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Scientific Research

Predictors of Discontinuation of Antipsychotic Therapy in Patients with Acute Schizophrenia: A 1-Year Observational Study with More Than 1000 Patients

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Abstract

Discontinuation of antipsychotic therapy has been a significant clinical issue among patients with schizophrenia, since the patients who discontinued antipsychotic treatment showed worse clinical and functional outcomes, and higher risks of relapse of schizophrenia symptoms and hospitalization. We conducted a *post-hoc* analysis of a post-marketing research with a 12-month follow-up period to identify the predictors for discontinuation of antipsychotic monotherapy in Japan. This is a prospective, naturalistic multicenter observational study, designed to evaluate the discontinuation rates of olanzapine monotherapy and non-olanzapine antipsychotic monotherapy in Japanese adult patients with acute schizophrenia. Patients were treatment-naïve, or had switched from other antipsychotics or from poly-pharmacotherapy to oral antipsychotic monotherapy. We analyzed the correlation of discontinuation of antipsychotic monotherapy with baseline characteristics of patients. A total of 1089 patients (578 patients treated with olanzapine and 511 with non-olanzapine antipsychotics) were eligible for analysis. By the end of the 12-month study period, 614 patients (56.4%) discontinued antipsychotic therapy. Multivariate logistic regression analyses indicated significantly lower discontinuation rates in all patients treated with antipsychotics: older age (Odds ratio [OR], 0.871; 95% confidence interval [CI], 0.797 to 0.953; p = 0.003), outpa-

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tient status (OR, 0.508; 95% CI, 0.383 to 0.675; p < 0.001), prior use of antipsychotics (OR, 0.693; 95% CI, 0.516 to 0.930; p = 0.015), and olanzapine group showed lower discontinuation rate than that of non-olanzapine group (OR, 1.416; 95% CI, 1.086 to 1.846; p = 0.010). The present study indicated that the outpatient status, older age, and prior use of antipsychotics have better adherence to antipsychotic treatment. In addition to these factors, use of anti-parkinson agents showed lower discontinuation rates in the olanzapine monotherapy group.

Keywords

Predictor of Discontinuation, Antipsychotic Monotherapy, Long-Term Observational Study, Schizophrenia

1. Introduction

Schizophrenia is a mental illness that involves a range of cognitive, behavioral, and emotional dysfunctions, as well as social and occupational dysfunctions [1]. Atypical antipsychotics have been widely used as a first-line therapy for the acute and maintenance phases of schizophrenia. Although a number of antipsychotics are available, monotherapy remains an important option due to lack of sufficient evidence for the efficacy and safety of poly-pharmacotherapy.

Discontinuation of antipsychotic therapy has been a significant clinical issue among patients with schizophrenia. Compared with patients who continued treatment with antipsychotics, patients who discontinued antipsychotic treatment showed worse clinical and functional outcomes and higher risks of relapse of schizophrenia symptoms and hospitalization [2]-[5]. In recent years, a number of studies conducted outside of Japan have investigated the predictors of antipsychotic adherence [3] [6]-[11].

We conducted this *post-hoc* analysis of a prospective, multicenter observational study to investigate the relationship between baseline characteristics of patients and discontinuation of antipsychotic monotherapies to identify the predictors for discontinuation in Japanese patients with acute schizophrenia.

2. Methods

2.1. Study Design and Patients Selection

This is a prospective, naturalistic multicenter observational study with 12-month follow-up, designed to evaluate the discontinuation rates of olanzapine monotherapy and non-olanzapine antipsychotic monotherapy in Japanese adult patients with acute schizophrenia in a routine clinical practice setting. The key eligibility criteria for this study were patients at least 20 years of age who were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders fourth Edition (DSM-IV) Text Revision with a Clinical Global Impression-Severity of Illness (CGI-S) Schizophrenia score of ≥4 at the start of monotherapy, and had acute symptoms developed within one month prior to the start of oral antipsychotic monotherapy. Patients were treatment-naïve, or had switched from other antipsychotics or from poly-pharmacotherapy to oral antipsychotic monotherapy. All patients provided informed consent before starting any study procedures, and this study was conducted in compliance with Helsinki Declaration and the guideline of Good Post-marketing Study Practice (GPSP).

2.2. Measurements

Patients were monitored until discontinuation of the study treatment. In this study, reasons for discontinuation included discontinuation of treatment with antipsychotic monotherapy, additional use of any other antipsychotics, lost to follow-up, discontinuation of treatment by request of the patient or decision of the investigator. We analyzed the correlation of discontinuation of antipsychotic monotherapy with baseline characteristics of patients (gender, age, body mass index [BMI], onset of illness, outpatient or inpatient status at the start of study treatment, history of schizophrenia, living status, prior use of antipsychotics, CGI-S Schizophrenia score, Brief Psychiatric Rating Scale [BPRS] score, use of concomitant medications [*i.e.*, anti-Parkinson agents, antidepres-

sants, anti-anxiety/sleep agents, antiepileptic agents, mood-stabilizers] at the start of monotherapy).

2.3. Statistical Analysis

The data were analyzed in all patients treated with antipsychotics, and patients with olanzapine monotherapy and with non-olanzapine antipsychotic monotherapy. Differences in baseline patient characteristics between patients who discontinued antipsychotic monotherapy before completion of the study period and those who continued antipsychotic monotherapy for 12 months were compared using Student's t-test, Fisher's exact test, or the Monte Carlo method. Multivariate logistic regression analyses were used to calculate odds ratios (OR) and 95% confidence intervals (CI) to determine baseline variables that predicted the likelihood of discontinuation of antipsychotic monotherapy. Univariate analyses were conducted for all collected baseline items. However, multivariate analyses were conducted only for those baseline items with no or few missing data. All statistical tests were conducted based on a 2-sided significance level of 0.05.

3. Results

This study enrolled 1124 patients from 72 centers in Japan and was conducted from January 2010 to August 2012. Of the enrolled patients, 35 patients were excluded: 9 due to lack of case report, 14 who were under 20 years of age, and 12 for concomitant use of multiple antipsychotics. A total of 1089 patients (578 patients treated with olanzapine and 511 with non-olanzapine antipsychotics) were eligible for analysis. In the non-olanzapine antipsychotic monotherapy group, atypical antipsychotics were administered to 487 patients (160 risperidone, 154 aripiprazole, 44 quetiapine, 67 blonanserin, 40 paliperidone, 16 perospirone, and 6 zotepine) and typical antipsychotics were administered to 24 patients (13 haloperidol, 4 bromperidol, 3 sulpiride, 2 chlorpromazine, 1 levomepromazine, and 1 fluphenazine). By the end of the 12-month study period, 614 patients (56.4%) discontinued antipsychotic monotherapy; 310 patients (53.6%) in the olanzapine monotherapy group and 304 patients (59.5%) in the non-olanzapine antipsychotic monotherapy group. The baseline characteristics of patients including those patients who discontinued the antipsychotic monotherapy and those who continued throughout the study period in both groups are shown in **Table 1**.

In all 1089 patients, discontinued patients were significantly more likely to be younger ($p < 0.001$), inpatient status ($p < 0.001$), with a higher CGI-S Schizophrenia score ($p = 0.022$), a lower BPRS Negative score ($p < 0.001$), a lower BPRS Anxiety/Depression score ($p < 0.001$), and a shorter history of schizophrenia ($p = 0.039$). In the 578 olanzapine monotherapy patients, discontinued patients were significantly more likely to be younger ($p < 0.001$), be an inpatient ($p = 0.005$), have a shorter history of schizophrenia ($p = 0.002$), not to have previously used antipsychotics ($p < 0.001$), have higher CGI-S Schizophrenia score ($p = 0.022$), have lower BPRS Negative score ($p < 0.001$), and not to have used anti-Parkinson agents ($p = 0.005$). In the 511 non-olanzapine antipsychotic monotherapy patients, discontinued patients were significantly more likely to be an inpatient ($p < 0.001$), have lower BPRS Negative score ($p = 0.039$), have lower BPRS Anxiety/Depression score ($p < 0.001$), not to have used antidepressants ($p = 0.022$), and not to have used anti-anxiety/sleep agents ($p = 0.048$). For other baseline characteristics variables, there was no significant difference between discontinued and continued patients.

The results of multivariate logistic analyses are summarized in **Table 2**. In all patients treated with antipsychotics, an older age (OR, 0.871; 95% CI, 0.797 to 0.953; $p = 0.003$), outpatient status (OR, 0.508; 95% CI, 0.383 to 0.675; $p < 0.001$), and prior use of antipsychotics (OR, 0.693; 95% CI, 0.516 to 0.930; $p = 0.015$) were significantly less likely to discontinue antipsychotic monotherapy. In the olanzapine monotherapy group, patients with older age ($p = 0.008$), outpatient status ($p = 0.020$), prior use of antipsychotics ($p = 0.004$), and use of anti-Parkinson agents ($p = 0.050$) were significantly less likely to discontinue olanzapine monotherapy. In the non-olanzapine antipsychotic monotherapy group, only outpatient status ($p < 0.001$) showed a significantly lower risk of discontinuation of antipsychotic monotherapy. **Figure 1** indicates the discontinuation odds ratios for all antipsychotics and each treatment group.

4. Discussion

The present study is a large prospective, naturalistic multicenter observational study that included Japanese patients with acute schizophrenia and provided important information on the baseline characteristics of patients which could predict continuation of the antipsychotic monotherapy.

Table 1. Baseline characteristics of patients.

Variable		Antipsychotics (all)					Olanzapine monotherapy group					Non-olanzapine antipsychotic group				
		Patients discontinued		Patients continued		p-value	Patients discontinued		Patients continued		p-value	Patients discontinued		Patients continued		p-value
Number		614		475			310		268			304		207		
Gender	Female	348	56.7%	254	53.5%	0.297[F)]	173	55.8%	139	51.9%	0.358[F)]	175	57.6%	115	55.6%	0.716[F)]
	Male	266	43.3%	221	46.5%		137	44.2%	129	48.1%		129	42.4%	92	44.4%	
Age (yr)	N	610		472		<0.001[S)]	309		265		<0.001[S)]	301		207		0.175[S)]
	Mean (SD)	45.3	(15.4)	48.4	(15.9)		44.1	(14.9)	48.5	(16.1)		46.5	(15.8)	48.4	(15.7)	
	<20	0	0.0%	0	0.0%		0	0.0%	0	0.0%		0	0.0%	0	0.0%	
	20 - 35	199	32.4%	117	24.6%		106	34.2%	67	25.0%		93	30.6%	50	24.2%	
	36 - 45	141	23.0%	101	21.3%		74	23.9%	54	20.1%		67	22.0%	47	22.7%	
	46 - 55	95	15.5%	79	16.6%	0.015[M)]	47	15.2%	50	18.7%	0.022[M)]	48	15.8%	29	14.0%	0.253[M)]
	56 - 65	105	17.1%	101	21.3%		51	16.5%	49	18.3%		54	17.8%	52	25.1%	
	≥66	70	11.4%	74	15.6%		31	10.0%	45	16.8%		39	12.8%	29	14.0%	
	Unknown	4	0.7%	3	0.6%		1	0.3%	3	1.1%		3	1.0%	0	0.0%	
BMI (kg/m^2)	N	288		209		0.798[S)]	158		130		0.661[S)]	130		79		0.826[S)]
	Mean (SD)	22.4	(4.5)	22.5	(4.0)		21.9	(3.7)	22.1	(4.0)		23.0	(5.2)	23.1	(4.0)	
Onset of illness	Recurrent	373	60.7%	275	57.9%		183	59.0%	163	60.8%		190	62.5%	112	54.1%	
	Initial	195	31.8%	146	30.7%	0.946[F)]	103	33.2%	75	28.0%	0.308[F)]	92	30.3%	71	34.3%	0.196[F)]
	Unknown	46	7.5%	54	11.4%		24	7.7%	30	11.2%		22	7.2%	24	11.6%	
Outpatient or inpatient status	Outpatient	214	34.9%	231	48.6%	<0.001[F)]	102	32.9%	119	44.4%	0.005[F)]	112	36.8%	112	54.1%	<0.001[F)]
	Inpatient	400	65.1%	244	51.4%		208	67.1%	149	55.6%		192	63.2%	95	45.9%	
History of schizophrenia (years)	N	416		303		0.039[S)]	220		184		0.002[S)]	196		119		0.704[S)]
	Mean (SD)	13.6	(13.5)	15.7	(14.5)		12.4	(13.2)	16.7	(14.8)		14.9	(13.7)	14.3	(14.0)	
Prior use of any antipsychotics*	Yes	206	33.6%	208	43.8%	<0.001[F)]	94	30.3%	125	46.6%	<0.001[F)]	112	36.8%	83	40.1%	0.460[F)]
	No	408	66.4%	267	56.2%		216	69.7%	143	53.4%		192	63.2%	124	59.9%	
CGI-S Schizophrenia Score**	N	614		475		0.022 [S)]	310		268		0.022 [S)]	304		207		0.275 [S)]
	Mean (SD)	4.9	(0.9)	4.9	(0.9)		5.0	(0.9)	4.8	(0.9)		4.8	(0.8)	4.7	(0.9)	
BPRS Total Score**	N	362		314		0.140[S)]	177		177		0.649[S)]	185		137		0.126[S)]
	Mean (SD)	58.6	(14.8)	60.3	(15.1)		59.9	(15.6)	60.7	(15.4)		57.2	(13.9)	59.7	(14.7)	
BPRS Positive Score**	N	362		314		0.860[S)]	177		177		0.650[S)]	185		137		0.950[S)]
	Mean (SD)	16.3	(4.8)	16.2	(4.9)		16.7	(5.1)	16.4	(4.7)		16.0	(4.6)	16.0	(5.1)	
BPRS Negative Score**	N	362		314		<0.001[S)]	177		177		<0.001[S)]	185		137		0.039[S)]
	Mean (SD)	10.0	(3.6)	11.1	(3.7)		9.7	(3.7)	11.0	(3.8)		10.3	(3.5)	11.1	(3.5)	
BPRS Anxiety/ Depression**	N	362		314		<0.001[S)]	177		177		0.480[S)]	185		137		<0.001[S)]
	Mean (SD)	11.8	(4.6)	12.9	(4.5)		12.0	(5.1)	12.8	(4.7)		11.2	(4.0)	13.2	(3.7)	

Continued

Use of anti-parkinson agents**	Yes	61	9.9%	64	13.5%	0.084[F)]	17	5.5%	33	12.3%	0.005[F)]	44	14.5%	31	15.0%	0.899[F)]
	No	553	90.1%	411	86.5%		293	94.5%	235	87.7%		260	85.5%	176	85.0%	
Use of antidepressants**	Yes	29	4.7%	33	6.9%	0.146[F)]	17	5.5%	14	5.2%	1.000[F)]	12	3.9%	19	9.2%	0.022[F)]
	No	585	95.3%	442	93.1%		293	94.5%	254	94.8%		292	96.1%	188	90.8%	
Use of anti-anxiety/sleep agents**	Yes	273	44.5%	234	49.3%	0.126[F)]	139	44.8%	124	46.3%	0.738[F)]	134	44.1%	110	53.1%	0.048[F)]
	No	341	55.5%	241	50.7%		171	55.2%	144	53.7%		170	55.9%	97	46.9%	
Use of antiepileptic agents**	Yes	81	13.2%	70	14.7%	0.480[F)]	45	14.5%	34	12.7%	0.546[F)]	36	11.8%	36	17.4%	0.092[F)]
	No	533	86.8%	405	85.3%		265	85.5%	234	87.3%		268	88.2%	171	82.6%	
Use of mood-stabilizers**	Yes	16	2.6%	12	2.5%	1.000[F)]	4	1.3%	7	2.6%	0.361[F)]	12	3.9%	5	2.4%	0.454[F)]
	No	598	97.4%	463	97.5%		306	98.7%	261	97.4%		292	96.1%	202	97.6%	

*Within 1 month before initiation of monotherapy; **At initiation of monotherapy. CGI-S: Clinical Global Impression-Severity of Illness; BPRS: Brief Psychiatric Rating Scale; SD: standard deviation. [F)]Fisher's exact test; [M)] Monte Carlo method; [S)]Student's t-test.

Table 2. Discontinuation odds ratios by baseline characteristics (multivariate logistic regression analyses).

Factor (test/reference)	All Antipsychotics			Olanzapine group			Non-olanzapine group		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Gender (female/male)	1.204	0.920 - 1.576	0.175	1.163	0.803 - 1.686	0.424	1.370	0.913 - 2.056	0.129
Age (units = 10 years old)	0.871	0.797 - 0.953	0.003	0.843	0.743 - 0.957	0.008	0.916	0.804 - 1.044	0.187
Onset of illness (recurrent/initial)	1.145	0.854 - 1.535	0.366	0.994	0.664 - 1.488	0.976	1.294	0.836 - 2.004	0.247
Outpatient or inpatient status (outpatients/inpatients)	0.508	0.383 - 0.675	<0.001	0.622	0.416 - 0.929	0.020	0.398	0.264 - 0.601	<0.001
Prior use of any antipsychotics* (yes/no)	0.693	0.516 - 0.930	0.015	0.549	0.366 - 0.824	0.004	0.886	0.568 - 1.383	0.595
CGI-S Schizophrenia Score** (units = 1)	1.049	0.900 - 1.223	0.540	1.078	0.879 - 1.322	0.468	1.058	0.830 - 1.348	0.650
Use of anti-parkinson agents** (yes/no)	0.844	0.553 - 1.288	0.431	0.500	0.250 - 0.999	0.050	1.155	0.644 - 2.071	0.629
Use of antidepressants** (yes/no)	0.827	0.472 - 1.448	0.506	1.243	0.553 - 2.792	0.599	0.576	0.252 - 1.315	0.190
Use of anti-anxiety/sleep agents** (yes/no)	0.860	0.653 - 1.133	0.285	0.988	0.679 - 1.437	0.950	0.707	0.463 - 1.079	0.108
Use of antiepileptic agents** (yes/no)	1.088	0.733 - 1.614	0.677	1.719	0.971 - 3.044	0.063	0.821	0.457 - 1.475	0.509
Use of mood-stabilizing drugs** (yes/no)	0.987	0.420 - 2.322	0.977	0.335	0.076 - 1.481	0.149	1.837	0.551 - 6.128	0.323
Treatment (Non-olanzapine/Olanzapine)	1.416	1.086 - 1.846	0.010						

*Within 1 month before initiation of monotherapy; **At initiation of monotherapy. CGI-S: Clinical Global Impression-Severity of Illness; OR: Odds ratio; CI, confidence interval. OR > 1 indicates that test item has higher risk of discontinuation of antipsychotic monotherapy than reference item.

Previous studies conducted outside of Japan have also identified some general predictors for continuation of antipsychotic therapy. Older age [3] [6] [8]-[11], male gender [6]-[8], and longer history of schizophrenia [9] were similarly identified to be associated with continuation of antipsychotic therapy. On the other hand, our results were that in the univariate analysis, older age, lower CGI-S Schizophrenia score, higher BPRS Negative score, higher BPRS Anxiety/Depression score, outpatient status, and longer history of schizophrenia were identified as a predictor of continuation. In multivariate analysis, an older age, outpatient status, and prior use of antipsychotics were significantly likely to continue antipsychotic monotherapy.

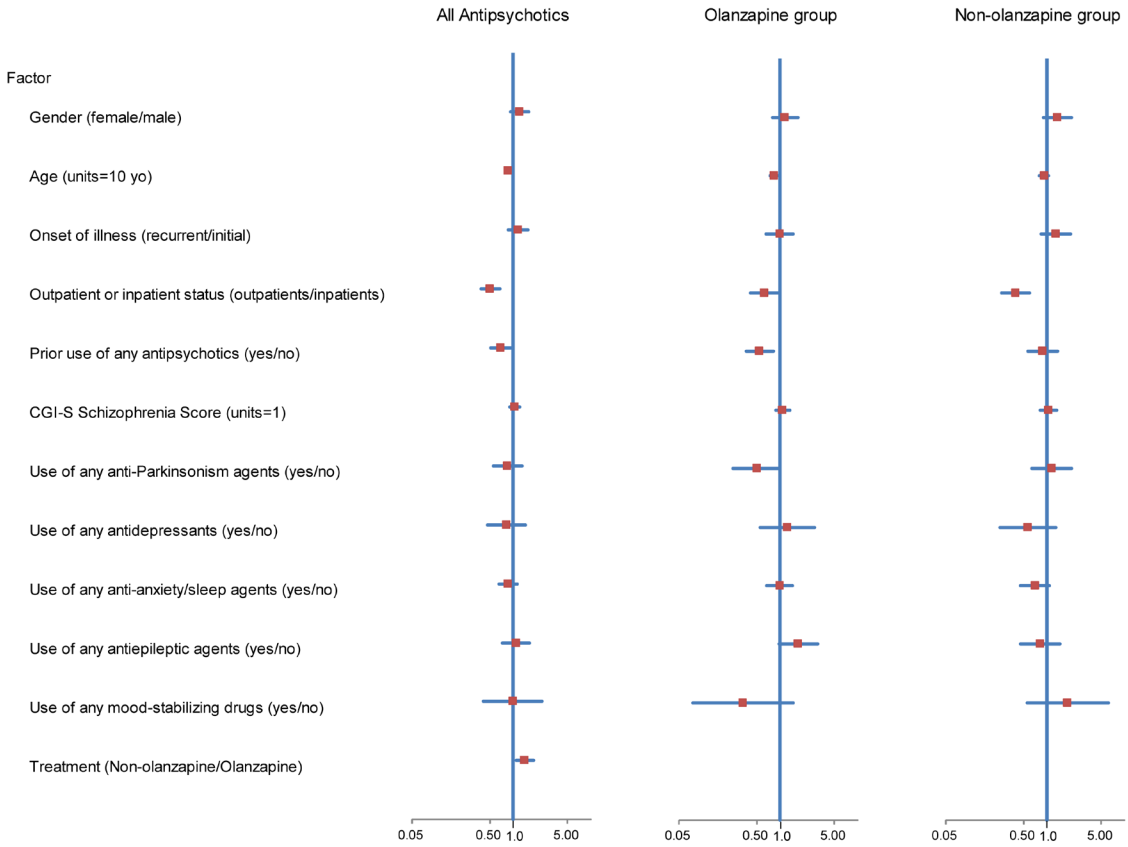

Figure 1. Discontinuation odds ratios by baseline characteristics.

Olanzapine showed higher continuation rates in several reports [12]-[15] and predictors of continuation of olanzapine treatment would be beneficial in a clinical practice. Older age, prior use of antipsychotics, and use of anti-Parkinson agents were identified as predictors of continuing with only olanzapine monotherapy. First of all, patients with ≥66 years of age administered olanzapine monotherapy were more likely to continue treatment. Although antipsychotics should be administered to older patients with caution, olanzapine could be a better therapeutic option for older patients with acute schizophrenia due to better treatment adherence. Secondly, patients administered olanzapine monotherapy who previously used antipsychotics or were using anti-Parkinson agents at the start of monotherapy were more likely to continue antipsychotic monotherapy. For those patients having insufficient efficacy, low treatment adherence or extrapyramidal adverse events during treatment with current antipsychotics, switching to olanzapine could be a suitable therapeutic option.

The results of the present study partially support a *post-hoc* analysis of the previous observational study to investigate safety profiles of olanzapine conducted in Japan. Although the previous observational study with a one-year follow-up period evaluated the association between baseline characteristics of patients with schizophrenia and continuation of olanzapine therapy, it included not only patients with acute schizophrenia but also chronic schizophrenia and was not limited to olanzapine monotherapy. In that study, multivariate logistic regression analyses showed significant association of four factors (longer history of schizophrenia, lower positive symptoms, higher negative symptoms, and better health-related quality of life) with continuation of olanzapine therapy, while univariate logistic regression analyses showed significant association of many factors, including older age, male gender, inpatients, longer history of schizophrenia, higher negative symptoms at baseline with continuation of olanzapine therapy [12]. In the present study, older age was identified to be associated with continuation of olanzapine monotherapy. Although missing data made it difficult to conduct multivariate regression analysis of schizophrenia history and symptom severity, our univariate regression analysis showed a longer history of schizophrenia and higher negative symptoms at baseline to be predictors for continuation of olanzapine monotherapy.

The present study includes important clinical findings for antipsychotic monotherapy in patients with acute schizophrenia, however there are some limitations. First of all, this is a naturalistic observational study with no randomization. To ensure the study reflected real-life clinical practice, choice of antipsychotics and the dose prescribed was at the discretion of the psychiatrist, although the study protocol stated that the oral antipsychotics should be prescribed within the approved dosage and administration in Japan. The analysis was performed individually in the olanzapine monotherapy group and the non-olanzapine antipsychotic monotherapy group, and thus comparison of the identified predictors between two groups requires careful interpretation. Secondly, patients who were lost to follow-up or changed their residence were also considered as "discontinuations" in the present study. As the follow-up period of the present study was limited to 12 months, identified predictors in the present study might not predict adherence in longer treatment. In the present study, all possible baseline characteristics that affected discontinuation may not have been collected, and missing data of the collected characteristics might have affected our results.

5. Conclusion

The present study provided clinical information about the predictors of adherence for antipsychotic treatment in patients with acute schizophrenia in the routine clinical practice setting. Our results indicated that the outpatient status, older age, and prior use of antipsychotics have better adherence to antipsychotic treatment. Older age, prior use of antipsychotics, and use of anti-Parkinson agents, might predict better adherence of olanzapine monotherapy.

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Disclosure

SF, JF and LA are employees of Eli Lilly Japan K.K. MI have received honoraria from Eli Lilly Japan K.K.

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