the case reports of successful treatment with aripiprazole,<sup>19,20</sup> risperidone,<sup>21,22</sup> olanzapine,<sup>23,24</sup> ziprasidone,<sup>25</sup> and clozapine.<sup>26</sup> In particular, catatonic stupor states have considerable potential for serious complications, which include dehydration, venous thrombosis, pulmonary embolism, and pneumonia. To determine the most effective antipsychotic for the treatment of acute schizophrenia with catatonic stupor, we reviewed the medical records of 39 patients with the diagnosis of schizophrenia with catatonic stupor.

## Methods

The sample data was obtained from the medical records of 450 patients with the diagnosis of schizophrenia, not including schizoaffective disorder, based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV),<sup>2</sup> who had received acute psychiatric inpatient treatment between January 2008 and December 2010 on the

acute psychiatric ward of the Okayama Psychiatric Medical Center. Among them, with the exclusion of patients with catatonic stupor associated with general medical conditions, drug withdrawal, and toxic drug states, 39 patients (8.7%) met the definition of schizophrenia with catatonic stupor during hospitalization. All patients had formal medical evaluations by an internist to rule out underlying medical conditions that might have contributed to their psychiatric symptoms. The diagnoses of schizophrenia in all 39 patients were reconfirmed during the maintenance phase through clinical interview by each attending physician.

Because our hospital had no specific treatment algorithm, patients with schizophrenia characterized by catatonia were merely treated with antipsychotics in the same way as those without catatonia at the discretion of the attending physician.

Retrospectively, we reviewed the medical records of 39 patients with the diagnosis of schizophrenia with catatonic stupor to investigate which antipsychotics were used for treatment during the period from admission to recovery from catatonia, at the time of discharge, and 12 and 30 months after discharge. We defined “recovery from catatonia” as a mental state without catatonic symptoms or recurrence of catatonia during hospitalization. All 39 patients had made a “recovery from catatonia” prior to discharge. To assess the severity, we routinely used the Bush–Francis Catatonia Rating Scale<sup>3</sup> and Clinical Global Impression–Severity scale in the acute and maintenance phases. We also investigated the presence of fever ( $>38^{\circ}\text{C}$ ), high serum creatine kinase (h-CK;  $>500$  IU/L), NMS (on the basis of the criteria for NMS of Caroff and Mann),<sup>27</sup> duration of catatonia, other pharmacotherapies, and co-treatment with ECT. We classified the condition of patients with stupor in the presence of both fever and h-CK as “severe,” and defined the others as “less severe.”

The Institutional Review Board of our hospital approved this study. Because data for this study were collected in the course of routine clinical care, and these data were analyzed retrospectively and anonymized, informed consent was neither sought nor obtained.

Statistical analysis was conducted using SPSS Statistics 19 (IBM Corporation, Armonk, NY, USA). Continuous variables were analyzed using the independent sample *t*-test; categorical variables were analyzed using the chi-square test. The level of significance was set at  $P < 0.05$ .

## Results

Of 39 patients with catatonic stupor, 28 and 11 patients met the criteria of less severe and severe stupor, respectively (Table 1).

Figure 1 is a flow chart of antipsychotics used for the 39 patients during the period from admission to recovery from catatonia.

Thirty-two patients (82.1%) had an established diagnosis of schizophrenia prior to presenting with catatonia. The mean duration of untreated psychosis of eleven patients with first-episode was  $31.0 \pm 46.2$  weeks. The mean time interval between the initial diagnosis of schizophrenia and the time-point of presentation with catatonia of 28 patients with multi-episode was  $13.8 \pm 10.4$  years.

The frequency of catatonic symptoms, in order of declining frequency, were as follows: immobility/stupor, mutism and staring, 39/39; posturing/catalepsy, 36/39; mannerism, 30/39; rigidity and withdrawal, 26/39; grimacing, 24/39; autonomic abnormality, 22/39; negativism, 20/39; excitement, 19/39; impulsivity, 14/39; gegenhalten, 10/39; ver-bigeration, 9/39; stereotypy, 7/39; waxy flexibility, 5/39; ambitendency, 4/39; automatic obedience and combativeness, 2/39; echopraxia/echolalia and perseveration, 1/39; mitgehen and grasp reflex, 0/39.

Our data shows that only quetiapine (QTP) was used at significantly higher rates at the time of recovery from catatonia ( $n=24$ , 61.5%,  $P<0.001$ ) and discharge ( $n=20$ ,

51.3%,  $P=0.002$ ) than at the time of admission ( $n=7$ , 17.9%). Similarly, of 29 patients who were not administered ECT, QTP was used at significantly higher rates at the time of recovery from catatonia ( $n=14$ , 48.3%,  $P=0.012$ ) than at the time of admission ( $n=5$ , 17.2%). However, at 12 and 30 months after discharge, the rates had decreased to 38.4% ( $n=15$ ,  $P=0.044$ ) and 25.6% ( $n=10$ ,  $P=0.41$ ).

The rate of QTP use was significantly higher in patients with severe stupor than in patients with less severe stupor at the time of recovery from catatonia ( $P=0.001$ ) and discharge ( $P<0.001$ ). The tendency was decreasing at 12 and 30 months after discharge ( $P=0.18$  and  $P=0.088$ ).

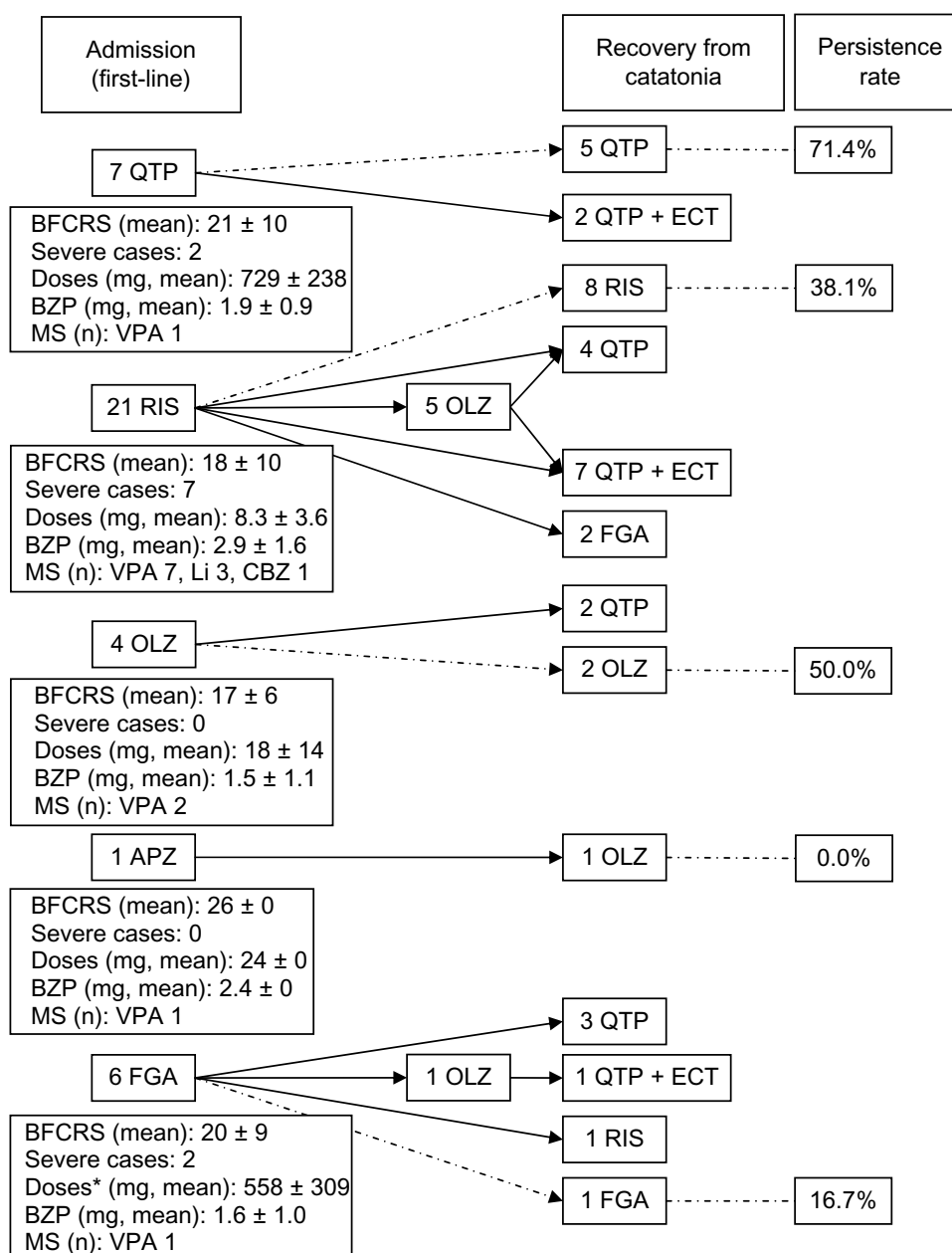
One and two patients developed NMS during treatment with first-generation antipsychotics and risperidone, respectively. Two of these three patients with NMS were treated by combination of medication and ECT, and another patient was treated with high-dose BZP. No patient treated with QTP as first-line treatment developed exacerbation of catatonia or severe extrapyramidal side effects.

The mean dosage ( $\pm$  standard deviation [range]) of QTP was 727 ( $\pm 212$  [300–1100]) mg/day at the time of recovery from catatonia ( $n=24$ ). Treatment with dosages of QTP near the approved maximum (750 mg/day in Japan) was safe under

**Table 1** Clinical data of 39 patients

	With less severe stupor [n=28]	With severe stupor [n=11]	P-value
<b>Characteristics</b>			
Age, mean $\pm$ SD [range]	42.0 $\pm$ 13.8 [20–72]	35.9 $\pm$ 14.8 [16–55]	0.26
Male/female, n (%)	10 (35.7)/18 (64.3)	5 (45.5)/6 (54.5)	0.82
First episode/relapse, n (%)	6 (21.4)/22 (78.6)	5 (45.5)/6 (54.5)	0.96
BFCRS, mean $\pm$ SD	15.57 $\pm$ 7.61	28.09 $\pm$ 7.54	0.00004
CGI-S of acute phase, mean $\pm$ SD	6.25 $\pm$ 0.59	6.81 $\pm$ 0.40	0.22
CGI-S of maintenance, mean $\pm$ SD	2.25 $\pm$ 0.89	2.45 $\pm$ 0.82	0.44
With fever/h-CK/NMS	1/7/0	1/1/1/3	–
Duration of catatonia, median [range]	7 [1–180]	28 [3–90]	0.35
BZP, mg daily, mean $\pm$ SD	2.09 $\pm$ 1.32	3.09 $\pm$ 1.63	0.052
Mood stabilizers (VPA/CBZ/Li), n	11 (8/1/2)	5 (4/0/1)	0.76
cECT, n (%)	4 (14.3)	6 (54.5)	0.017
<b>Antipsychotics chosen, QTP [cECT]/others (RIS, OLZ, other SGA, FGA)/none, n</b>			
Admission	5/23 (14, 4, 1, 4)/0	2/9 (7, 0, 0, 2)/0	0.65
Recovery from catatonia	13 [4]/15 (9, 3, 0, 3)/0	11 [6]/0/0	0.0015
Discharge	9/19 (8, 5, 0, 6)/0	11/0/0	0.00014
12 months after discharge	9/19 (7, 4, 2, 6)/0	6/4 (1, 1, 2, 0)/1	0.18
30 months after discharge	5/22 (9, 6, 4, 3)/1	5/5 (2, 1, 2, 0)/1	0.088
<b>Dosages of QTP, mg daily, mean <math>\pm</math> SD [range]</b>			
Recovery from catatonia	754 $\pm$ 247 [300–1100]	695 $\pm$ 167 [450–900]	0.50
Discharge	850 $\pm$ 146 [600–1100]	632 $\pm$ 206 [400–900]	0.013
12 months after discharge	439 $\pm$ 162 [200–700]	592 $\pm$ 169 [400–900]	0.11
30 months after discharge	640 $\pm$ 351 [300–1200]	615 $\pm$ 49 [575–700]	0.88

**Abbreviations:** BFCRS, Bush–Francis Catatonia Rating Scale; BZP, benzodiazepine dosage (lorazepam equivalent) at time of recovery from catatonia; CBZ, carbamazepine; cECT, co-treatment with electroconvulsive therapy; CGI-S, Clinical Global Impression–Severity; FGA, first-generation antipsychotic; h-CK, serum creatine kinase  $>500$  IU/L; Li, lithium carbonate; NMS, neuroleptic malignant syndrome; OLZ, olanzapine; QTP, quetiapine; RIS, risperidone; SD, standard deviation; SGA, second-generation antipsychotic; VPA, sodium valproate.



**Figure 1** A flow chart of antipsychotics used for 39 patients during the period from admission to recovery from catatonia.

**Note:** \*Equivalent to chlorpromazine.

**Abbreviations:** APZ, aripiprazole; BFCRS, Bush–Francis Catatonia Rating Scale; BZP, benzodiazepine dosage (lorazepam equivalent); CBZ, carbamazepine; ECT, electroconvulsive therapy; FGA, first-generation antipsychotic; Li, lithium carbonate; MS, mood stabilizers; OLZ, olanzapine; QTP, quetiapine; RIS, risperidone; VPA, sodium valproate.

conditions in which other antipsychotics are risky. From the time of recovery from catatonia to discharge, the mean dosages of QTP for patients who were administered ECT decreased (from 805 to 733 mg/day), and those for patients who were not administered ECT increased (from 671 to 727 mg/day). Only one patient was treated with high-dose BZP (7.2 mg, equivalent to lorazepam 6 mg or more daily), and 33 patients were treated with low-dose BZP. From the time of recovery from catatonia to 30 months after discharge,

QTP was switched to other antipsychotics for 16/24 patients (insufficient efficacy, eight; sedation, three; hyperglycemia, two; weight gain, one; initiation of depot, two), and other antipsychotics were switched to QTP for 2/15 patients (dysphoria, one; extrapyramidal side effects, one).

## Discussion

To our knowledge, this is the first report of a naturalistic investigation indicating that QTP might be a promising

agent in the treatment of acute schizophrenia with catatonic stupor. Further, QTP might be more effective than other antipsychotics in the presence of catatonic stupor, fever, and h-CK. Only QTP was used at significantly higher rates at the time of recovery from catatonia and discharge than at the time of admission. The same was true in patients who were not administered ECT. The rate of QTP use at the time of recovery from catatonia and discharge was significantly higher in patients with severe stupor than in patients with less severe stupor. On the other hand, the rates had decreased at 12 and 30 months after discharge. Therefore, QTP was specifically more effective during the acute phase than the maintenance phase in the treatment of schizophrenia with catatonic stupor. However, five limitations apply.

First, the rate of QTP use is not necessarily equivalent to the effectiveness of QTP because our research was performed at a single hospital without a specific treatment algorithm and we investigated the medical records retrospectively. Thus, the possibility of physicians' preferences in drug selection cannot be ruled out. The attending physician might have chosen QTP with the possibility in mind that the underlying causes of catatonia were mood disorders such as bipolar depression, for which QTP is effective and first-line treatment.<sup>28</sup> Most catatonic patients suffer from mood disorders.<sup>5,6</sup> If a history of present illness is unclear, the underlying cause of catatonia cannot be confirmed because it is difficult to conduct a structured interview with patients with catatonic stupor. However, all of the physicians at Okayama Psychiatric Medical Center during the period of study did not have a marked predilection for QTP. We most frequently used risperidone as first-line treatment for patients with acute schizophrenia characterized by catatonic stupor in the same way as those without catatonia. Further, we generally chose QTP or olanzapine as second-line treatment if first-line antipsychotics were not efficacious or poorly tolerated. Eventually most patients recovered from catatonia and were discharged with QTP or a combination of QTP and ECT. Moreover, we would like to consider the prescription of antipsychotics of patients with the diagnosis of schizophrenia without catatonia ( $n=175$ ), who received acute psychiatric hospital treatment between April 2008 and March 2009 at our psychiatric acute inpatient ward. Although the investigation period is different from that of this report, the rate of QTP use for non-catatonic schizophrenia patients was continuously about 10% (admission, 9.7%; discharge, 8.0%; 12 months after discharge, 13.2%) in our hospital.<sup>29</sup>

Second, this study is a retrospective chart review and the sample size ( $n=39$ ) is too small. Third, the effectiveness of BZP combined with mood stabilizers was not considered.

Fourth, a more favorable outcome might have been obtained from high-dose BZP without antipsychotics during catatonia. Only one patient had been treated with high-dose BZP in our case series. High-dose BZP trial remained a first option in the treatment of catatonia whatever the condition associated with.<sup>4,30</sup> Antipsychotic treatment might be one factor that resulted in the development of catatonia. Fifth, clozapine, which may have beneficial effects for catatonia in psychotic patients,<sup>31</sup> was not used during the acute phase in this study.

The mean dosages of QTP at discharge for patients with severe stupor was significantly lower than those for patients with less severe stupor, because patients with severe stupor were administered ECT at a significantly higher rate than patients with less severe stupor. From the time of recovery from catatonia to discharge, the dosages of QTP for patients who were administered ECT had decreased to improve the tolerability of medication, and the dosages of QTP for patients who were not administered ECT had increased to treat remaining psychotic symptoms.

Catatonia is thought to be predominantly caused by dopamine hypoactivity, specifically at  $D_2$  receptors, which leads to an increase in the release of glutamate in an attempt to increase dopamine activity.<sup>32</sup> In studies on rat models, QTP was shown to increase the release of dopamine, norepinephrine, and glutamate in the medial prefrontal cortex in a dose-dependent fashion without affecting the release of serotonin or gamma-aminobutyric acid levels in the same area.<sup>33</sup> BZP potentiates the action of gamma-aminobutyric acid, which can inhibit glutamate hyperactivity.<sup>32</sup> It is possible that there are combined effects of QTP and BZP in the treatment of catatonia.

To further support the hypoactive  $D_2$  receptor theory, several case reports exist that demonstrate high-potency typical antipsychotics either causing or worsening catatonia.<sup>31,32</sup> The antagonism of  $D_2$  receptors by QTP is the weakest of all antipsychotics. The affinity for  $D_2$  receptors of QTP is weaker than that of intrinsic dopamine (loose binding),<sup>34,35</sup> and it is the most rapid to dissociate from  $D_2$  receptors (transient blockade).<sup>36,37</sup> Thus, QTP may be tolerable when patients are at risk of NMS if treated with antipsychotics. However, it is necessary to consider the benefits and risks of QTP because cases of NMS have been reported in conjunction with all antipsychotics including QTP.<sup>38</sup>

Although the efficacy of QTP in the treatment of acute schizophrenia with catatonic stupor cannot be confirmed given the small number of cases, retrospective study design which merely describes physician preference and the concurrent use of ECT and/or BZP, our study indicated that this



antipsychotic agent may be somewhat better tolerated in patients with catatonic stupor.

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## Disclosure

The authors report no conflicts of interest in this work.

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