Psychopharmacology (2019) 236:723–730
https://doi.org/10.1007/s00213-018-5101-7

ORIGINAL INVESTIGATION

Incidence and predictors of acute akathisia in severely ill patients with first-episode schizophrenia treated with aripiprazole or risperidone: secondary analysis of an observational study

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Received: 14 June 2018 / Accepted: 31 October 2018 / Published online: 15 November 2018

Abstract

Rationale In the antipsychotic treatment of schizophrenia with little medication history, especially in drug-naïve cases, predictors of side effects are important. However, predictors of antipsychotic-induced akathisia remain unclear.

Objectives This study aimed to investigate the incidence and predictors of acute akathisia in severely ill patients with first-episode schizophrenia spectrum disorders (FES).

Methods This is a secondary analysis of our retrospective observational study. Data were obtained from 129 consecutive patients with FES involuntarily hospitalized in a tertiary psychiatric public hospital and treated with aripiprazole or risperidone. The primary outcome was the presence of acute akathisia during the first 1 month. A Cox proportional hazard model was used to examine significant predictors of the onset of akathisia.

Results Acute akathisia was diagnosed in 54 patients (42%). Neither antipsychotics (aripiprazole or risperidone), duration of untreated psychosis, iron deficiency, sex, age nor baseline symptomatic severity was identified as an independent predictor of akathisia. Rapid risperidone initiation significantly increased the onset of akathisia (adjusted hazard ratio [HR], 6.47; 95%; 95% confidence interval [CI], 1.94–21.65; $p = 0.002$), but rapid aripiprazole initiation did not (adjusted HR, 1.08; 95% CI, 0.50–2.31; $p = 0.84$). A significant interaction was found between rapid antipsychotic initiation and the risk of akathisia with aripiprazole versus risperidone ($p = 0.027$).

Conclusions Severely ill patients with FES initiating aripiprazole or risperidone could have a high risk for akathisia. Rapid risperidone initiation should be avoided because of the risk for akathisia, and careful monitoring of akathisia may be necessary for all patients initiating aripiprazole.

Keywords Akathisia · Antipsychotic · Schizophrenia · Incidence · Risk factor

Introduction

Acute akathisia is a psychomotor syndrome characterized by subjective and objective components such as an inner restlessness, irritability, increased motor activity, and repetitive movements (Barnes 1989; Kane et al. 2009). It is usually associated with initiating or increasing the dose of antipsychotics, or with reducing the dose of anticholinergics (Sachdev 1995a, b). Acute akathisia may adversely affect a patient's prognosis. It may increase the risk of suicide (Hansen 2001; Seemüller et al. 2012) and dropping out of treatment (Berardi et al. 2000). Systematic reviews suggest that acute akathisia is less likely with second-generation antipsychotics (SGAs) than with first-generation antipsychotics (FGAs) (Zhang et al. 2013; Zhu et al. 2017). However, the incidence of akathisia in patients with first-episode schizophrenia spectrum disorders (FES) who are treated with SGAs is not low (6–31%) (McEvoy et al. 2007; Kahn et al. 2008; Crespo-Facorro et al. 2006, 2014).

Bunta Yoshimura died on 14 August 2018 before publication of this work was completed.

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When prescribing an antipsychotic to patients with FES, especially drug-naïve patients, we often cannot refer to the history of medication and adverse events. Therefore, it is important to understand the predictors of acute akathisia. Among SGAs, aripiprazole and risperidone are associated with a higher risk of acute akathisia than quetiapine and olanzapine (Juncal-Ruiz et al. 2017; Zhu et al. 2017). However, predictors of the development of acute akathisia, other than therapeutic agents, remain unclear. The relationships are inconclusive between akathisia and substance abuse (Maat et al. 2008; Potvin et al. 2009; Hansen et al. 2013; Juncal-Ruiz et al. 2017), iron deficiency (serum iron or ferritin levels) (Horiguchi 1991; Barnes et al. 1992; Soni et al. 1993; Hofmann et al. 2000; Kuloglu et al. 2003; Cotter and O'Keeffe 2007; Juncal-Ruiz et al. 2017), duration of illness (Hansen et al. 2013), cognitive dysfunction (Kim and Byun 2007), acculturation (Sundram et al. 2008), and rapid antipsychotic initiation (Miller et al. 1997; Poyurovsky 2010; Takeuchi et al. 2018). One study restricted to FES showed that a need for hospitalization and more severe symptomatology were risk factors in the development of acute akathisia (Juncal-Ruiz et al. 2017).

We have reported the outcomes of algorithm-based pharmacotherapy in patients with FES who were involuntarily hospitalized (Yoshimura et al. 2017). The patients in the study could be at high risk for acute akathisia because all patients needed hospitalization, and their mean baseline symptomatology was severe. Because of the issue of metabolic side effects and weight gain, olanzapine is specifically excluded from our algorithm as an initial choice of antipsychotic medication; this is in line with the 2009 Schizophrenia Patient Outcomes Research Team recommendations (Buchanan et al. 2010), the psychopharmacology algorithm project at the Harvard South Shore Program (Osser et al. 2013), the Royal Australia and New Zealand College of Psychiatrists guidelines (Galletly et al. 2016), and the NAVIGATE program (Robinson et al. 2015). Therefore, most patients in our previous study were treated with aripiprazole or risperidone, with a relatively high risk of acute akathisia, as first-line antipsychotic treatment. However, few studies reported the risk of acute akathisia related to risperidone and aripiprazole administration for severely ill patients with FES (Kane et al. 2009). One study reported that FES patients treated with risperidone reported less severe symptoms of akathisia than those treated with haloperidol but did not report the incidence of akathisia in each group (Schooler et al. 2005). Though the risks of efficacy and safety of risperidone and aripiprazole for patients with FES were investigated in one multiple antipsychotics comparison study, the risk of akathisia in each antipsychotic was not reported in detail (Josiassen et al. 2010). To address the knowledge gap in the literature, we aimed to investigate the incidence and predictors of acute akathisia in patients with FES at high risk for akathisia who were treated with SGAs, who thus have a high probability of developing akathisia. Therefore, we conducted a secondary analysis of our previous observational study (Yoshimura et al. 2017).

Methods

Study design and setting

This is a secondary analysis of our retrospective observational study (Yoshimura et al. 2017). In that study, we performed a chart review of 160 patients (continuous sampling) with a diagnosis of FES, who were involuntarily admitted to the acute inpatient ward of the Okayama Psychiatric Medical Center between October 2012 and October 2015 owing to imminent risk of harming themselves or others or being unable to care for themselves in the context of severe symptomatic deterioration. Our hospital is a tertiary psychiatric public hospital in the city of Okayama, Japan, which has a population of approximately 700,000. Signed informed consent forms for hospital treatment were obtained from the patients' legal guardians or representatives. Patients admitted with FES had been treated with algorithm-based pharmacotherapy at the acute inpatient ward of our hospital.

FES was defined using the following criteria: (1) the first episode of psychosis; (2) duration of untreated psychosis (DUP) ≤ 5 years; (3) no prior treatment with antipsychotic medication, or if previously treated, total lifetime antipsychotic treatment < 4 weeks; and (4) fulfilled the International Classification of Diseases, Tenth Revision (ICD-10) criteria for schizophrenia (F20), delusional disorder (F22), acute and transient psychotic disorder (F23), schizoaffective disorder (F25), or other nonorganic/unspecified psychotic disorder (F28/29). We included patients treated with aripiprazole or risperidone as a first-line trial. Patients were excluded for any of the following reasons: (1) meeting ICD-10 criteria for drug dependence; (2) meeting ICD-10 criteria for mental retardation; or (3) having a history of neurological disease or head injury.

The Institutional Review Board of our hospital approved this study. Informed consent for publication was neither sought nor obtained because data for this study were collected during routine clinical care, analyzed retrospectively, and anonymized.

Algorithm-based pharmacotherapy

Choice of antipsychotics (a) In principle, SGAs (other than olanzapine and clozapine) were used in first- and second-line trials owing to well-known risks of metabolic complications. (b) For patients who failed to tolerate their first-line trial because of extrapyramidal symptoms, olanzapine or an alternative first-line antipsychotic was chosen for a second-line trial. (c) If a patient presented with catatonic symptoms,

olanzapine could be chosen for the first-line trial. (d) Initiation of clozapine was suggested after failure of a third-line trial.

Dosage of antipsychotics Antipsychotics were initiated at a lower dosage (1–3 mg risperidone equivalent). If a patient showed no significant improvement, the dose was titrated up to ≥ 6 mg risperidone equivalents (Gardner et al. 2010). Titration speed was left to the decision of each psychiatrist.

Monotherapy (a) In general, monotherapy with antipsychotics was advocated. (b) However, temporary combination therapy with intramuscular olanzapine, intramuscular haloperidol, oral quetiapine, or oral levomepromazine was allowed for agitation.

Duration of trials If tolerated, the duration of each antipsychotic trial at optimal dosage was > 4 weeks.

Concomitant medications Use of benzodiazepines (tapered after control of agitation; ≤ 8 mg lorazepam equivalents) and anticholinergic drugs (not used prophylactically; ≤ 6 mg biperiden equivalents). Antidepressants and mood stabilizers were used without restriction.

Data collection and outcome measures

Clinical ratings were routinely administered by B.Y. or K.S., and included the 18-item Brief Psychiatric Rating Scale (BPRS) (Woerner et al. 1988), with each item rated from 1 (not present) to 7 (extremely severe), Drug-induced Extrapyramidal Symptoms Scale (DIEPSS) (Inada et al. 1996) with the akathisia item (0, absent; 1, questionable; 2, mild; 3, moderate; 4, severe), Clinical Global Impressions scale (CGI) (US Dept. Health, Education, and Welfare 1976), and Global Assessment of Functioning (GAF) (Jones et al. 1995) at admission and discharge. The DIEPSS and CGI were assessed 2 weeks and 1 month after admission and monthly thereafter.

We defined the presence of first-line antipsychotic-induced acute akathisia using the following criteria: (1) discontinuation of first-line antipsychotic owing to akathisia in the first 1 month, (2) use of antiakathisia drugs (beta blockers, anticholinergics, benzodiazepines, or 5-HT2A receptor antagonists such as mirtazapine) for first-line antipsychotic-induced akathisia in the first 1 month, or (3) akathisia owing to first-line antipsychotics determined by a score ≥ 2 (mild) on the akathisia item of the DIEPSS at week 2 or month 1, or at discharge if a patient was discharged within 2 weeks. The akathisia item of the DIEPSS was rated by the authors based on both the clinical observation and the patient report following the DIEPSS rater's manual (Inada 1996). Each severity of akathisia symptoms was clearly described in the rater's manual. The inter-rater reliability of the DIEPSS was reported to be excellent. In the validation study of the DIEPSS, the intraclass correlation (ICC) ranged from 0.89 to 0.99 between the pairs of the raters (Inada et al. 1996).

Lacking consensus (Takeuchi et al. 2018), we defined "rapid antipsychotic initiation" as increasing aripiprazole to 20 mg/day or more, or risperidone to 4 mg/day or more, in the first 5 days. We investigated the mean corpuscular volume (MCV) of blood samples at admission in all 160 patients as a surrogate parameter for the assessment of iron deficiency using automated methods because we did not routinely analyze serum iron or ferritin levels. Iron deficiency anemia normally presents with microcytic anemia (low MCV), and microcytic anemia mainly comprises iron deficiency anemia (Camaschella 2015).

Statistical analysis

Cumulative probability of survival (time to the onset of acute akathisia) was estimated with the Kaplan–Meier method. The Cox proportional hazard model was used to investigate the association between onset of acute akathisia and clinical- and treatment-related characteristics. Patients were censored at use of anticholinergics for extrapyramidal symptoms other than akathisia, discontinuation of first-line antipsychotic owing to side effects other than acute akathisia, or the end of the observational period (1 month after admission), whichever occurred first. Multivariate Cox proportional hazard regression was carried out with the presence of first-line antipsychotic-induced acute akathisia as the dependent variable. The independent variables introduced as possible predictors were antipsychotics (aripiprazole or risperidone), age, sex, DUP, MCV of red blood cells, BPRS anxiety score at baseline, BPRS total score at baseline, and rapid antipsychotic initiation. Additionally, we conducted subgroup analyses in patients treated with aripiprazole and in those with risperidone. The abovementioned dependent and independent variables, other than antipsychotics, were included in each subgroup analysis. Finally, we also tested for interaction between rapid antipsychotic initiation and risk of acute akathisia with aripiprazole versus risperidone. Statistical tests were two-tailed with 95% confidence intervals (CIs). All statistical analyses were performed using IBM SPSS Version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Of 160 patients with FES who were involuntarily admitted and treated with an algorithm-based pharmacotherapy, records for seven patients were not available for assessment, and six patients had not completed even one adequate antipsychotic trial. We excluded nine patients treated with quetiapine as the first-line trial, five patients treated with olanzapine, and three

patients with other antipsychotics. Thus, we analyzed the medical records of 129 patients (aripiprazole, $n = 78$, 60%; risperidone, $n = 51$, 40%) (Fig. 1). There were no missing clinical rating data in all 129 patients.

Clinical characteristics and treatment-related factors are shown in Table 1. Most patients were diagnosed with schizophrenia ($n = 109$, 84%). Only four patients (3%) had substance abuse. Baseline symptomatology of patients treated with risperidone and aripiprazole was severe (BPRS, 72.2 and 67.7; CGI-Severity of Illness, 6.2 and 6.0; GAF, 17.8 and 20.6). Rapid antipsychotic initiation was conducted in 66 patients (51%).

Acute akathisia was diagnosed in 54 patients (42%) during the follow-up period. Table 2 showed the number of acute akathisia and the distribution of its severity in each group (aripiprazole or risperidone). Out of 54 patients, 12 (22%) discontinued first-line antipsychotic owing to akathisia, 39 (72%) were treated with antiakathisia drugs for akathisia, and three patients (6%) were not treated with antiakathisia drugs but were diagnosed using the DIEPSS (score ≥ 2 on the akathisia item) at week 2 or month 1 (Fig. 1). Though one third of patients with akathisia (18/54) were first tried dose reduction of first-line antipsychotics, all of them finally needed discontinuation of the first-line antipsychotics or use of antiakathisia drugs. The Kaplan–Meier survival analysis of acute akathisia in the first month is shown in Fig. 2, and the cumulative rate of developing acute akathisia was 52% (95% CI, 40%–63%). The prevalence of other extrapyramidal symptoms was significantly higher in patients with acute akathisia than in those without acute akathisia (50/54 vs. 39/75; $p < 0.001$).

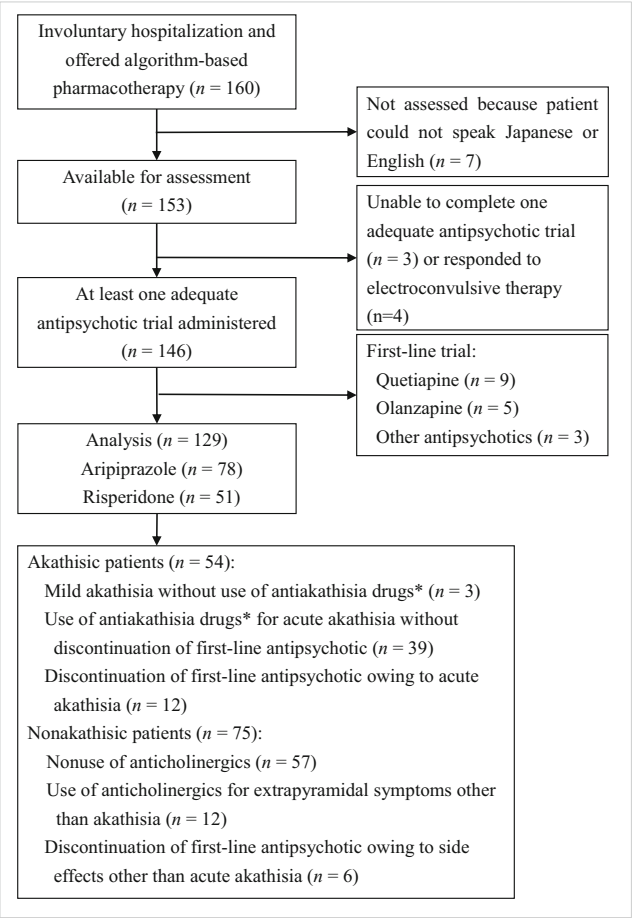

Fig. 1 Flow diagram of patients. *Beta blockers, anticholinergics, benzodiazepines, or 5-HT2A receptor antagonists (e.g., mirtazapine)

In all 129 patients treated with aripiprazole or risperidone, the multivariate Cox proportional hazard model only identified rapid antipsychotic initiation as an independent predictor of developing acute akathisia (adjusted hazard ratio [HR], 1.96; 95% CI, 1.09–3.51; $p = 0.025$). Subgroup analyses showed that rapid risperidone initiation significantly increased the onset of acute akathisia (adjusted HR, 6.47; 95% CI, 1.94–21.65; $p = 0.002$), but rapid aripiprazole initiation did not (adjusted HR, 1.08; 95% CI, 0.50–2.31; $p = 0.84$) (Table 3). Figure 2 shows survival curves of acute akathisia in each subgroup (aripiprazole or risperidone with/without rapid antipsychotic initiation). A significant interaction was found between the differential risks of aripiprazole and risperidone for acute akathisia among patients with and without rapid antipsychotic initiation (p-interaction = 0.027).

Discussion

In this study, we investigated the incidence and predictors of acute akathisia in 129 severely ill patients with FES and treated with aripiprazole or risperidone, using a chart review and multivariate Cox regression. The results showed that 40% of patients presented with acute akathisia in the first month; however, most patients who developed antipsychotic-induced akathisia did not discontinue the antipsychotic because akathisia symptoms were resolved by antiakathisia drugs, or because they had mild symptoms. No baseline clinical characteristics could independently predict acute akathisia. Only rapid risperidone initiation significantly increased the risk for acute akathisia; rapid aripiprazole initiation did not. Regardless of rapid antipsychotic initiation, aripiprazole had a clinically significant risk for akathisia.

As expected, the incidence of acute akathisia in our study was markedly high. Among SGAs, aripiprazole and risperidone most frequently induce acute akathisia (Zhu et al. 2017), and patients who require hospitalization or those with severe symptomatology are likely to develop acute akathisia (Juncal-Ruiz et al. 2017). Our investigation is the first study of severely ill patients with FES to report that rapid antipsychotic initiation significantly increased the risk for acute akathisia in acute treatment with risperidone, but not with aripiprazole. A previous 4-week prospective study among acutely ill admitted patients showed that rapid antipsychotic initiation

Table 1 Clinical characteristics and medications of patients

	Risperidone	Aripiprazole
n	51	78
Age (years), mean (SD)	29.7 (11.0)	30.6 (10.7)
Sex (male), *n* (%)	26 (51.0)	30 (38.5)
DUP (weeks), mean (SD)	34.2 (56.8)	47.5 (64.3)
Drug-naïve, *n* (%)	27 (52.9)	60 (76.9)
Diagnosis (ICD-10), *n* (%)		
Schizophrenia	42 (82.4)	67 (85.9)
Delusional disorder	0 (0.0)	2 (2.6)
Acute and transient psychotic disorder	3 (5.9)	5 (6.4)
Schizoaffective disorder	4 (7.8)	4 (5.1)
Other nonorganic/unspecified psychotic disorder	2 (3.9)	0 (0.0)
Previous substance abuse, *n* (%)	2 (3.9)	2 (2.6)
Rating scales at baseline, mean (SD)		
BPRS total score	72.2 (10.8)	67.7 (11.0)
BPRS anxiety score	4.9 (1.5)	4.5 (1.5)
CGI-S	6.2 (0.8)	6.0 (0.7)
GAF	17.8 (8.1)	20.6 (7.7)
MCV of red blood cells (fL), mean (SD)	89.9 (5.0)	88.3 (6.0)
Rapid antipsychotic initiation[a], n (%)	28 (54.9)	38 (48.7)
Antipsychotic doses at day 5 (mg/d), mean (SD)	3.4 (1.3)	19.5 (7.2)
Concomitant medications		
Anticholinergics[b] (maximum dose), mg/d, mean (SD)	1.0 (1.5)	1.1 (1.5)
Benzodiazepines[c] (maximum dose), mg/d, mean (SD)	2.3 (2.3)	2.2 (2.3)
Beta blockers, *n* (%)	4 (7.8)	7 (9.0)
Mirtazapine, *n* (%)	0 (0.0)	3 (3.8)
SSRI/SNRI, *n* (%)	3 (5.9)	2 (2.6)
Varproic acid, *n* (%)	4 (8.0)	1 (1.3)
Intramuscular antipsychotics, *n* (%)	5 (9.8)	7 (9.0)

BPRS, 18-item Brief Psychiatric Rating scale; *CGI-S*, Clinical Global Impressions–Severity of Illness scale; *DUP*, duration of untreated psychosis; *GAF*, Global Assessment of Functioning; *ICD-10*, International Classification of Diseases, Tenth Revision; *MCV*, mean corpuscular volume; *SNRI*, serotonin and norepinephrine reuptake inhibitors; *SSRI*, selective serotonin reuptake inhibitors

[a] Increasing aripiprazole to 20 mg/day or more, or risperidone to 4 mg/day or more, in the first 5 days

[b] Biperiden equivalents

[c] Lorazepam equivalents

Table 2 The number of akathisias in each antipsychotic group

	Risperidone	Aripiprazole
n	51	78
Akathisia (%)	21 (41.2)	33 (42.3)
Severity of akathisia[a] (%)		
0, absent	29 (56.9)	42 (53.8)
1, questionable	4 (7.8)	14 (17.9)
2, mild	10 (19.6)	17 (21.8)
3, moderate	7 (13.7)	5 (6.4)
4, severe	1 (2.0)	0 (0.0)

[a] The number of patients with akathisia did not match the number of patients rated 2 (mild) or more with akathisia item on the DIEPSS. It was because some patients suffered and recovered from akathisia due to discontinuation of first-line antipsychotic or use of antiakathisia drugs between the two evaluation period with the DIEPSS (week 2 and month 1)

significantly influenced the development of akathisia; however, most patients in that study were treated with FGAs (Miller et al. 1997). A recent meta-analysis of randomized controlled trials reported that no significant difference was found in the severity of akathisia between rapid and slow antipsychotic initiation groups in acute patient studies; however, the meta-analysis did not include any studies of aripiprazole or risperidone in acute patients (Takeuchi et al. 2018). A previous pooled analysis of three randomized clinical trials in patients with FES receiving SGAs or haloperidol identified a need for hospitalization and severe symptomatology as independent predictors of acute akathisia; however, rapid antipsychotic initiation was not included as an independent variable in the regression model (Juncal-Ruiz et al. 2017).

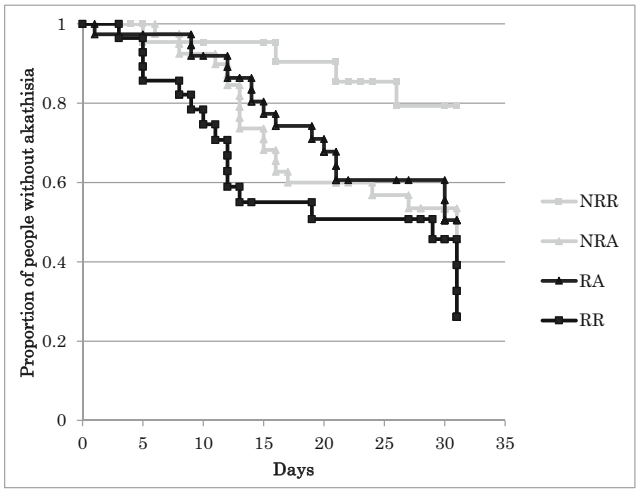

Fig. 2 Kaplan–Meier survival analysis of acute akathisia in each subgroup. A significant interaction was found between rapid antipsychotic initiation and the risk of akathisia with aripiprazole versus risperidone ($p = 0.027$). NRA, nonrapid aripiprazole initiation; NRR, nonrapid risperidone initiation; RA, rapid aripiprazole initiation; RR, rapid risperidone initiation

The interaction between rapid antipsychotic initiation and risk of acute akathisia with aripiprazole versus risperidone was statistically significant. Rapid antipsychotic initiation increased the risk only with risperidone treatment. This is pharmacologically plausible. The drug concentration generally reaches steady-state level after therapy with a constant dose for at least 4 to 6 half-lives. The half-lives of risperidone and the active metabolite (9-hydroxy-risperidone) are 2–4 and 17–23 h, respectively. By contrast, the half-life of aripiprazole is as long as 60–80 h (Hiemke et al. 2017). Therefore, when the aripiprazole dosage is rapidly increased, the drug concentration does not rapidly reach steady-state level even though initial high dose of aripiprazole especially for agitated psychotic patients is recommended (McGavin and Goa 2002) and was reported to be effective (Takaki and Yoshimura 2012). In severely ill patients with FES, we propose refraining from rapid risperidone initiation because of the risk for acute akathisia, and we recommend careful observation for signs of aripiprazole-induced acute akathisia, even if the dosage is not rapidly increased.

Several limitations of this study should be acknowledged. First, the choice of first-line antipsychotic was not randomized but was left to the decision of each treating psychiatrist. In addition, the outcome assessors were unblinded. Thus, biases in our results could not be completely avoided even though we showed the results adjusted with the potential confounders by the Cox proportional hazard model. Second, the single-site study with a small sample size, especially in the subgroup analyses, might limit the generalizability of our results. Third, the observation period of 1 month could be too short because the onset of acute akathisia had not reached a plateau at month 1. Fourth, misdiagnosis of agitation/anxiety secondary to psychotic symptoms as akathisia and vice versa is possible because the diagnosis of akathisia is complicated, especially in mild cases (Kane et al. 2009). In addition to this, we might fail to capture subjective distress inside the patients due to acute akathisia. Fifth, the MCV of blood samples was included as a surrogate parameter for the assessment of iron deficiency because we could not assess serum iron or ferritin levels. Lastly, a specific characteristic of patients with FES in our investigation was the minor comorbidity of substance abuse, which may influence the prevalence of akathisia (Maat et al. 2008; Potvin et al. 2009; Hansen et al. 2013).

In conclusion, in the treatment of severe FES, it may be important to avoid rapid risperidone initiation in terms of the risk for acute akathisia, and to closely monitor all patients initiating aripiprazole for signs of acute akathisia, even when it is not rapidly increased. This study demonstrated that both aripiprazole and risperidone frequently induce acute akathisia in severely ill patients with FES. No baseline clinical characteristic independently predicted the onset of acute akathisia.

Table 3 Adjusted hazard ratios for acute akathisia using Cox proportional hazard model

	All HR (95% CI)	($n = 129$) p value	Aripiprazole HR (95% CI)	($n = 78$) p value	Risperidone HR (95% CI)	($n = 51$) p value
Aripiprazole (reference: risperidone)	1.10 (0.61–2.00)	0.75				
Age	0.98 (0.95–1.01)	0.14	0.98 (0.95–1.01)	0.27	1.00 (0.95–1.07)	0.87
Sex (male)	1.22 (0.69–2.18)	0.49	1.20 (0.59–2.47)	0.61	1.26 (0.43–3.73)	0.67
DUP	1.00 (0.99–1.00)	0.77	1.00 (0.99–1.01)	0.78	1.00 (0.99–1.01)	0.87
Rapid antipsychotic initiation[a]	1.96 (1.09–3.51)	0.025	1.08 (0.50–2.31)	0.84	6.47 (1.94–21.65)	0.002
BPRS (total score) at baseline	0.99 (0.96–1.02)	0.39	0.99 (0.96–1.03)	0.70	0.97 (0.93–1.02)	0.28
BPRS ("anxiety" score) at baseline	1.08 (0.85–1.36)	0.54	1.00 (0.75–1.34)	0.99	1.16 (0.71–1.90)	0.54
MCV of red blood cells	1.00 (0.95–1.05)	0. 91	1.00 (0.94–1.06)	0.92	0.95 (0.86–1.06)	0.37

HR, hazard ratio; *BPRS*, 18-item Brief Psychiatric Rating Scale; *CI*, confidence interval; *DUP*, duration of untreated psychosis; *MCV*, mean corpuscular volume

[a] Increasing aripiprazole to 20 mg/day or more, or risperidone to 4 mg/day or more, in the first 5 days

Rapid antipsychotic initiation significantly increased the risk only in treatment with risperidone but not with aripiprazole, and a significant interaction was found between the differential risks of aripiprazole and risperidone in patients with and without rapid antipsychotic initiation.

Acknowledgments The authors appreciate that Mr. Kohei Kitagawa substantially helped in the data collection. The authors thank each attending physician at the Okayama Psychiatric Medical Center for data collection. We also thank Analisa Avila, ELS, of Edanz Group (www.edanzediting.com) for editing a draft of this manuscript.

Contributors B.Y. and R.S. designed the study. R.S., M.T., and K.S. supervised the study. Y.Y. and S.S. analyzed the data. B.Y. drafted the report. All authors approved the final manuscript.

Compliance with ethical standards

The Institutional Review Board of our hospital approved this study.

Conflict of interest Dr. Yoshimura has received honoraria for his participation as a speaker at educational events sponsored by Janssen. Dr. Sato has received honoraria for his participation as a speaker at educational events sponsored by Otsuka, Janssen, and Dainippon-Sumitomo. Dr. Sakamoto has received unrestricted research funding from Eli Lilly, which was deposited into research accounts at Okayama University Hospital. Dr. Sakamoto has received honoraria for his participation as a speaker at an educational event sponsored by Otsuka. Dr. Tsukahara, and Dr. So report no additional financial or other relationship relevant to this article.

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