

Antipsychotics for delirium in the general hospital setting in consecutive 2453 inpatients: a prospective observational study

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Objective: Attention to risk of antipsychotics for older patients with delirium has been paid. A clinical question was whether risk of antipsychotics for older patients with delirium would exceed efficacy of those even in the general hospital setting.

Methods: A prospective observational study proceeded over a 1-year period at 33 general hospitals, where at least one psychiatrist worked full time. Subjects were patients who developed delirium during their admission due to acute somatic diseases or surgery, and who received antipsychotics for delirium. The primary outcome was rates and kinds of serious adverse events.

Results: Among 2834 patients who developed delirium, 2453 patients received antipsychotics, such as risperidone (34%), quetiapine (32%), and parenteral haloperidol (20%), for delirium. Out of 2453 patients, 22 serious adverse events (0.9%) were reported. Aspiration pneumonia was the most frequent (17 patients, 0.7%), followed by cardiovascular events (4 patients, 0.2%) and venous thromboembolism (1 patient, 0.0%). There was no patient with a fracture or intracranial injury due to a fall. No one died because of antipsychotic side effects. The mean Clinical Global Impressions—Improvement Scale score was 2.02 (SD 1.09). Delirium was resolved within 1 week in more than half of the patients (54%).

Conclusions: In the general hospital setting under management including fine dosage adjustment and early detection of side effects, risk of antipsychotics for older patients with delirium might be low, in contrast to antipsychotics for dementia in the nursing home or outpatient settings. A point may be not how to avoid using antipsychotics but how to monitor their risk. © 2013 The Authors. *International Journal of Geriatric Psychiatry* published by John Wiley & Sons, Ltd.

Key words: delirium; antipsychotic; adverse event; risperidone; quetiapine; perospirone; olanzapine; aripiprazole; haloperidol; aspiration pneumonia

History: Received 22 March 2013; Accepted 31 May 2013; Published online 25 June 2013 in Wiley Online Library (wileyonlinelibrary.com)

DOI: 10.1002/gps.3999

Introduction

Delirium is an acute change in cognition with altered consciousness and impaired attention that fluctuates over time (American Psychiatric Association, 2000). Reportedly, its prevalence ranges from 11% to 33% on admission, and its incidence during the hospital stay ranges between 3% and 56% (Michaud *et al.*, 2007). With an increasingly aging population, delirium will increase further in the general hospital setting. However, there is no approved medication for delirium. In clinical practice, antipsychotics are widely used for treatment according to clinical guidelines (American Psychiatric Association, 1999). In 2005, the Food and Drug Administration warned that the treatment of behavioral disorders in older patients with dementia with antipsychotic medications was associated with increased mortality, analyzing a total of 17 placebo-controlled trials (US Food and Drug Administration, 2005). Although the background data of the warning were not disclosed, a meta-analysis of randomized placebo-controlled trials on atypical antipsychotic drug treatment for dementia supported it just after the warning came out (Schneider *et al.*, 2005). Therefore, the data source of the meta-analysis and those of the warning may have been almost the same. Thus, we can see the basis of the warning through the content of the meta-analysis. Remarkably, the randomized placebo-controlled trials analyzed in the meta-analysis were performed in nursing homes and outpatients where medical management may have been inferior to that of a general hospital setting. Nevertheless, we have had hesitation in prescribing antipsychotics for delirium even in a hospital setting because the warning came out. We therefore prospectively examined whether antipsychotics for delirium would cause serious outcomes even in the general hospital setting under management by psychiatrists and whether risk of antipsychotics for older patients with delirium would exceed their efficacy even in such a clinical setting.

Methods

Design

This prospective observational study proceeded over a 12-month period (1 October 2011 to 30 September 2012) in 33 general hospitals where at least one psychiatrist worked full time. All study protocols were approved by the institutional review board of Juntendo University School of Medicine. The approved protocol

did not require informed consent from patients because the design was not experimental but naturalistic and because the data in this observational study remained anonymous and were analyzed in the aggregate.

Subjects

Any sudden change in mental state of patients during their admission due to acute somatic diseases or surgery has resulted in immediate referral to psychiatrists participating in the study, who were all specialists of consultation and liaison psychiatry. Among such patients, the subjects of this study were patients who developed delirium and who received antipsychotics for delirium. The diagnosis of delirium was made by the psychiatrists according to the DSM-IV-TR (American Psychiatric Association, 2000). Delirium assessments were undertaken serially until discharge. Whether a patient was treated with an antipsychotic drug or not was determined by the psychiatrists according to clinical requirement. Although antipsychotic use was psychiatrists' discretion, needless administration of antipsychotics did not seem to happen because of the priority of non-pharmacological management for delirium. Non-pharmacological management of delirium includes treatment of all potential underlying causes and the provision of supportive care including minimize drug side effects, correct electrolytic disturbances and dehydration, improve communication and orientation, limit sensory underload or overload, involve and inform significant others, and favor mobilization. Antipsychotic treatment was managed by the psychiatrists until it was not needed. Data collection was consecutive.

Outcome measure

With respect to serious adverse events, we referred to the FDA MEDWATCH criteria (<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>) and focused on aspiration pneumonia, cardiovascular events, fractures due to falls, intracranial injuries due to falls, and venous thromboembolism, which concerned psychiatrists in clinical practice in situations of antipsychotic use for delirium. Also, we planned to record other serious adverse events related to death, life-threatening diseases, prolonged hospitalization, disability, or permanent damage during antipsychotic medication. The primary outcome was the rate of such serious adverse events.

Psychiatrists, primary treating physicians, and bedside nurses noted the adverse events and discussed

whether the events were antipsychotic side effects considering baseline preexisting conditions as a comparison.

Other information collected includes the following: (1) demographic characteristics such as age and gender; (2) kinds of antipsychotics prescribed and their maximum dose (mg/day); (3) the most contributory factor for etiology of delirium; (4) comorbidity of dementia; (5) opioid prescribing; (6) motor variant of delirium according to the Data-based Definition of Motor Subtypes (Meagher *et al.*, 2008); (7) the Clinical Global Impressions—Improvement Scale (CGI-I: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse) (Guy, 1976) for evaluating the effects of antipsychotics on delirium; (8) the number of patients with extrapyramidal symptoms after receiving antipsychotics, and their severity according to the Drug-induced Extrapyramidal Symptom Scale (DIEPSS), which includes parkinsonism, akathisia, dystonia, and dyskinesia, and is a five-point measure of intensity (0 = no symptom to 4 = severe) (Inada, 1996); (9) psychotropic drugs combined with antipsychotics; (10) duration of delirium; (11) clinical course; and (12) the reason for death to patients applicable.

From our experience, we expected that most antipsychotic medication for delirium would last a short period, and rescue doses of the same antipsychotics would be often added. Therefore, we expected that it would be difficult to determine modal doses in quite a few patients, and that, in such a situation, maximal doses would be more reliable than modal doses.

Psychiatrists who were experts on consultation-liaison psychiatry determined the most contributory factor of delirium for each patient essentially according to the Delirium Etiology Rating Checklist (Trzepacz, 1999).

Delirium resolution was determined by no longer demonstrating signs of delirium defined in the DSM-IV-TR. Psychiatrists at each site attended patients with delirium daily until their discharge or more than 2 weeks after delirium resolution. Therefore, delirium duration in the present study may be reliable.

Statistics

Data were analyzed using SPSS 20-J software (IBM Japan, Tokyo, Japan). All the results were based on the kind of antipsychotics used. Differences between categorical variables were calculated using chi-square test. Differences among groups in demographic and clinical characteristics were calculated with Kruskal–Wallis test, and post

hoc Dunn's multiple comparisons test was used. *p*-value of less than 0.05 was regarded as statistically significant.

Results

Demography and clinical characteristics

A total of 2834 patients developed delirium during the study period. Among them, non-pharmacological management alone was indicated to 381 patients because delirium lasted only a few hours or one night, or was less severe. The other 2453 patients received antipsychotics for delirium (Table 1). Risperidone was the most frequently prescribed among them (835 patients, 34%), and quetiapine was the second (779 patients, 32%). The third frequent prescription was haloperidol (480 patients, 20%), which was all administered parenterally. The fourth was perospirone (88 patients, 3.6%), followed by olanzapine (87 patients, 3.5%) and aripiprazole (61 patients, 2.5%).

The mean age of 2453 patients with antipsychotics was 73.5 (SD 12.5) years. Kruskal–Wallis test revealed a significant difference in age between the groups ($p < 0.0001$). Post hoc Dunn's multiple comparisons test showed that there was no significant difference in age only between patients with olanzapine and patients with aripiprazole. The rate of men among them was 63%. The rate of men in patients with aripiprazole was significantly lower than other patients (48% vs. 64%, $p = 0.014$).

The most contributory factor for etiology of delirium was listed in Table 2. Postoperative factor was the most frequent (20%), followed by neoplasm (systemic) (11%) and infection (systemic) (10%).

The rate of comorbid dementia was 30%. The rate was significantly higher in patients with perospirone than in other patients (42% vs. 30%, $p = 0.019$), whereas the rates in patients with haloperidol and in patients with olanzapine were significantly lower than the rate in other patients, respectively (20% vs. 33%, $p < 0.0001$; 20% vs. 31%, $p = 0.033$).

The rate of opioid prescription was 18%. The rates in patients with olanzapine and in patients with haloperidol were significantly higher than the rate in other patients, respectively (32% vs. 18%, $p = 0.0011$; 27% vs. 16%, $p < 0.0001$).

The rate of hypoactive delirium was 7.5%. The rate was significantly higher in patients with aripiprazole than in other patients (33% vs. 6.9%, $p < 0.0001$).

The mean maximum dose of quetiapine (71.8 mg/day, SD 87.5) was smaller than that of risperidone (1.35 mg/day, SD 0.96), considering

Table 1 Baseline characteristics of patients with antipsychotic medication for delirium

	Total	Risperidone	Quetiapine	Perospirone	Olanzapine	Aripiprazole	Haloperidol	Others
Number of patients (%)	2453	835 (34)	779 (32)	88 (3.6)	87 (3.5)	61 (2.5)	480 (20)	123 (5.0)
Age, years ^a	73.5 (12.5)	73.5 (12.5)	74.4 (12.5)	77.2 (10.4)	66.6 (15.1)	70.2 (11.8)	71.9 (12.4)	77.0 (9.7)
Men, n (%) ^b	1554 (63)	544 (65)	475 (61)	54 (61)	53 (61)	29 (48)	322 (67)	77 (63)
Asian, n (%)	2453 (100)	835 (100)	779 (100)	88 (100)	87 (100)	61 (100)	480 (100)	123 (100)
Dementia, n (%) ^c	741 (30)	259 (31)	261 (34)	37 (42)	17 (20)	15 (25)	95 (20)	57 (46)
Opioid prescription, n (%) ^d	449 (18)	121 (14)	128 (16)	13 (15)	28 (32)	13 (21)	129 (27)	17 (14)
Hypoaffective delirium, n (%) ^e	185 (7.5)	70 (8.4)	46 (5.9)	7 (8.0)	7 (8.0)	20 (33)	29 (6.0)	6 (4.9)

Data represent mean (SD) or n (%), unless otherwise indicated.

^aKruskal–Wallis test revealed significant difference in age between the groups ($p < 0.0001$).

^bThe rate of men in patients with aripiprazole was significantly lower than other patients ($p = 0.014$).

^cThe rate was significantly higher in patients with perospirone than in other patients ($p = 0.019$), whereas the rates in patients with haloperidol and in patients with olanzapine were significantly lower than the rate in other patients, respectively ($p < 0.0001$; $p = 0.033$).

^dThe rates in patients with olanzapine and in patients with haloperidol were significantly higher than the rate in other patients, respectively ($p = 0.0011$; $p < 0.0001$).

^eThe rate was significantly higher in patients with aripiprazole than in other patients ($p < 0.0001$).

Table 2 The most contributory factor for etiology of delirium

Drug intoxication	141 (5.7)
Alcohol withdrawal	47 (1.9)
Drug withdrawal	16 (0.7)
Metabolic/endocrine disturbance	56 (2.3)
Traumatic brain injury	39 (1.6)
Seizures	4 (0.2)
Infection (intracranial)	14 (0.6)
Infection (systemic)	246 (10)
Neoplasm (intracranial)	71 (2.9)
Neoplasm (systemic)	262 (11)
Cerebrovascular	143 (5.8)
Heart failure	172 (7.0)
Respiratory failure	126 (5.1)
Liver failure	65 (2.6)
Renal failure	65 (2.6)
Parkinson's disease	14 (0.6)
Other central nervous system disease	56 (2.3)
Radiation	7 (0.3)
Fracture	101 (4.1)
Postoperative	480 (20)
Connective tissue disease	17 (0.7)
Environmental change	164 (6.7)
Other	147 (6.0)

The most contributory factor for each patient was listed.

dose equivalency (Gardner *et al.*, 2010) (Table 3). The mean maximum doses of olanzapine (10.2 mg/day, SD 11.1) and haloperidol (6.40 mg/day, SD 5.05) were larger than that of risperidone, considering dose equivalency.

The rate of antipsychotic monotherapy without any psychotropic drugs was 66%. The rate was significantly higher in patients with perospirone than in other patients (48% vs. 34%, $p = 0.011$). Table 4 shows the psychotropic concomitant with antipsychotic medication for delirium.

The numbers of patients who switched from another antipsychotic drug that was prescribed first because of insufficient efficacy or side effects were as follows: risperidone, 63 (7.5%); quetiapine, 45 (5.8%); perospirone, 7 (8.0%); olanzapine, 8 (9.2%); and aripiprazole, 3 (4.9%). There was no significant difference in the rate between the groups.

As to clinical course, 51% of patients returned home (Table 3). The rate was significantly higher in patients with risperidone than in other patients (55% vs. 49%, $p = 0.0097$). Meanwhile, 16% of patients died. The rate was significantly higher in patients with haloperidol than in other patients (29% vs. 13%, $p < 0.0001$). All of 386 (16%) patients died of original diseases, most of which were cancer, as evidenced by a total of 449 (18%) patients with opioid prescribed as shown in Table 1. Basically, antipsychotics were discontinued as soon as delirium disappeared. Therefore, most patients received antipsychotic medication for a short period except terminal cases of cancer, in which delirium often lasted just before death.

Table 3 Outcomes of patients with antipsychotic medication for delirium

	Total (n = 2453)	Risperidone (n = 835)	Quetiapine (n = 779)	Perospirone (n = 88)	Olanzapine (n = 87)	Aripiprazole (n = 61)	Haloperidol (n = 480)	Others (n = 123)
Maximum dose, mg/day	2.02 (1.09)	1.35 (0.96) 2.13 (1.10)	71.8 (87.5) 1.74 (0.96)	8.09 (5.27) 1.85 (0.89)	10.2 (11.1) 1.93 (1.05)	7.23 (7.03) 2.16 (1.33)	6.40 (5.05) 2.32 (1.16)	2.02 (1.09)
CGI-I ^a								
Duration of delirium, n (%)								
≤1 week ^b	1332 (54)	411 (49)	471 (60)	49 (56)	58 (67)	26 (43)	249 (52)	68 (55)
≤2 weeks	520 (21)	210 (25)	147 (19)	17 (19)	15 (17)	15 (25)	92 (19)	24 (20)
>2 weeks	601 (25)	214 (26)	161 (21)	22 (25)	14 (16)	20 (33)	139 (29)	31 (25)
Course, n (%)								
Return home ^c	1249 (51)	456 (55)	405 (52)	39 (44)	39 (45)	26 (43)	227 (47)	57 (46)
Institutionalization	695 (28)	222 (27)	261 (34)	31 (35)	25 (29)	18 (30)	95 (20)	43 (35)
Death ^d	386 (16)	108 (13)	79 (10)	12 (14)	21 (24)	11 (18)	139 (29)	16 (13)
In hospital	123 (5.0)	49 (5.9)	34 (4.4)	6 (6.8)	2 (2.3)	6 (9.8)	19 (4.0)	7 (5.7)

Data represent mean (SD) or n (%), unless otherwise indicated. CGI-I, Clinical Global Impressions—Improvement Scale.

^aKruskal–Wallis test revealed significant difference in age between the groups ($p < 0.0001$).

^bThe rate of delirium within one week was significantly higher in patients with olanzapine than in other patients ($p = 0.025$).

^cThe rate was significantly higher in patients with risperidone than in other patients ($p = 0.0097$).

^dAll death were related to aggravation of previous physical condition. The rate was significantly higher in patients with haloperidol than in other patients ($p < 0.0001$).

Table 4 Psychotropic concomitant with antipsychotic medication for delirium

	Total (n = 2453)	Risperidone (n = 835)	Quetiapine (n = 779)	Perospirone (n = 88)	Olanzapine (n = 87)	Aripiprazole (n = 61)	Haloperidol (n = 480)	Others (n = 123)
Any psychotropic, n (%) ^a	846 (34)	338 (40)	217 (28)	42 (48)	20 (23)	10 (16)	180 (38)	39 (31)
Intermediate-acting hypnotic	194 (7.9)	76 (9.1)	48 (6.2)	3 (3.4)	6 (6.9)	1 (1.6)	53 (11)	7 (5.7)
Ultra-short-acting hypnotic	134 (5.5)	53 (6.3)	36 (4.6)	9 (10)	2 (2.3)	0	22 (4.6)	12 (9.8)
Short-acting hypnotic	112 (4.6)	45 (5.4)	35 (4.5)	7 (8.0)	4 (4.6)	1 (1.6)	18 (3.8)	2 (1.6)
Tetracyclic antidepressant	89 (3.6)	43 (5.1)	24 (3.1)	6 (6.8)	1 (1.1)	2 (3.3)	9 (1.9)	4 (3.3)
Anxiolytic	61 (2.5)	26 (3.1)	9 (1.2)	3 (3.4)	2 (2.3)	1 (1.6)	17 (3.5)	3 (2.4)
Anticonvulsant	31 (1.3)	14 (1.7)	7 (0.9)	3 (3.4)	2 (2.3)	0	5 (1.0)	0
Miltazapine	19 (0.8)	3 (0.4)	10 (1.3)	1 (1.1)	1 (1.1)	1 (1.6)	3 (0.6)	0
Other	206 (8.4)	78 (9.3)	48 (6.2)	10 (11)	2 (2.3)	4 (6.6)	53 (11)	11 (8.9)

Data represent mean (SD) or n (%), unless otherwise indicated.

^aThe rate was significantly higher in patients with perospirone than in other patients ($p = 0.011$).

Table 5 Serious adverse events and extrapyramidal symptoms during antipsychotic medication for delirium

	Total (<i>n</i> = 2453)	Risperidone (<i>n</i> = 835)	Quetiapine (<i>n</i> = 779)	Perospirone (<i>n</i> = 88)	Olanzapine (<i>n</i> = 87)	Aripiprazole (<i>n</i> = 61)	Haloperidol (<i>n</i> = 480)	Others (<i>n</i> = 123)
Serious adverse event, <i>n</i> (%) ^a	22 (0.9)	8 (1.0)	5 (0.6)	0 (0)	2 (2.3)	0 (0)	5 (1.0)	3 (2.4)
Aspiration pneumonia	17 (0.7)	7 (0.8)	4 (0.5)	0	2 (2.3)	0	3 (0.6)	1 (0.8)
Cardiovascular event	4 (0.2)	1 (0.1)	1 (0.1)	0	0	0	0	2 (1.6)
Fractures due to falls	0	0	0	0	0	0	0	0
Intracranial injury due to falls	0	0	0	0	0	0	0	0
Venous thromboembolism	1 (0.0)	0	0	0	0	0	1 (0.2)	0
Others	0	0	0	0	0	0	0	0
Extrapyramidal symptoms								
Rate, <i>n</i> (%) ^b	137 (5.6)	53 (6.3)	34 (4.4)	8 (9.1)	4 (4.6)	2 (3.3)	30 (6.3)	6 (4.9)
Severity (DIEPSS), median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Data represent mean (SD) or *n* (%), unless otherwise indicated. DIEPSS, Drug-induced Extrapyramidal Symptom Scale.

^aThere was no significant difference in the rate between the groups ($p = 0.40$).

^bThere was no significant difference in the rate between the groups ($p = 0.22$).

Psychiatrists determined whether each death was associated with antipsychotics from close observation. As a result, deaths of patients in the present study did not include antipsychotic side effects.

Serious adverse events

A total of 22 serious adverse events (0.9%) were reported among 2453 patients with antipsychotics (Table 5). There was no significant difference in the rate between the groups ($p = 0.40$). Aspiration pneumonia was the most frequent (17 patients, 0.7%), followed by cardiovascular events (4 patients, 0.2%) and venous thromboembolism (1 patient, 0.0%). There was no patient with a fracture or intracranial injury due to a fall. No one died because of antipsychotic side effects.

Only nine out of 22 patients with serious adverse events (41%) were given doses above mean maximal dose for each antipsychotic drug in the present study. Furthermore, the doses above mean maximal dose were less than one standard deviation except one patient. Thus, serious adverse events might not have been associated with maximal doses of antipsychotics.

Among 17 patients who developed aspiration pneumonia during antipsychotic medication, three of them were considered to have a causal relation with antipsychotic use by the physician in charge and a psychiatrist of each site. Also, other five cases were likely to have a causal relation with antipsychotic use, as extrapyramidal

symptoms appeared simultaneously. In the rest nine cases, however, it was unclear whether they had a causal relation with antipsychotic use, as they had neither extrapyramidal symptoms nor signs of excessive sedation. Thus, eight cases of aspiration pneumonia during antipsychotic medication may have been side effects of antipsychotic, whereas the other nine cases might have been related to aggravation of previous physical condition.

Details about four patients with cardiovascular events were as follows: rapid decline of systolic blood pressure, two patients with quetiapine; bradycardia, one patient with blonanserin; and ventricular tachycardia, one patient with tiapride. In the last case, the physician in charge and a cardiologist did not consider close relationship between the ventricular tachycardia and administration of tiapride because ventricular tachycardia did not appear when tiapride was given again. Thus, among four cardiovascular events, three events were considered to be antipsychotic side effects, whereas one event was not.

Extrapyramidal symptoms

The rate of extrapyramidal symptoms among 2453 patients with antipsychotics was 5.6% (Table 5). Perospirone was the most frequent (9.1%), followed by risperidone (6.3%) and haloperidol (6.3%). However, there was no significant difference in the rate

between the groups ($p = 0.22$). As the mean maximum dose of haloperidol was higher than that of risperidone considering dose equivalency, it is remarkable that there was no difference in the rate of extrapyramidal symptoms between haloperidol and risperidone. Reportedly, extrapyramidal symptoms with intravenous haloperidol may be less frequent than those with oral haloperidol (Menza *et al.*, 1987). As all haloperidol administrations were intravenous in the present study, the occurrence of extrapyramidal symptoms might have been as low as the occurrence of those with risperidone. The rate of extrapyramidal symptoms in patients with olanzapine was low (4.6%), although the mean maximum dose of olanzapine was higher than that of risperidone. With respect to the severity of extrapyramidal symptoms, the median score of the DIEPSS was 0.0 in any group.

Effects of antipsychotics on delirium

The mean CGI-I score of 2453 patients with antipsychotics was 2.02 (SD 1.09) (Table 3). Kruskal–Wallis test revealed significant difference in CGI-I between the groups ($p < 0.0001$). Post hoc Dunn's multiple comparisons test showed that there was no significant difference only between patients with olanzapine and patients with perospirone. Even the worst mean score in patients with haloperidol was 2.32 (SD 1.16), suggesting high effects of antipsychotics on delirium.

With respect to the duration of delirium, 54% of patients were within 1 week, whereas 25% of patients were more than 2 weeks. The rate of delirium within 1 week was significantly higher in patients with olanzapine than in other patients (67% vs. 54%, $p = 0.025$).

The differences between patients whose delirium was resolved within 1 week and patients whose delirium lasted more than 1 week

Twelve out of 1332 patients (0.9%) in which delirium was resolved within 1 week had serious adverse events, whereas 10 out of 1121 patients (0.9%) in which delirium lasted more than 1 week had them (relative risk = 1.01, $p = 0.98$). Unexpectedly, thus, we could not find an association between the duration of delirium and the occurrence of serious adverse events.

Patients whose delirium lasted more than 1 week were slightly older, were less improved, and had higher rates of opioid prescription, hypoactive delirium, extrapyramidal symptoms, and death related to aggravation of previous physical condition than patients whose delirium was resolved within 1 week (Table 6).

Discussion

The present study showed that the incidence of serious adverse events during antipsychotic treatment for delirium in the general hospital setting under management by psychiatrists was 0.9% among 2453 patients. Most of them were aspiration pneumonia (0.7%), and cardiovascular events were only 0.2% (four patients). Because one of the four cardiovascular events was not likely caused by antipsychotic medication, and because nine cases of aspiration pneumonia might have been related to aggravation of previous physical condition as mentioned in the Results section, the incidence of serious side effects might have been less than 0.9%. The association between use of antipsychotics in older people and risk of pneumonia has also been reported previously (Knol *et al.*, 2008). Remarkably, there was no patient who died because of antipsychotic side effects. High

Table 6 The differences between patients whose delirium was resolved within 1 week and patients whose delirium lasted more than 1 week

Duration of delirium	Within 1 week ($n = 1332$)	More than 1 week ($n = 1121$)	p
Age, years	73.4 (12.4)	73.5 (12.2)	0.038
Men, n (%)	835 (63)	719 (64)	0.48
Dementia, n (%)	412 (31)	329 (29)	0.42
Opioid prescription, n (%)	200 (15)	249 (22)	<0.0001
Hypoactive delirium, n (%)	71 (5)	114 (10)	<0.0001
CGI-I	1.65 (0.93)	2.48 (1.11)	<0.0001
Serious adverse event, n (%)	12 (0.9)	10 (0.9)	0.98
Extrapyramidal symptoms, n (%)	45 (3.4)	92 (8.2)	<0.0001
Death, n (%) ^a	149 (11)	237 (21)	<0.0001

Data represent mean (SD) or n (%), unless otherwise indicated. CGI-I, Clinical Global Impressions—Improvement Scale.

^aAll deaths were related to aggravation of previous physical condition.

quality clinical observation by psychiatrists in the general hospital setting, including fine dosage adjustment in individual patients and early detection of side effects, may have contributed in avoiding bad clinical course. So far, to our knowledge, there has no prospective observational study on the incidence of serious adverse events during antipsychotic treatment for delirium enrolling such a large number of patients in the general hospital setting under management by psychiatrists.

Although there is a retrospective cohort study utilizing insurance data sources (Wang *et al.*, 2005), causal relation between serious adverse events and antipsychotic treatment could not be specified from such data without close observation. In a meta-analysis of 15 randomized placebo-controlled clinical trials of atypical antipsychotic drugs to treat patients with Alzheimer disease or dementia, 118 deaths in the atypical antipsychotic drug groups and 40 in the placebo groups were summed up, which was a simple pooled incidence of 3.5% and 2.3% per trial, respectively (Schneider *et al.*, 2005). The locations in which the trials were performed were nursing homes (11 trials) or outpatient settings (4 trials), where high quality close observation by specialists could not have been expected. In such settings, relatively high incidence of death during antipsychotic treatment for older patients may have happened. Another explanation for the difference in outcome between the retrospective cohort study and the present study may be the length of antipsychotic treatment. In the former study, the administration of antipsychotics may have lasted for a long period because the target was behavioral symptoms with dementia. In contrast, the length of antipsychotic treatment in the present study was short, as delirium was resolved within 1 week in more than half of the patients. In a recent cohort study providing evidence of the risk of using antipsychotics in older residents in nursing homes, the rates of delirium were only 5.7–8.8% among psychiatric morbidity (Huybrechts *et al.*, 2012). In discussing the use of antipsychotics for older people, delirium that is expected to last shortly should be separated from other behavioral and psychological symptoms with dementia.

In another retrospective study including 326 older hospitalized patients with delirium at an acute care community hospital, administration of antipsychotics has been reported not to be associated with increased risk of mortality (Elie *et al.*, 2009). In the present study, which included a much larger number of patients, no patient died because of antipsychotic administration. In the general hospital setting under management by psychiatrists, antipsychotics for

delirium would not necessarily cause serious outcome as long as antipsychotic medication lasts only a short period.

There were significant differences in mean age, rate of men, rate of dementia, rate of opioid prescription, rate of hypoactive delirium, and mean maximum dose among the various antipsychotics, suggesting some practice pattern differences for use among the various antipsychotics. Haloperidol was parenterally administered to patients who could not take medicine orally, suggesting that such patients may have been severer in somatic conditions than those with other antipsychotics. The results of higher rate of opioid prescription, higher mean maximum dose, and the worst mean CGI-I score than those of other antipsychotic groups may support that. In patients with olanzapine, higher rate of opioid prescription, higher mean maximum dose, younger age, and lower rate of dementia were observed than others. A long plasma half-life of olanzapine compared with other antipsychotics may have resulted in the choice for such younger patients with severer somatic conditions. In patients with aripiprazole, a higher rate of hypoactive delirium was observed than others. Less sedative property of aripiprazole compared with other antipsychotics may have resulted in the choice for hypoactive delirium (Marder *et al.* 2003). In patients with perospirone, older age and higher rate of dementia were observed than others. A short plasma half-life of perospirone as well as quetiapine compared with other antipsychotics may have resulted in the choice for older demented patients with concerns about the prolongation of a plasma half-life and subsequent disturbance of sleep–wake cycles (Ma *et al.* 2007). In patients with quetiapine, lower mean maximum dose and the best mean CGI-I score than others were characteristic, suggesting that quetiapine may have been given patients with simple delirium.

The present study showed that the mean CGI-I score was the level of “much improved”, suggesting that effects of antipsychotics on delirium were apparent. So far, effectiveness of antipsychotics on delirium has been reported in some systematic reviews based on experimental studies including a small number of patients (Lacasse *et al.*, 2006; Lonergan *et al.*, 2007). More recently, efficacy and safety of quetiapine for delirium was demonstrated in two randomized, double-blind, placebo-controlled studies, although the numbers of patients in those studies were relatively small (Devlin *et al.*, 2010; Tahir *et al.*, 2010). Thus, evidence about efficacy and safety of antipsychotics in patients with delirium has been accumulating. Our findings of the very low incidence of serious side effects during antipsychotic treatment for delirium in real clinical practice

with a large number of patients support such experimental data, although neither randomized nor placebo-controlled design of this study does not render an opinion about efficacy.

Strengths of this study are a large number of patients with delirium included, availability of causal relationship between adverse events and antipsychotic use due to prospective and close observation by psychiatrists, non-pharmaceutical support, and mirroring real clinical practice. A limitation is non-experimental data so that antipsychotics could not be compared with each other. Another limitation is that the numbers of patients with perospirone, olanzapine, and aripiprazole were relatively small so that the findings about these drugs are not conclusive. Our conclusion can be clearly drawn from a well-designed controlled study, although implementation of a controlled study on delirium treatment in such a large number of patients is challenging.

Conclusions

In the general hospital setting under management including fine dosage adjustment in individual patients and early detection of side effects, antipsychotics might have a low risk in the treatment of patients with delirium, in contrast with antipsychotics for dementia in the nursing home or outpatient settings. A point may be not how to avoid using antipsychotics but how to monitor the risk of antipsychotics once delirium develops.

Conflict of interest

All authors declare that they have no conflict of interest.

Key points

- Out of 2453 patients who received antipsychotics for delirium, 22 had serious adverse events (0.9%), in which aspiration pneumonia, cardiovascular events, and venous thromboembolism were observed.
- Delirium was resolved within 1 week in more than half of the patients.
- In the general hospital setting under management including fine dosage adjustment in individual patients and the early detection of side effects, antipsychotics might have a low risk in the treatment of patients with delirium.

Acknowledgements

This work was supported by grants from the Japan Society for the Promotion of Science (Grant-in-Aid for Scientific Research (C): 23591728). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit the paper for publication.

The authors thank Dr. Koji Chikama, Dr. Keiichiro Mori (Department of Psychiatry, Kurume University School of Medicine), Dr. Katsuyuki Ukai (Department of Geriatric Psychiatry, Kamiida Daiichi General Hospital), Dr. Shigeo Ito (Department of Psychiatry, Nippon Medical School Musashikosugi Hospital), Dr. Ken Iwata (Department of Psychiatry, Tokyo Metropolitan Hiroo Hospital), Dr. Shin Yokoyama, Dr. Hiroshi Arai, Dr. Takehisa Takahashi (Department of Psychiatry, Nagano Red Cross Hospital), Dr. Akihiko Machino, Dr. Hiroaki Jitsuiki (Department of Psychiatry, Hiroshima University Hospital), Dr. Itaru Miura (Department of Psychiatry, Fukushima Medical University), Dr. Akira Okada (Department of Psychiatry, Nara Hospital Kinki University Faculty of Medicine), Dr. Hideto Hirotsune, Dr. Kunihiro Yamaji, Dr. Michiyo Unechi (Department of Psychiatry, National Hospital Organization Osaka National Hospital), Dr. Hiroaki Kawasaki, Dr. Hiroshi Mitsuyasu (Department of Psychiatry, Kyushu University Hospital), Dr. Satoko Maruta (Department of Neuropsychiatry, St. Marianna University School of Medicine), Dr. Yoshiro Yoshida (Department of Psychiatry, Osaka Red Cross Hospital), Dr. Takashi Hosaka (Department of Psychiatry, St. Luke's International Hospital), Dr. Shuichi Katsuragawa (Department of Psychiatry, Toho University Sakura Medical Center), Dr. Tatsuro Hayakawa (Department of Psychiatry, International Medical Center of Japan Kounodai Hospital), Dr. Koichi Miyakawa (Department of Psychiatry, Juntendo University Urayasu Hospital), Dr. Tetsuya Shiraishi, Dr. Masaomi Iyo (Department of Psychiatry, Graduate School of Medicine, Chiba University), Dr. Aya Hojo (Department of Psychiatry, Tokyo Metropolitan Tama Medical Center), Dr. Shigeki Sato (Department of Psychiatry, Japanese Red Cross Narita Hospital), Dr. Geni Hazama, Dr. Takafumi Kobayashi (Department of Psychiatry, Shimane Prefectural Central Hospital), Dr. Toru Tanaka (Department of Psychiatry, Kikukawa General Hospital), and Dr. Shinga Ezaki (Department of Geriatric Psychiatry, Koyukai Memorial Hospital), for the collection of data.

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