

# The efficacy of antipsychotics for prolonged delirium with renal dysfunction

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**Aim:** Delirium is commonly encountered in daily clinical practice. To identify predictors influencing outcomes, we retrospectively examined the characteristics of inpatients with delirium who required psychiatric medication during hospitalization.

**Methods:** We extracted all new inpatients (n=523) consulted for psychiatric symptoms at Fukushima Medical University Hospital between October 2011 and September 2013. We selected 203 inpatients with delirium diagnosed by psychiatrists. We analyzed data from 177 inpatients with delirium who received psychiatric medication. We defined an “early improvement group” in which delirium resolved in  $\leq 3$  days after starting psychiatric medication, and a “prolonged group” with delirium lasting for  $> 3$  days. Among the 83 inpatients with renal dysfunction (estimated glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup>), we defined an “early improvement group with renal dysfunction” in which delirium resolved in  $\leq 3$  days after starting psychiatric medication and a “prolonged group with renal dysfunction” with delirium lasting for  $> 3$  days. We then examined differences between groups for different categorical variables.

**Results:** Dose of antipsychotic medication at end point was significantly lower in the prolonged group with renal dysfunction than in the early improvement group with renal dysfunction.

**Conclusion:** The results suggest that maintaining a sufficient dose of antipsychotics from an early stage may prevent prolongation of delirium even in inpatients with renal dysfunction.

**Keywords:** antipsychotic, prolonged delirium, chronic kidney disease, pharmacokinetics

## Introduction

Delirium is an acute disorganization of mental status, characterized by deficits of attention and awareness, cognitive and perceptive dysfunctions, and disturbances in circadian rhythm, and is commonly encountered in daily clinical practice among elderly inpatients.<sup>1</sup> Delirium involves many important issues, including greater hospitalization time, exhaustion of medical staff and family members, delayed recovery, and increased mortality rates,<sup>2–5</sup> but can generally be improved by removing the cause and providing appropriate pharmacotherapy. Lee et al<sup>6</sup> reported that prolonged delirium defined as symptoms lasting for  $> 4$  weeks was seen in 20% of inpatients after hip fracture surgery. Another study showed that elevated plasma concentrations of markers of endothelial activation and blood–brain barrier/neurological injury during critical illness were associated with prolonged delirium.<sup>7</sup> Cognitive involvement (eg, delirium) and dementia are commonly seen in patients with renal dysfunction.<sup>8</sup> Chronic kidney disease has been reported to lead to cognitive alterations (eg, delirium) through factors such as neuronal damage caused by uremic toxins, cerebrovascular ischemic lesions, oxidative stress, chronic inflammation, anemia, hyperhomocysteinemia, and endothelial dysfunction.<sup>9</sup> However, no reports appear to have investigated correlations between prolonged delirium and medications from the perspective of renal function. The present

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retrospective study examined the characteristics of inpatients with delirium at Fukushima Medical University Hospital with the aim of identifying predictors of outcomes.

## Methods

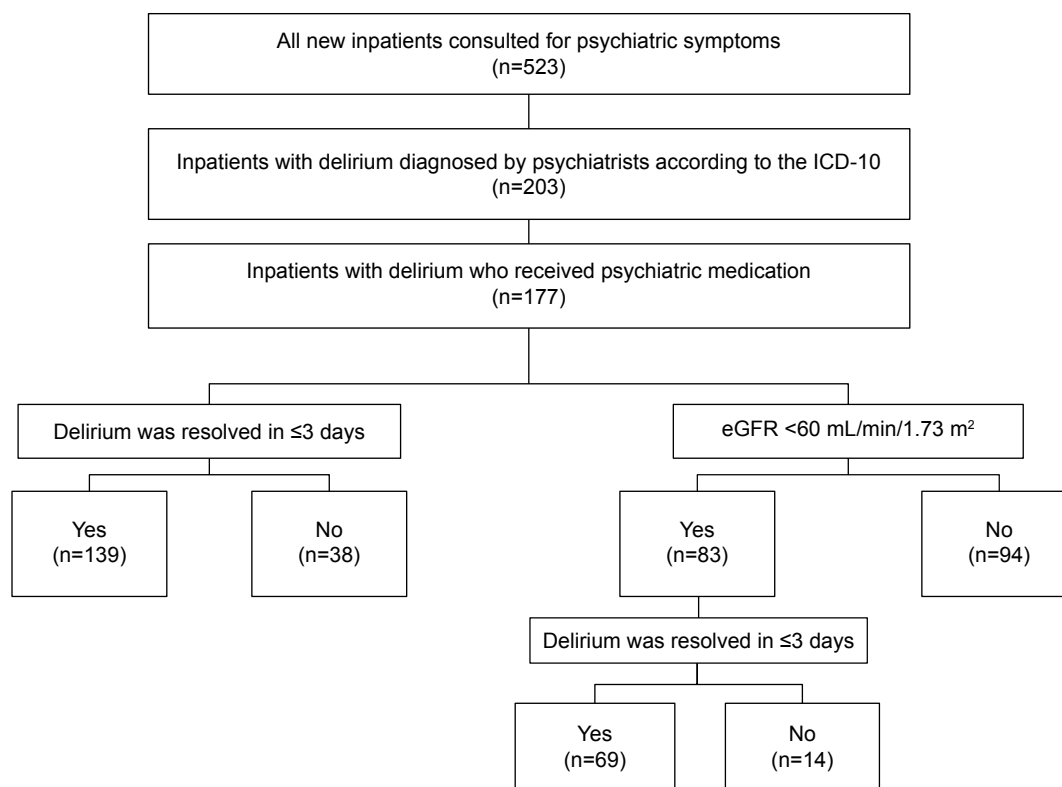
### Study design and subjects

We extracted all new inpatients ( $n=523$ ) consulted for psychiatric symptoms at Fukushima Medical University Hospital between October 2011 and September 2013. Of these, we selected 203 inpatients with delirium diagnosed by psychiatrists according to the International Classification of Diseases-10th revision (ICD-10).<sup>10</sup> We analyzed data from 177 inpatients with delirium who received psychiatric medication (Figure 1). All analyses in this study were conducted anonymously in a linkable fashion. The ethics committee at Fukushima Medical University waived the need for patient consent for this retrospective review since all data were anonymized and kept confidential. This study was approved by the ethics committee at Fukushima Medical University (No 1746).

### Measurements

Using medical records, the following information was collected for delirium cases: sex (male or female), age (18–49,

50–64, or  $\geq 65$  years), department from which consultation originated (departments of internal medicine, emergency medicine, surgery, otolaryngology, ophthalmology, dermatology, anesthesia, urology, obstetrics and gynecology, orthopedics, neurosurgery, or cardiac surgery), precipitating factors (infection, anemia, renal failure, postoperative state, liver failure, malignancy, intracranial lesion, steroid, benzodiazepine, opioid, and alcohol), or predisposing factors (rate of comorbid dementia; Lipowski classified cause of delirium under precipitating, predisposing, or facilitating factors),<sup>11,12</sup> duration of delirium, mortality rate (as of 3 months after initiation of psychiatric medication), psychiatric medication used and dose (in chlorpromazine equivalents [CPZ-eq]), and laboratory findings (concentrations of C-reactive protein [CRP], hemoglobin [Hb], and aspartate aminotransferase [AST], and estimated glomerular filtration rate [eGFR]). In this retrospective study, we reviewed medical records for notes by the psychiatrist at the time of first psychiatric examination and judged precipitating, predisposing, and facilitating factors. We judged improvement or non-improvement of delirium by reviewing medical records for notes from the psychiatrist. Laboratory data were determined as values at the time of first examination by the psychiatrist. We defined



**Figure 1** Flow of patients through the study.

**Abbreviations:** eGFR, estimated glomerular filtration rate; ICD-10, International Classification of Diseases, 10th revision.

**Table 1** Patient characteristics

Characteristics	Male	Female	Total
Total	119 (67.2%)	58 (32.8%)	177
Age (years)			
18–49	3 (1.7%)	2 (1.2%)	5 (2.9%)
50–64	22 (12.4%)	8 (4.5%)	30 (16.9%)
≥65	94 (53.1%)	48 (27.1%)	142 (80.2%)
Precipitating factors			
Infection			154 (87%)
Anemia			145 (81.9%)
Renal failure			83 (46.9%)
Postoperative state			63 (35.6%)
Liver failure			55 (31.1%)
Malignancy			46 (26%)
Intracranial lesion			27 (15.3%)
Steroid			16 (9%)
Benzodiazepine			15 (8.5%)
Opioid			15 (8.5%)
Alcohol			14 (7.9%)
Dementia	34 (19.2%)	22 (12.4%)	56 (31.6%)
Duration of delirium (days) (mean ± SD)	3.3±4.4	2.7±3.4	3.1±4.1
Death	17 (9.6%)	10 (5.6%)	27 (15.3%)

**Note:** Mean period from psychiatric medication to resolution of delirium was 3.1±4.1 days.

hypoactive delirium as a condition in which an inpatient might display lethargy, reduced motor activity, incoherent speech, and lack of interest (Tables 1–3).<sup>12,13</sup> Delirium was diagnosed by psychiatrists according to the ICD-10.<sup>10</sup>

Among the 177 inpatients, we defined an “early improvement group” (n=139) in which delirium resolved in ≤3 days

**Table 2** Characteristics of the early improvement and prolonged groups

Characteristics	Early improvement group (n=139)	Prolonged group (n=38)	p-value
Duration of delirium (days) (mean ± SD)	1.4±0.7	9.2±5.4	0 <sup>a*</sup>
Age (years) (mean ± SD)	75±12	73±14	0.501 <sup>a</sup>
Sex (male/female)	91/48	28/10	0.436 <sup>b</sup>
Hypoactive delirium, n (%)	11 (7.9)	4 (10.5)	0.742 <sup>b</sup>
Opioid prescription, n (%)	11 (7.9)	2 (5.3)	0.737 <sup>b</sup>
Dementia, n (%)	40 (28.8)	16 (42.1)	0.167 <sup>b</sup>
Death, n (%)	19 (13.7)	8 (21.1)	0.308 <sup>b</sup>
CRP (mg/dL) (mean ± SD)	7.1±7.2	8.1±6.7	0.431 <sup>a</sup>
Hb (g/dL) (mean ± SD)	10.2±2	9.9±1.9	0.574 <sup>a</sup>
eGFR (mL/min) (mean ± SD)	62±36	75±37	0.052 <sup>a</sup>
AST (U/L) (mean ± SD)	48±56	42±45	0.470 <sup>a</sup>

**Notes:** Statistical test: Fisher’s exact test and independent *t*-test for analysis of ordinal data. No significant differences in characteristics of early improvement or prolonged groups are evident, except for duration of delirium and eGFR. <sup>a</sup>Significantly different. <sup>b</sup>Independent *t*-test; <sup>c</sup>Fisher’s exact test.

**Abbreviations:** AST, aspartate aminotransferase; CRP, C-reactive protein; Death, mortality rate as of 3 months after initiation of psychiatric medication; Dementia, rate of comorbid dementia; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Hypoactive delirium, rate of hypoactive delirium; Opioid prescription, rate of opioid prescription.

**Table 3** Characteristics of early improvement group with renal dysfunction and prolonged group with renal dysfunction

Characteristics	Early improvement group with renal dysfunction (n=69)	Prolonged group with renal dysfunction (n=14)	p-value
Duration of delirium (days) (mean ± SD)	1.3±0.6	8.6±5.9	0 <sup>a,*</sup>
Age (years) (mean ± SD)	77±10	74±13	0.379 <sup>a</sup>
Sex (male/female)	48/21	10/4	1 <sup>b</sup>
Hypoactive delirium, n (%)	3 (4.3)	1 (7.1)	0.53 <sup>b</sup>
Opioid prescription, n (%)	7 (10.1)	1 (7.1)	1 <sup>b</sup>
Dementia, n (%)	20 (29)	5 (35.7)	0.75 <sup>b</sup>
Death, n (%)	12 (17.4)	4 (28.6)	0.456 <sup>b</sup>
CRP (mg/dL) (mean ± SD)	8.7±7.5	8.2±6.8	0.800 <sup>a</sup>
Hb (g/dL) (mean ± SD)	9.8±2	9.9±2.3	0.867 <sup>a</sup>
eGFR (mL/min) (mean ± SD)	33.5±17	37±18	0.582 <sup>a</sup>
AST (U/L) (mean ± SD)	52±65	41±49	0.503 <sup>a</sup>

**Notes:** Statistical test: Fisher’s exact test and independent *t*-test for analysis of ordinal data. No significant difference is evident in characteristics of the early improvement group with renal dysfunction and the prolonged group with renal dysfunction except duration of delirium. <sup>a</sup>Significantly different. <sup>b</sup>Independent *t*-test; <sup>c</sup>Fisher’s exact test.

**Abbreviations:** AST, aspartate aminotransferase; CRP, C-reactive protein; Death, mortality rate as of 3 months after initiation of psychiatric medication; Dementia, rate of comorbid dementia; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Hypoactive delirium, rate of hypoactive delirium; Opioid prescription, rate of opioid prescription.

after initiation of psychiatric medication and a “prolonged group” (n=38) in which delirium lasted for >3 days. This cut-off of 3 days was set based on the mean period from initiation of psychiatric medication to resolution of delirium of 3.1±4.1 days. Among the 83 inpatients with renal dysfunction (eGFR <60 mL/min/1.73 m<sup>2</sup>), we defined an “early improvement group with renal dysfunction” (n=69) in which delirium resolved in ≤3 days after initiation of psychiatric medication and a “prolonged group with renal dysfunction” (n=14) in which delirium lasted for >3 days. We then examined differences in categorical variables between groups.

## Statistical analysis

Statistical tests were performed using SPSS version 21 software (International Business Machines Corp., Armonk, NY, USA). Differences between groups for each categorical variable were calculated using Fisher’s exact test and independent *t*-tests. Fisher’s exact test was used for analyses of categorical data (eg, sex, rate of hypoactive delirium, rate of opioid prescription, rate of comorbid dementia, and mortality rate). Independent *t*-tests were applied for analyses of continuous data (eg, duration of delirium, age, CRP, Hb, eGFR, and AST). Values of *p*<0.05 were regarded as statistically significant.

## Results

### Characteristics of study participants

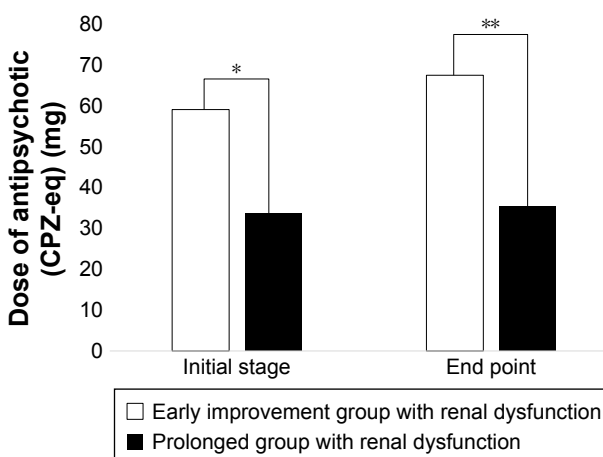
Table 1 shows the characteristics of inpatients in this study. The mean age of inpatients was  $74.3 \pm 12.4$  years, with 67.2% male and 32.8% female. The department from which consultation originated was most frequently one of the internal medicine departments (32.8%), followed by the emergency department (14.7%) and surgery department (13.6%). Among the departments of internal medicine, we found that the most common origin of consultation was the department of nephrology (27.6%), followed in descending order by the departments of gastroenterology, cardiovascular medicine, and pulmonary medicine. As precipitating factors, we detected infectious diseases (CRP  $>0.3$  mg/dL, 87%) as the most common, followed by anemia (Hb  $<11$  g/dL for females or  $<13$  g/dL for males, 81.9%), renal dysfunction (eGFR  $<60$  mL/min/1.73 m<sup>2</sup>, 46.9%), postoperative status (35.6%), liver dysfunction (AST  $>40$  U/L, 31.1%), malignant tumor (26%), brain disease (15.3%), steroids (9%), benzodiazepines (8.5%), opioids (8.5%), and alcohol (7.9%). The rate of inpatients with comorbid dementia as a predisposing factor was 31.6%. By subtypes of delirium, hyperactive type comprised 8.5%. With respect to the duration of delirium, mean period from psychiatric medication to resolution of delirium was  $3.1 \pm 4.1$  days. About 78.5% of inpatients resolved delirium within 3 days and 15.3% of inpatients had died by 3 months after starting psychiatric medication.

### Summary of psychiatric drug used in this study

Among the 177 inpatients in this study, 66.1% received antipsychotic drugs in the initial stage (mean dose,  $92.3 \pm 68.1$  mg CPZ-eq) and 71.8% were receiving antipsychotic drugs at the end point (mean dose,  $101.2 \pm 77.1$  mg CPZ-eq). Risperidone was the most frequently prescribed antipsychotic, followed by quetiapine, perospirone, haloperidol, and tiapride. As initial prescriptions, frequencies were as follow: risperidone, 43%; quetiapine, 26%; perospirone, 15%; haloperidol, 14%; and tiapride, 2%. As end prescriptions, frequencies were as follow: risperidone, 36%; quetiapine, 24%; perospirone, 16%; haloperidol, 13%; and tiapride, 11%.

### Characteristics of early improvement and prolonged groups

Fisher's exact test showed no significant differences in rate of antipsychotic use at either initial stage or end point between early improvement and prolonged groups. Independent



**Figure 2** Dose of antipsychotic (CPZ-eq) in the early improvement group with renal dysfunction and prolonged group with renal dysfunction.

**Notes:** \*\* $p < 0.05$ ; \* $p < 0.1$ . Independent *t*-test shows that the dose of antipsychotic in the initial stage is marginally but significantly lower in the prolonged group with renal dysfunction than in the early improvement group with renal dysfunction ( $t(25.801) = 1.827$ ;  $p = 0.079$ ), and dose at end point is also significantly lower in the prolonged group with renal dysfunction than in the early improvement group with renal dysfunction ( $t(31.401) = 2.221$ ;  $p = 0.034$ ). Early improvement group with renal dysfunction, eGFR  $<60$  mL/min/1.73 m<sup>2</sup> and delirium resolved in  $\leq 3$  days; prolonged group with renal dysfunction, eGFR  $<60$  mL/min/1.73 m<sup>2</sup> and delirium lasting for  $>3$  days.

**Abbreviations:** CPZ-eq, chlorpromazine-equivalents; eGFR, estimated glomerular filtration rate.

*t*-testing also showed no significant differences in dose of antipsychotic at either initial stage or end point between early improvement and prolonged groups.

### Characteristics of early improvement group with renal dysfunction and prolonged group with renal dysfunction

Fisher's exact test showed no significant difference in rate of antipsychotic use at either initial stage or end point between the early improvement group with renal dysfunction and the prolonged group with renal dysfunction. Independent *t*-testing showed that the dose of antipsychotic at the initial stage was marginally but significantly lower in the prolonged group with renal dysfunction than in the early improvement group with renal dysfunction ( $t(25.801) = 1.827$ ;  $p = 0.079$ ), and dose at end point was also significantly lower in the prolonged group with renal dysfunction than in the early improvement group with renal dysfunction ( $t(31.401) = 2.221$ ;  $p = 0.034$ ; Figure 2).

## Discussion

We performed this retrospective study to examine data from 177 inpatients with delirium who received psychiatric medication between October 2011 and September 2013 at Fukushima Medical University Hospital. The dose of

antipsychotic in the initial stage was marginally but significantly lower in the prolonged group with renal dysfunction than in the early improvement group with renal dysfunction, and the dose at end point was also significantly lower in the prolonged group with renal dysfunction than in the early improvement group with renal dysfunction.

First, we examined predictors of the outcome of delirium. In 2014, Hatta et al<sup>14</sup> noted significant differences in rates of opioid prescription, hypoactive delirium, extrapyramidal symptoms and mortality, and Clinical Global Impressions-Improvement Scale<sup>15</sup> score, between 1,332 inpatients in whom delirium resolved within 1 week and 1,121 inpatients in whom delirium lasted for >1 week. The study found no significant differences between an early improvement group (delirium resolved in  $\leq 3$  days) and a prolonged group (delirium lasting for >3 days) in terms of sex, age, rate of comorbid dementia, opioid prescription, subtypes of delirium, mortality, or laboratory findings. The present study of 177 inpatients yielded results similar to the findings of Hatta et al<sup>14</sup> for their 2,453 inpatients in terms of sex, age, rate of comorbid dementia, rate of hypoactive delirium, and mortality, but differed markedly in the rate of opioid prescription (8.5% vs 18%, respectively). The difference in opioid prescription might be related to the differences in findings. In addition, we thought that differences in prescription tendencies by region and medical attendants might have affected our results. Further studies are needed to clarify other factors such as daily living activities before admission, and body mass index.

We then considered antipsychotic medication for delirium. We found no significant difference in antipsychotic dose between early improvement and prolonged groups. However, doses of antipsychotic at both the initial stage and the end point were lower in the prolonged group with renal dysfunction than in the early improvement group with renal dysfunction. No significant differences in other clinical information were found between the early improvement group with renal dysfunction and the prolonged group with renal dysfunction (Table 3). In inpatients with renal dysfunction, an insufficient dose of antipsychotic might prolong delirium. Elevated blood concentrations of an antipsychotic or its active moiety during renal dysfunction may be connected to side effects such as extrapyramidal symptoms.<sup>16</sup> However, pharmacokinetics under conditions of renal dysfunction are yet to be clarified for all drugs used to treat delirium.<sup>17</sup> We thus carefully set the initial dose at a low level and subsequently increased or decreased the dose as needed. On the other hand, identification of other effects reflecting poor general

status that we did not investigate in this study might allow psychiatrists to reduce the dose of antipsychotic. We hope to perform further supplementary examinations and investigations in the future.

## Limitations

Various limitations to the present study must be considered when interpreting the results. We did not judge improvements in delirium using a standardized objective scale, because Clinical Global Impressions-Improvement Scale<sup>15</sup> score results were not available in this retrospective study. We hope to examine the use of Clinical Global Impressions-Improvement Scale<sup>15</sup> scores in the future.

Because prolongation of delirium may be associated with the use of or changes in medications, further investigation of the adverse effects of pharmacotherapy is warranted.

Likewise, because discharge (to home or other hospitals) may be related to duration of delirium and number of hospitalization days, further analysis should be performed.

We also wish to examine differences between university hospitals and city hospitals. As our hospital has only 10 dialysis machines, analysis of results from hospitals with more opportunities for dialysis is needed in the future. Finally, we would like to undertake a prospective examination in a fixed-dose setting.

## Conclusion

We collected and analyzed data from 177 inpatients with delirium who received psychiatric medication between October 2011 and September 2013 at Fukushima Medical University Hospital. The results suggested that a sufficient dose of antipsychotics from the early stage may prevent prolongation of delirium, even in inpatients with renal dysfunction.

## Disclosure

The authors report no conflicts of interest in this work.

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