illness (Lieberman et al., 1993; Szymanski et al., 1996). However, most of the patients relapse into psychotic episodes even after attaining amelioration of their preceding episodes (T.S.S.R. Group, 1992; Robinson et al., 1999). This progressive clinical course is thought to be part of the disease process, indicative of continuing brain dysfunction, while other factors, including effects of the antipsychotic medications being used for treatment, are also thought to play a role in this clinical progression (Zipursky et al., 2013).

Dopamine supersensitivity psychosis (DSP) was first identified in the 1970s (Chouinard et al., 1978), and from 22–43% of all patients with schizophrenia suffer from this psychosis (Chouinard et al., 1988; Chouinard, 1991). The features of DSP include development of tolerance to antipsychotic therapeutic effects, such that even high doses of antipsychotics no longer control symptoms, and an acute exacerbation of symptoms on discontinuing antipsychotics or even after minor stress (Kirkpatrick et al., 1992; Moncrieff, 2006; Chouinard and Chouinard, 2008; Fallon and Dursun, 2011). It is thought that these features may be an integral factor in the development of relapse vulnerability and treatment-resistant psychosis. It has been estimated that more than half of treatment-resistant schizophrenia (TRS) cases may be related to DSP (Iyo et al., 2013). The mechanisms underlying DSP are not fully understood yet, but may be closely associated with the increased density of dopamine D2 receptors (DRD2), which increases behavioral sensitivity to dopamine, following chronic treatment with antipsychotics, as reported in animal models (Inoue et al., 1997; Samaha et al., 2007, 2008; Tadokoro et al., 2012; Iyo et al., 2013). DSP may be also accelerated more profoundly by first-generation antipsychotics than second-generation antipsychotics (Correll et al., 2004; Li et al., 2009; Iyo et al., 2013). Thus, although up-regulation of dopamine D2 receptors (DRD2), induced by antipsychotic therapy blockade, may underlie DSP, an effective treatment strategy for patients with DSP has yet to be established.

We have recently put forward a hypothesis on the mechanisms and treatment strategy for patients with DSP (Iyo et al., 2013). Briefly, optimal DRD2 occupancy by antipsychotics is higher in patients with DSP, leading to the need for higher doses of antipsychotics to achieve a clinical result. However, in these cases, greater quantities of the drug may be eliminated relative to standard doses, as the elimination half-life of the drug may remain the same, independent of the dose load. This greater level of elimination causes drug concentrations to fluctuate across both upper and lower lines of the optimal therapeutic window, particularly for high-dose oral antipsychotics with a relatively short half-life. Furthermore, endogenous dopamine may bind to larger numbers of DRD2, producing enhanced effects. Therefore, in patients with DSP, antipsychotics administered in a form that will yield stable blood concentrations within optimal therapeutic ranges may be of greater use in improving severe and unstable symptoms than the usual tablet formats.

Risperidone long-acting injection (RLAI) was the only long-acting injectable second-generation antipsychotic drug available in Japan at the start of this study. The width between peak and trough blood concentration of RLAI is 32 to 42% smaller than that of oral-risperidone (RIS) using equivalent doses (Eerdenkens et al., 2004). We recently reported that RLAI treatment successfully ameliorated unstable positive symptoms in two DSP cases with TRS (Kimura et al., 2013). Here, we aim to explore the hypothesis that an atypical long-acting agent can prove clinically efficacious in TRS patients with DSP.

2. Methods

2.1. Study design

This is a multicenter, observational study, with a prospective design for assessing clinical outcomes in patients with TRS. The primary objective is to verify the effectiveness of RLAI, that is, the percent change in total BPRS during a 12-month follow-up of the patients. We recruited patients with TRS, who had been selected to receive RLAI by their physicians in clinical setting, from May 2010 to September 2011 and divided them into two groups, defined by the presence or absence of DSP. The assessment of DSP in patients was evaluated by two experienced psychiatrists (H.K. and N.K.). Physicians were given no specific instructions for administering RLAI and oral antipsychotics, although they were instructed to give oral antipsychotics for at least 3 weeks following RLAI initiation and to inject RLAI every two weeks, in accordance with the approved labeling. Physicians were allowed to prescribe antiparkinsonism agents, benzodiazepines and mood stabilizers at their own discretion. Briefly, physicians were encouraged to treat participants so as to achieve maximal clinical effect with minimal side effects. This study was approved by the ethics committees of all participating research facilities. Written informed consent was obtained from all participants after providing them with a full explanation of the study.

2.2. Patients

Patients were eligible for study inclusion if they had a diagnosis of schizophrenia or schizoaffective disorder according to the Structured Clinical Interview for DSM-IV (First et al., 1995). We applied the broad eligibility criteria (Juarez-Reyes et al., 1996) for TRS in the present study, as follows. A patient who scored below 60 in the Global Assessment of Functioning (GAF) at least one year before entering this study and who met either or both of the following two criteria. 1) Non-responder criterion: failure to respond to at least two antipsychotics belonging to two different chemical classes, at dosages equivalent to or greater than 600 mg/day chlorpromazine equivalent (CPZeq) for at least 4 weeks. 2) Intolerance to antipsychotics criterion: TD with moderate or greater severity assessed by ESRS, causing profound distress to the patient. Exclusion criteria for this study were: previous treatment with RLAI and/or clozapine, a history of illegal drug use or substance dependence, the presence of any other AxisIdisorders except for schizophrenia or schizoaffective disorder, mental retardation, pregnancy or any severe physical disease, and the presence of poor medication adherence.

2.3. Measurements

2.3.1. Dopamine supersensitivity psychosis

Presence of DSP was defined using criteria proposed by Chouinard (1991). That is, 1) withdrawal psychosis: acute relapse or exacerbation of psychosis appearing after a dose reduction or discontinuation of antipsychotics, within 6 weeks for oral medication or 3 months for intramuscular medication. This episode must be observed within the last 5 years. Or 2) developing tolerance to antipsychotic effects: This is defined as when an acute relapse or exacerbation of psychosis occurs, independent of a dose reduction or discontinuation of antipsychotic therapy, which cannot be successfully controlled by a 20% increased titration of drug. Or 3) psychotic symptoms which are new to the patient, or of greater severity, occurring immediately after a decrease in drug dosage. Or 4) a history or presence of TD. Based on available information from medical records and hospital staff, if at least one of the listed items above was present, the participant was diagnosed as having a history of DSP. The inter-rater reliability between the two assessors (H.K. and N.K.) was .88. If non identical diagnoses were reached, a consensus-based judgment by these two assessors was applied to the case.

2.3.2. Clinical measurements

The patients were evaluated at baseline (T0), and then after three (T1), six (T2), nine (T3), and twelve months (T4). The primary outcome measure was the percent change in the Brief Psychiatric Rating Scale (BPRS: 18 items, 1–7 scale for each item: Overall and Gorham, 1962) score from T0 to T4. The secondary outcome measures were recorded changes every three months in GAF and Clinical Global Impressions—Severity of Illness (CGI-S). For analyses of patient numbers showing a

response on BPRS during the study, responders were defined as patients showing a reduction of greater than 20% from baseline. Extrapyramidal symptoms (EPS) were evaluated using the Extrapyramidal Symptom Rating Scale (ESRS: 0–257 point that is summed from all of the factors including the last four sections of clinical impressions: Chouinard and Margolese, 2005). Compliance with treatment medication was monitored using by both a self-rating visual analog scale for patient and objective observation by their respective physicians, which rated medication administration from 0 to 100% (Garfield et al., 2011). If these measurements differed from each other by no more than 25%, the mean of both values was used as the patient's adherence rate. To reliably evaluate with these measurements, physicians on the study underwent several rounds of assessment training.

2.4. Statistical analysis

All analyses were conducted using SPSS, version 19.0 (IBM, NY, US). Data analyses were conducted on an intent-to-treat basis including all dropout cases (Fig. 1). Analyses for the primary efficacy measure were performed using a mixed-effects model repeated-measures analysis (Gueorguieva and Krystal, 2004). Treatment group, time and each time-by-group interaction were included as fixed effects, while baseline scale scores and age were included as covariates. The within-subject factor was considered as a random effect. Compound symmetry was used.

Logistic regression analyses was also performed to look at the effect of treatment group on the outcome measure of treatment response or nonresponse at T4, with age, sex, duration of illness, baseline BPRS and ESRS scores, treatment adherence and the presence or absence of DSP included as items. Continuous and categorical variables were compared by independent t test and chi-square test, respectively. A P value of .05 was set as the threshold of significance.

3. Results

3.1. Patient characteristics and analysis of drop-out cases

Of the 115 patients screened, 21 patients were excluded due to meeting exclusion criteria, being lost to follow-up or refusing to participate before the evaluation for DSP, yielding a final analytic sample of 94 patients (Fig. 1: DSP group: N = 61, NonDSP group: N = 33).

Baseline demographics and clinical characteristics were similar between the two groups (Table 1). The BPRS positive symptoms score showed no difference between the two groups, whereas the BPRS negative symptoms score and ESRS score in the DSP group were significantly higher than those of the NonDSP group ($P < .001$). A total of 75 patients (79.8%) completed the 12-month RLAI treatment. There was no significant difference in the dropout rates between the two groups: 14.8% (N = 9) in the DSP group and 30.3% (N = 10) in the NonDSP group ($P > .05$). Seven DSP and 7 NonDSP patients left the study due to an exacerbation of psychotic symptoms. Two DSP patients discontinued due to dystonia and akathisia, and 3 NonDSP patients discontinued due to constipation, hyperglycemia and dystonia.

3.2. Treatment with RLAI and other oral antipsychotics, medication adherence

The mean daily total CPZeq-dose of oral antipsychotics at baseline was about 1000 mg in both groups (Table 1). The subjects received quite variable types and combinations of antipsychotics with variable dose ranges. The primary types of antipsychotics used in the present patients were risperidone (1–18 mg), olanzapine (4–40 mg) and quetiapine (200–825 mg). Percent rate of RLAI patients receiving dose of 25 mg, 37.5 mg and 50 mg at T4 was 13.5%, 19.2% and 67.3% respectively in the DSP group, and 13.0%, 21.7% and 65.2% respectively in the NonDSP group. For daily oral antipsychotics dosing (CPZeq-dose), the mean (±SD) doses at T4 were 605 (791) mg/day and 471 (421) mg/day in the DSP group and the NonDSP group, respectively. There was a significant main effect for Time ($F = 9.70$, $P < .001$), but no main effect for Group ($F = 0.37$, $P > .05$) or for an interaction of Time × Group ($F = 0.07$, $P > .05$). There was no significant difference in the total amount of daily oral antipsychotics and RLAI dose (CPZeq), at T4, between the two groups nor were there significant time effects during the treatment between the groups (Table 2).

Mood stabilizers were prescribed for 19 of 61 DSP patients and 14 of 33 NonDSP patients. Among them, 13 DSP patients and 9 NonDSP patients took sodium valproate at T0: their distributions and their mean doses did not differ between the two groups. These doses tended to be lower during the study, though not significantly, in both groups (data not shown). Regarding benzodiazepine and antiparkinsonism agents, none of the groups showed any significant differences either in baseline doses or in dose changes between T0 and T4.

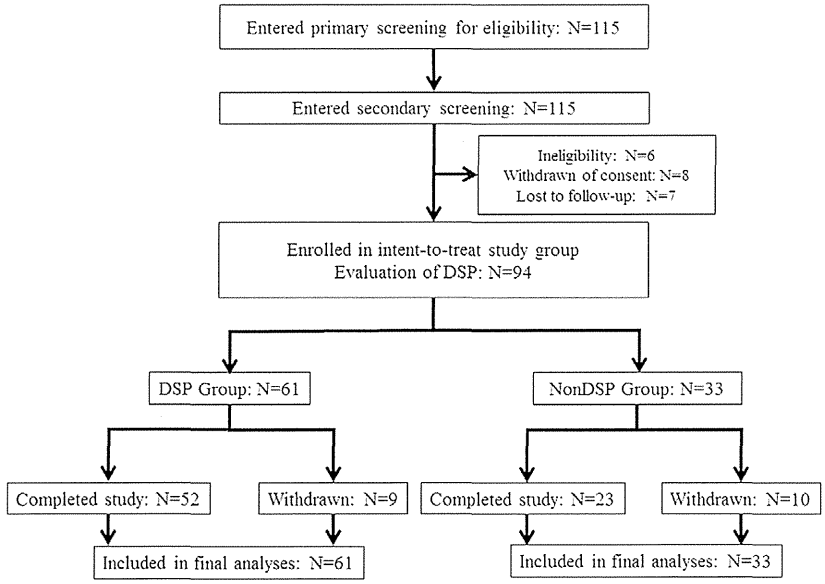

Fig. 1. Overview of participant flow. Initially, 115 patients were screened. Of these, 21 were lost to the study due to meeting the exclusion criteria, being lost to follow-up, or a withdrawal of consent before evaluation of DSP status, yielding a final analytic sample of 94 patients (DSP group: N = 61, NonDSP group: N = 33).

Table 1
Characteristics of eligible participants.

	DSP group N = 61	NonDSP group N = 33	All patients N = 94	Statistical value[c]
Age (years)	43.6 (14.7)	48.5 (11.1)	45.4 (13.7)	N.S.
[Age range]	[18–69]	[26–69]	[18–69]	
Sex (male/female)	30/31	17/16	47/47	N.S.
Duration of illness (years)	20.4 (12.5)	21.2 (11.9)	20.7 (12.3)	N.S.
Inpatient/outpatient	32/29	14/19	46/48	N.S.
Non-responder/intolerance to antipsychotics	57/4	33/0	90/4	N.S.
Diagnosis				
Schizophrenia	58	29	87	
Schizoaffective disorder	3	4	7	
DSP type				
Withdrawal psychosis	41	–	41	–
Tolerant to antipsychotics	35	–	35	–
Relapse with great severity	27	–	27	–
Tardive dyskinesia	24	–	24	–
Antipsychotics dose (CPZeq: mg)	1084.6 (741.4)	960.1(444.1)	1040.4 (651.7)	N.S.
[Dose range]	[0–4512.5]	[200–2050.0]	[0–4512.5]	
BPRS				
Total score	63.0 (18.6)	58.5 (15.7)	61.4 (17.7)	N.S.
Positive symptom score[a]	17.0 (5.5)	16.7 (5.6)	16.9 (5.5)	N.S.
Negative symptom score[b]	13.0 (3.8)	10.8 (3.1)	12.2 (3.7)	P = .004
CGI-S	5.5 (1.1)	5.3 (1.0)	5.4 (1.0)	N.S.
GAF	30.9 (13.1)	32.7 (11.4)	31.5 (12.5)	N.S.
ESRS	34.2 (32.4)	17.8 (17.5)	28.5 (29.1)	P = .001
Adherence	89.2	80.6	86.3	N.S.

Data are mean (SD) [absolute range]. Unless otherwise noted, differences between the DSP and NonDSP groups were not statistically significant (P > .05).
Abbreviations: DSP = dopamine supersensitivity psychosis, CPZeq = chlorpromazine equivalent, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impression Severity, GAF = Global Assessment of Functioning, ESRS = Extrapyramidal Symptom Rating Scale.
[a] The summed scores for conceptual disorganization (#4), suspiciousness (#11), hallucination (#12), and unusual thoughts (#15).
[b] The summed scores for emotional withdrawal (#3), motor retardation (#13), and blunted affect (#16).
[c] Statistical result of each comparison between the DSP and NonDSP groups. Student's t test is applied for continuous variables and the chi-square test is applied for categorical variables.

Adherence to treatment medication, which was measured by a self-administered visual analog scale at T0, T2 and T4, was 89.2%, 92.2% and 90.0% in the DSP group and 80.6%, 86.8% and 88.4% in the NonDSP group, respectively (Table 1). The difference between the self-administered visual analog scale by each patient and assessment of medication adherence rate by his/her physician was within 25% in all patients. Throughout the study period, all patients received RLAI procedures at over 90% of the scheduled visits (once every two weeks).

3.3. Primary outcome measures

Mixed-model analysis of the percentage change in BPRS total scores from baseline to 12 months showed significant improvement in DSP relative to NonDSP patients. This difference was observed from T1 to T4 at each time point analysis (Fig. 2A and Table 2). Average BPRS total scores in both groups were also significantly decreased after the 12-month treatment period (P < .05). Based on percentage changes in BPRS positive and negative symptom scores, DSP patients showed significantly greater improvements compared with NonDSP patients (Fig. 2B, C and Table 2).

Furthermore, we analyzed the percentage BPRS changes only among inpatients with DSP (N = 32) whose adherence was approximately 100%, because they took their medication under staff observation. The results revealed that BPRS scores at T0 and T4 were 68.1 ± 20.3 and 53.6 ± 25.2, respectively, indicating change of more than 20%, suggesting that amelioration in the DSP group was not caused simply by improvement of medication adherence.

3.4. Secondary outcome measures

The mean CGI and GAF scores significantly improved in both groups. The CGI and GAF scores significantly decreased and increased respectively, in each DSP and NonDSP group (P < .05). The improvements during treatment were significantly more pronounced in the DSP

Table 2
Follow-up assessment outcomes over all time points up to 12 months.

BPRS total score	DSP group		NonDSP group		
	Score at T4	Percentage change in score	Score at T4	Percentage change in score	P value[a]
BPRS total score	42.1 (18.0)[b]	33.0 (19.9)	44.3 (16.5)[b]	17.0 (20.5)	<.01
Positive symptom score	11.3 (5.5)[b]	33.3 (22.9)	12.1 (5.2)	16.7 (27.7)	<.01
Negative symptom score	8.8 (3.9)[b]	31.7 (24.0)	8.6 (2.7)[b]	16.6 (22.2)	<.01
CGI-S	3.8 (1.4)[b]		4.3 (1.3)[b]		<.01
GAF	49.2 (16.9)[b]		42.5 (14.9)[b]		<.01
ESRS	19.2 (23.6)[b]		18.1 (16.7)		N.S.
Antipsychotics dose (CPZeq: mg)	1034.7 (823.4)		870.5 (466.9)		N.S.
Adherence (%)	90.0		88.4		N.S.

Data are mean (SD). T4 indicate time points at 12 months. The numbers of patients at T4 were 52 in the DSP group and 23 in the NonDSP group.
Abbreviations: N.S. = not significant.
[a] P values for the comparison in % change score or each measurement score between the DSP and NonDSP groups. The treatment comparison was a liner contrast based on a mixed-effects model with three fixed effects (time, treatment group, and time-treatment group interaction). The within-subject factor was considered as a random effect.
[b] P < .01 comparisons in each score between baseline (T0) and T4 within the group.

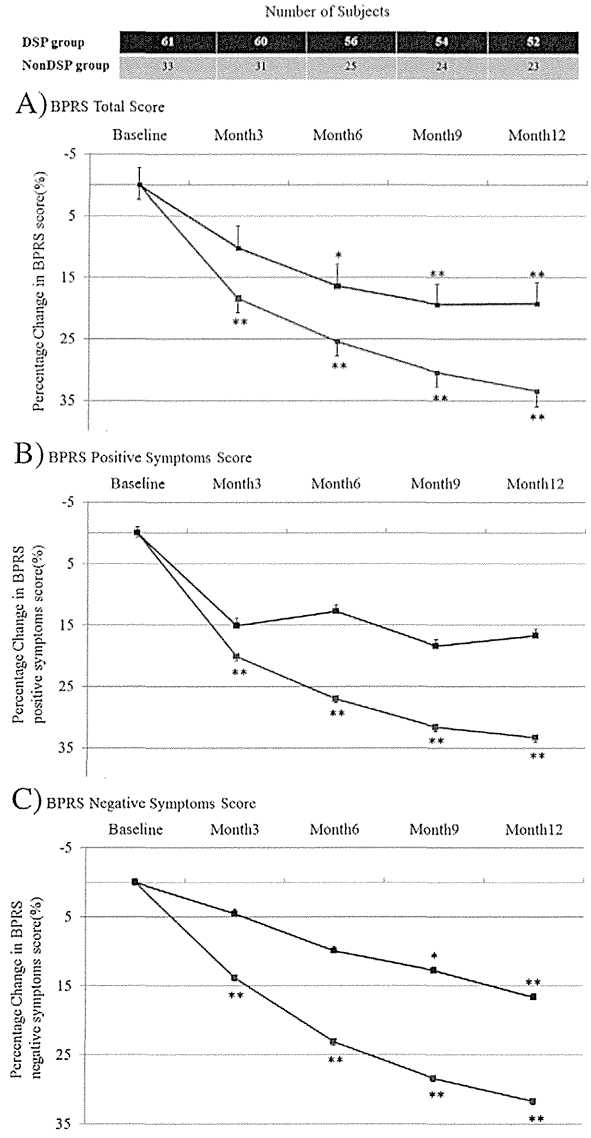

Fig. 2. Percentage change in BPRS total, positive and negative symptom scores over time. The red and blue lines indicate changes in the DSP and the NonDSP group, respectively. Error bars indicate standard error of the mean. Percentage changes in BPRS total, positive and negative symptom scores were analyzed using mixed effects model repeated-measures analysis. There were significant differences in A) total, B) positive and C) negative symptom scores between the DSP and NonDSP group ($P < .01$). $^{*}P < .05$ and $^{**}P < .01$ represent significant improvement in each group and the percentage change in BPRS score from baseline respectively.

group relative to the NonDSP group. Mean ESRS scores showed no significant difference between the two groups at the end of the study (Table 2). However, there were significant reductions in this value from T0 to each subsequent time point in the DSP group, whereas there was no change in the NonDSP group. Furthermore, the TD score of ESRS was significantly lower in the completers of the DSP group. On the other hand, no patients in the NonDSP group exhibited new TD during the study period.

Responder rates were 62.3% (N = 38) in the DSP group and 21.2% (N = 7) in the NonDSP group, indicating a significant difference ($\chi 2 = 14.5$, $P < .001$) between the two groups.

Logistic regression analysis revealed DSP as the only factor significantly related to RLAI response (odds ratio = 6.90, $P < .01$: Table 3).

4. Discussion

To our knowledge, this is the first study to investigate the efficacy of a 12-month RLAI treatment regime in patients with TRS and DSP. The treatment yielded significantly greater improvement in psychiatric symptoms and global functioning in DSP patients compared with DSP-free patients. DSP patients also showed a higher response rate (62%) relative to those without DSP (21%). Multiple logistic regression analyses revealed that the presence of DSP greatly contributed to clinical improvements in this study. Furthermore, at the end of the study, patients who received high antipsychotic doses (both oral antipsychotics and RLAI), took comparable daily oral antipsychotic doses at baseline prior to RLAI initiation. These results imply that adjunctive RLAI treatment with a gradual reduction of oral antipsychotics can help to promote a remarkable improvement in DSP patients. Unsurprisingly, DSP patients showed severer EPS at baseline, including TD, a neurological DRD2 supersensitivity (Sasaki et al., 1995a, 1995b) and an important criteria in the diagnosis of DSP (Chouinard, 1991; Fallon and Dursun, 2011). In the DSP group, the possibility that RLAI treatment lessens severe EPS was observed. Taken together, our findings suggest that achieving and maintaining stable therapeutic blood levels of antipsychotics could improve symptoms in patients with severe and treatment-resistant DSP, supporting our original hypothesis (Iyo et al., 2013). In addition, the development of other long acting injectable antipsychotics, such as other classes of atypical antipsychotics or longer-acting forms, may be desirable for the treatment of DSP.

The ESRS score and the TD score were lower overall in the DSP group, whereas no change was observed in the NonDSP group. When we consider that the mean of the total chlorpromazine equivalent doses was not different between the entry (T0) and the end (T4) of this study, we can infer that the reduced fluctuation of plasma antipsychotic levels contributes not only to the stabilization of psychosis but also to the reduction in antipsychotic-induced EPS and TD, which can be considered neurological manifestations of dopamine supersensitivity.

In this study, DSP patients exhibited significant negative symptoms at baseline, which improved remarkably during treatment. Antipsychotics are capable of improving negative and depressive symptoms, depending on the extent to which positive symptoms and EPS are reduced (Tandon, 2011). In DSP patients, the dramatic improvement in positive symptoms and EPS plays a contributory role in the improved negative symptoms and general functioning.

Table 3
Multiple logistic regression model of factors associated with responders.

	Partial regression coefficient	P value	Odds ratio	95% confidence intervals
Presence of DSP	1.93	<.01	6.90	2.19–21.80
BPRS at baseline				
Total score	−0.02	.45	0.98	0.92–1.04
Positive symptom score	0.01	.87	1.01	0.86–1.19
Negative symptom score	0.07	.46	1.07	0.90–1.28
ESRS	<−0.01	.79	1.00	0.98–1.02
Sex	−0.23	.63	0.95	0.31–2.05
Age	−0.02	.58	0.99	0.94–1.04
Duration of illness	<0.01	.94	1.00	0.94–1.06
Adherence	0.19	.38	1.20	0.80–1.82

One part of DSP patients didn't respond to the treatment. One possible reason may be sub-optimal dosing, with the combined RLAI and oral antipsychotic treatment. If the total dosages were too low to achieve optimal receptor occupancy, or if the elimination half-life of the oral drugs was too short to maintain optimal occupancy, RLAI therapy may not be sufficient to control disease symptoms. In Japan, the maximum dose of RLAI is limited to 50 mg/2-week, which is estimated to produce an occupancy range of 65.4 to 74.4% (Remington et al., 2006), corresponding to the optimal range for patients with a first schizophrenic episode (Kapur et al., 2000). Further studies are needed to clarify the accuracy of this data and its validity for subsequent episodes.

The study treatment provided only limited efficacy for NonDSP patients. In this group, positive symptoms failed to show significant improvement, while the negative symptoms showed only slight significant improvement. Reports highlight that patients with deficit syndrome (Galderisi and Maj, 2009) respond poorly to antipsychotic treatment and show profound continued negative symptoms. It is possible that there were a significant number of patients with deficit syndrome within our NonDSP cohort. That said, there may be patients with other types of confounding factors, as schizophrenia is known to be a heterogeneous disease (Tandon et al., 2009; Insel, 2010; Kanahara et al., 2013). Clozapine is known to improve symptoms in deficit syndrome (Rosenheck et al., 1999; Kelly et al., 2010). It is highly possible that in these patients, the mechanistic action is not via blockade of DRD2, but by modulation of other sites, such as the N-methyl-D-aspartate receptor, a candidate target of clozapine in the treatment of schizophrenia (Hashimoto, 2011; Miyamoto et al., 2012). However, further studies are needed to fully explore this point.

To date, there are two previous reports on clinical trials using RLAI in TRS (Procyshyn et al., 2010; Volonteri et al., 2010), although in these studies, patients were switched from other antipsychotics to RLAI. This differs from our study where RLAI was used adjunctively. In one study, a 6-month RLAI treatment achieved a 60% response rate in treatment-resistant patients with severe symptoms (Volonteri et al., 2010). The other study failed to show an advantage for RLAI (Procyshyn et al., 2010). Neither of these studies made special reference to DSP, nor did they report on the dosages of antipsychotics in use before patients entered the study. Therefore, it is unknown what percentage, if any of their study participants suffered from DSP and whether the doses of RLAI were high enough to improve symptoms in these studies.

As with all reports of this nature, there are some limitations to this study. First, this was a relatively short term observational study, because our aim was to maximize efficacy of the RLAI regime to effect improved conditions for TRS patients. A randomized, controlled study with a longer follow-up duration is needed to confirm our observation. Second, we didn't directly measure D2 receptor occupancy or the fluctuation of plasma levels of antipsychotics. Therefore, further studies, including direct measurements of these parameters, are needed to confirm our hypothesis on the mechanisms underlying DSP and treatment of patients with DSP. Third, the medication adherence level may affect the results to some extent in this study, since it has been suggested that most patients actually are under partial adherence (Oehl et al., 2000), especially patients with TRS, like our participants. Therefore, we evaluated our patients' adherence using self-reported data and the observations of their physicians. The results confirmed no differences between these two reports, although we didn't use pill-count methods. Furthermore, we analyzed BPRS scores and their changes only among the inpatients with DSP, whose adherence rates could be considered almost 100%, and the results were similar to those obtained by the analysis of all patients with DSP. In this light, we consider that the present results on the improvement of symptoms were not likely attained simply by improvements in medication adherence alone.

In conclusion, our study demonstrated that adjunctive RLAI treatment significantly improved psychotic symptoms and global functioning in TRS patients with DSP. While clozapine is considered the standard antipsychotic drug of choice for TRS (Kane et al., 1988), it is associated with serious adverse events, such as agranulocytosis and diabetes mellitus (Fakra and Azorin, 2012). This study suggests that therapeutic regimes using antipsychotics with long elimination half-lives may prove suitable alternatives to clozapine for this cohort of patients.

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Conflict of interest

Dr. Kimura reported honoraria from Janssen, Meiji Seika and Otsuka. Dr. Kanahara received grant funding from Grant-in-Aid for Young Scientists (B) (grant number is 25860989) from Japan Society for the Promotion of Science (JSPS) and grant of Heisei-24 Schizophrenia research field from SENSHIN Medical Research Foundation and reported honoraria from Eli Lilly, Otsuka and Janssen. Dr. N. Komatsu reported honoraria from Eli Lilly, Otsuka, Janssen, Yoshitomi and Ono. Dr. Ishige reported honoraria from Janssen, Eli Lilly, Otsuka and Astellas. Dr. Yamanaka reported honoraria from Otsuka, Dainippon Sumitomo, Janssen and Eli Lilly. Dr. Sasaki reported honoraria from Otsuka, Dainippon Sumitomo, Pfizer, Eli Lilly and Mochida. Dr. T. Hashimoto received grant funding from Ministry of Health, Labour and Welfare and reported honoraria from Mochida and Meiji Seika. Dr. Hasegawa reported honoraria from Eli Lilly, Astellas, Otsuka, Dainippon Sumitomo, GlaxoSmithKline and Shionogi. Dr. Shiina reported grant funding from Ministry of Health, Labour and Welfare. Dr. Sekine reported honoraria from Eli Lilly, Otsuka and Janssen. Dr. Watanabe reported honoraria from Eli Lilly and Dainippon Sumitomo. Dr. Shimizu reported honoraria from Meiji Seika, Mochida, Eli Lilly, Janssen and Yoshitomi. Dr. K. Hashimoto received the research grant or consultant fee from Abbott, Astellas, Otsuka and Taisho. Dr. Iyo received consultant fee from Eli Lilly, Dainippon Sumitomo, Pfizer and Abbott and reported honoraria from Janssen, Eli Lilly, Otsuka, Meiji Seika, Astellas, Dainippon Sumitomo, Ono, GlaxoSmithKline, Takeda, Mochida, Kyowa Hakko, MSD, Eisai, Daiichi-Sankyo, Novartis, Teijin, Shionogi, Hisamitsu and Asahi Kasei. Dr. Muneoka, Dr. Yoshimura, Dr. Suzuki, Dr. H. Komatsu, Dr. Ishikawa and Dr. Shiraishi reported no conflict of interest.

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Effectiveness of Information Technology Aided Relapse Prevention Programme in Schizophrenia excluding the effect of user adherence: A randomized controlled trial

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ABSTRACT

Background: A relapse prevention program called the Information Technology Aided Relapse Prevention Programme in Schizophrenia (ITAREPS) has been developed and is reported to be highly effective. However the effectiveness was influenced by user adherence to the protocol of the program, the exact effectiveness and the role of the ITAREPS have been partially uncertain.
Objective: The purpose of this study is to evaluate the effectiveness of the ITAREPS excluding the effect of user adherence to the protocol of the program.
Method: We attempted to perform a randomized controlled trial by the devised method with visiting nurse service. Outpatients with schizophrenia were randomized to the ITAREPS (n = 22) or control group (n = 23) and were observed for 12 months.
Results: The risk of rehospitalization was reduced in the ITAREPS group (2 [9.1%]) compared with the control group (8 [34.8%]) (hazard ratio = 0.21, 95% CI 0.04–0.99, $p = 0.049$; number needed to treat (NNT) = 4, 95% CI 2.1–35.5). The mean number of inpatient days was significantly lower in the ITAREPS group (18.5 days) compared with the control group (88.8 days) ($p = 0.036$). The ratio of the number of rehospitalizations to that of relapses was significantly lower ($p = 0.035$) and the mean change in total BPRS scores at relapse from baseline was significantly less in the ITAREPS group ($p = 0.019$).
Conclusions: The relapse prevention effectiveness of the ITAREPS was high, and we confirmed that the ITAREPS, i.e., detecting signs of relapse and increasing medication during the warning state, is an effective intervention during the early stages of relapse.

1. Introduction

Schizophrenia often follows a chronic course. Many patients respond to early antipsychotic drug therapy, but 80% relapse within 5 years of onset (Robinson et al., 1999). Repeated relapses lead to worsening of prognosis, such as poorer response to treatment (McGlashan, 1988), organic changes in the brain (Mathalon et al., 2001), and increased suicide rate (Wiersma et al., 1998). Therefore, preventing relapses and rehospitalization are extremely important for patients with schizophrenia. Recent systematic reviews have shown that antipsychotic drug therapy can reduce the recurrence rate of schizophrenia (Leucht et al., 2012). However, this therapy is often interrupted because of patient compliance and side effects (Keith, 2006); antipsychotic drug therapy strategies for the maintenance phase of schizophrenia are not well established (Takeuchi et al., 2012).

A relapse prevention program called the Information Technology Aided Relapse Prevention Programme in Schizophrenia (ITAREPS) has

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been developed and is reported to be highly effective (Španiel et al., 2008a, 2008b). The ITAREPS presents a mobile phone-based telemedicine solution for weekly remote patient monitoring and disease management in schizophrenia and psychotic disorders in general. The program provides health professionals with home telemonitoring via a PC-to-phone short message service (SMS) platform that identifies prodromal symptoms of relapse, to enable early intervention and prevent unnecessary hospitalizations. Participants enrolled in the ITAREPS (the patient and her/his family member) were instructed to complete a 10-item Early Warning Sign Questionnaire (EWSQ) by a short message service (SMS) request sent weekly by an automated system to their mobile phones. Attendance of a family member at the ITAREPS was highly recommended, albeit optional. Reporting on psychometric properties and structure of EWSQ has been published elsewhere (Španiel et al., 2008a, 2008b). Individual EWSQ scores were sent by participants back to the ITAREPS as an SMS. If a total EWSQ score exceeds a given score threshold, an automatically generated ALERT is declared and a treating psychiatrist is notified by an e-mail message. According to a specific procedure, the presence of early warning signs warrants an immediate increase in baseline maintenance dose of antipsychotic by 20% within the next 24 h. Once an ALERT was declared, it continued for the next 3 week ALERT PERIOD, providing that the following 6 consecutive EWSQ scores showed no worsening of symptoms. If so, the ALERT PERIOD was withdrawn and the event announced to psychiatrist via e-mail along with recommendation concerning subsequent tapering down of the medication to the pre-ALERT dose. During the ALERT PERIOD, patients were to return answered questionnaires twice weekly upon SMS request. In addition to that, more conservative score thresholds were adopted. If EWSQ scores exceeded those modified thresholds anytime during the ALERT PERIOD, an ALERT EMERGENCY was announced via e-mail. In such a case the ALERT PERIOD was extended for a further 3 weeks after each ALERT EMERGENCY message. Thus, by incorporating information technology, this program is a method to prevent relapse by predicting early signs and administering pharmacological intervention. As a result of introducing this new relapse prevention program, a before-and-after 2-year comparative study reported a 60% decrease in the number of hospitalizations (Španiel et al., 2008a, 2008b).

Although this research report indicated excellent results, it included the following unclear issues. It was reported that the effectiveness of relapse prevention was correlated with the subject's response rate to the questions and had the added restriction of not understanding the actual state of pharmacological intervention when in a warning state. Consequently, it is unclear whether the relapse prevention effectiveness of the ITAREPS only reflects the psychoeducational effectiveness or differences in user adherence to the protocol of the program such as the response rate to the questions or whether increasing medication during the warning state is important (Volavka, 2008).

In this study, we employed visiting nurses, wherein one of their basic tasks in Japan is to check patient's medication compliance and psychiatric condition for prevention of relapse when they visit his/her home, and were asked to perform one part of this relapse prevention program to exclude the effects of user adherence. More specifically, visiting nurses were asked to question patients through phone calls rather than a SMS. Consequently, we were able to obtain reliable responses from all patients regardless of their adherence. We also prescribed 20% of the baseline maintenance dose of antipsychotic drugs to patients in advance, for a quick and reliable increase in their dose during the ALERT PERIOD regardless of whether patients undergo medical examination. Furthermore, the visiting nurses verified that the patient had increased their oral medication during the ALERT PERIOD by visiting patient's home directly. The objective of this study was to verify the effectiveness of the ITAREPS in preventing relapses by performing a randomized controlled trial using the ITAREPS that was not influenced by the effect of user adherence to the protocol.

2. Methods

2.1. Trial design

This trial was a multicenter, prospective, open-labeled, randomized controlled trial. The trial was carried out at four institutions (Chiba University Hospital, Shizuoka Psychiatric Medical Center, Iida Hospital, and Matsubara Hospital) across Japan and was approved by the ethics committee of each institution. Subjects were recruited from March to July 2010, and each subject was observed for 12 months.

2.2. Subjects

The subjects were outpatients at the institutions cooperating in the trial. The selection criteria included 20–65-year-old patients diagnosed with schizophrenia defined by the Diagnostic and Statistical Manual of Mental Health Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria, those who were receiving an oral antipsychotic drug, those who had a landline or mobile phone, and those who had a history of hospitalization due to worsening of psychiatric symptoms. All patients provided their written informed consent. The exclusion criteria included patients with a history of other mental illnesses without any complications, those not suffering from organic brain disease or other serious mental illnesses, and those diagnosed by a doctor to be at risk of suicide when consent was provided.

2.3. Randomization

The administrators at each institution who were independent of the evaluators and physicians administering treatment carried out the randomization. The administrators only knew the patient's code number, name, date of birth, and stratification criteria. They allocated patients using a minimization method that adjusted imbalances in the subject's background at the start of the study.

2.4. Measurement items

We measured the number of rehospitalizations on the basis of worsening of psychiatric symptoms, the period until rehospitalization, and the total number of rehospitalization days in each group. We also used the Brief Psychiatric Rating Scale (BPRS) to assess psychiatric symptoms, and recorded changes in the total BPRS score at the time of rehospitalization after the start of the trial. Furthermore, we considered relapses based on worsening of psychiatric symptoms that did not require hospitalization. The definition of relapse is not fixed; it has been defined in several ways in other studies (Gleeson et al., 2010). In this study, if a doctor decided during a routine examination that there had been a relapse due to worsening of psychiatric symptoms, all relapses and changes in the total BPRS score from the start of the trial were recorded. The subject's voluntary adverse effect reports were collected during each routine examination while performing clinical assessments.

2.5. Intervention

Subjects were randomized into an ITAREPS group and a control group. Visiting nurses asked the subjects in both groups about each item of the EWSQ through phone calls weekly, in order to exclude the effects of user adherence to the protocol. After visiting nurses questioned the subjects in the ITAREPS group, visiting nurses input the subjects' answers into a computer, which automatically assessed the subjects' answers according to a given score threshold and detected early warning signs. When early warning signs were detected, subjects were prompted by visiting nurses through phone call to take additional medications prescribed in advance (20% of the baseline maintenance dose of antipsychotic drugs) within the next 24 h. Visiting nurses also visited patients' home to verified that subjects had indeed increased their oral medication

during the ALERT PERIOD in addition to routine nursing care (checking symptoms, recommending early medical examinations, etc.). In the control group, the visiting nurses assessed the answers by the subjects through phone calls and predicted relapses. The nurses were instructed to conduct nursing care visits as usual, whether or not they predicted relapses.

2.6. Statistical analysis

The ITAREPS and control groups were compared by performing an intention-to-treat analysis that included all group-allocated subjects. Fisher's exact test and the Mann–Whitney *U*-test were used for the baseline comparison based on the quality of the data, number of rehospitalizations, average number of rehospitalization days, number of inpatient days on each rehospitalization, and a comparison of the number of relapses. The Kaplan–Meier method and the log-rank test were used to analyze the comparisons between the two groups during the time after randomization to rehospitalization. Hazard ratio was calculated using a proportional hazard analysis to determine the rehospitalization rates in the two groups. Comparisons of the changes in the total BPRS scores were analyzed using an analysis of covariance considering the score at the start of the trial. Statistical significance was set at $p < 0.05$. Statistical analysis was performed with SPSS for Windows version 19.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Of the 399 potential participants who met the participation criteria, received an explanation of the study, and provided their consent in writing, 45 were randomized to the ITAREPS group (n = 22) and control group (n = 23). Approximately 10% of the subjects of each group withdrew from the trial for reasons other than rehospitalization due to worsening of psychiatric symptoms. We performed an intention-to-treat analysis on the results, including cases of subject drop-outs due to hospitalization for physical illness and for their own convenience (Fig. 1). The background elements for the subjects in each group at the start of the trial are shown in Table 1. Group characteristics were almost the same. The computer made 1111 automatic assessments in the ITAREPS group, among which signs of relapse according to EIA were detected 75 times. No adverse effects were reported by researchers or subjects.

Table 1
The demographic and baseline characteristics.

	ITAREPS group (n = 22)	Control group (n = 23)	*p*
Gender, n male:female	12:10	13:10	1.00[a]
Family member participation, n Yes:No	18:4	19:4	1.00[a]
Age, years (mean ± SD)	42.3 ± 11.8	44.0 ± 9.3	0.54[b]
Age at onset, years (mean ± SD)	25.5 ± 8.7	24.7 ± 9.0	0.79[b]
Illness duration, years (mean ± SD)	16.9 ± 11.6	19.3 ± 9.6	0.25[b]
Baseline total BPRS score (mean ± SD)	15.6 ± 8.9	17.9 ± 7.8	0.27[b]
Period after last hospital discharge, months (mean ± SD)	35 ± 61	46 ± 51	0.44[b]

ITAREPS = Information Technology Aided Relapse Prevention Programme in Schizophrenia.
SD = standard deviation.
BPRS = Brief Psychiatric Rating Scale.
[a] Fisher's exact test.
[b] Mann–Whitney *U* test.

3.1. Period until rehospitalization and the number of rehospitalization days

Two rehospitalizations were observed during the 12 months for the 22 patients in the ITAREPS group (9.1%), and eight rehospitalizations were observed for the 23 patients in the control group (34.8%). The average period until rehospitalization was calculated using the Kaplan–Meier method using the log-rank test and was significantly longer in the ITAREPS group than in the control group (log rank, 4.53, $p = 0.033$)

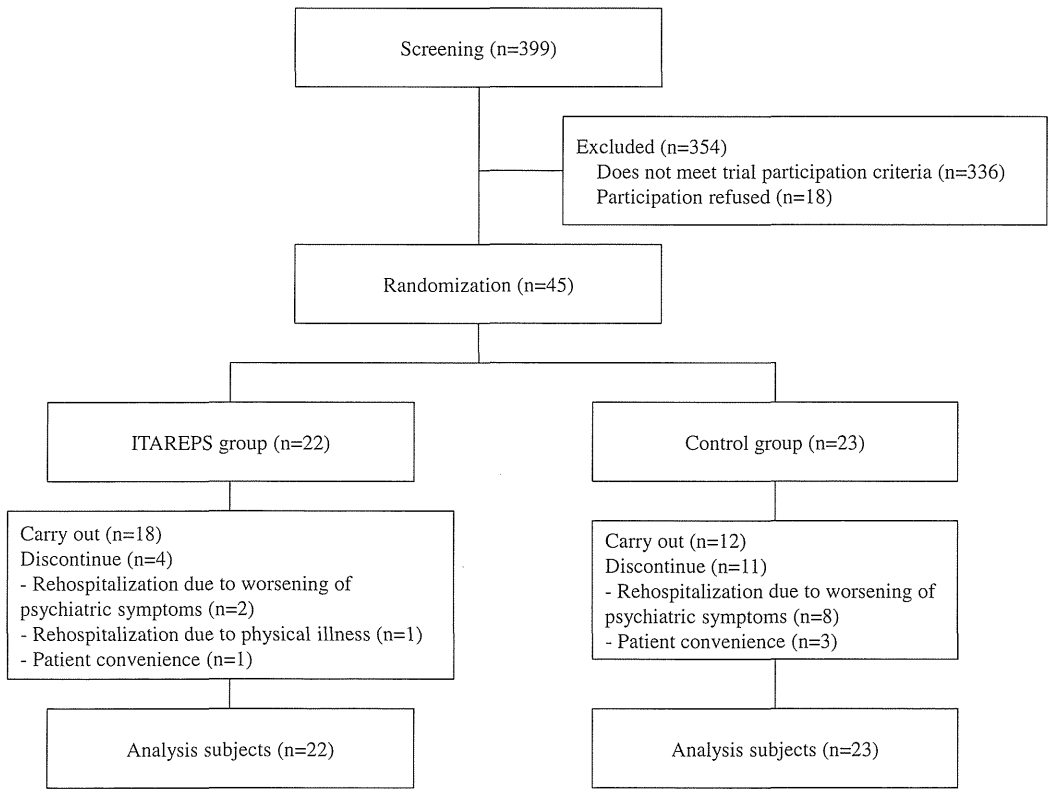

Fig. 1. Enrollment, randomization, and follow-up of the study patients.

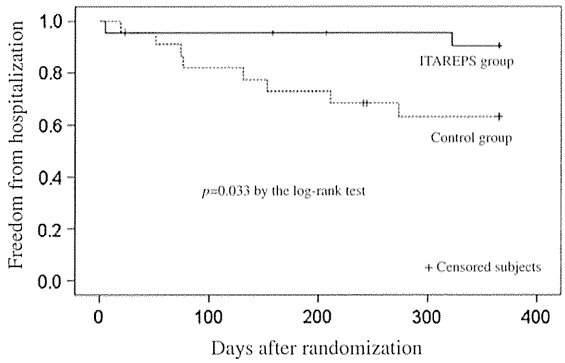

Fig. 2. Time to rehospitalization after randomization.

(Fig. 2). The risk of rehospitalization was reduced in the ITAREPS group compared with the control group (hazard ratio = 0.21, 95% confidence interval (CI) 0.04–0.99, $p = 0.049$; number needed to treat (NNT) = 4, 95% CI 2.1–35.5). The total number of rehospitalization days was significantly lower in the ITAREPS group (37 days) compared with the control group (710 days) ($p = 0.023$). The number of inpatient days on each rehospitalization was also significantly lower in the ITAREPS group (18.5 days) compared with the control group (88.8 days) ($p = 0.036$) (Table 2).

3.2. Number of relapses and changes in total BPRS score

Seven relapses including rehospitalization during the 12 months of observation occurred in the 22 patients in the ITAREPS group and nine relapses occurred in the 23 patients in the control group, with no statistically significant differences. However, the ratio of the number of rehospitalizations to that of relapses was significantly lower in the ITAREPS group than in the control group ($p = 0.035$). No statistically significant differences were observed for the mean change in total BPRS scores at rehospitalization in either group. However, the mean change in total BPRS scores at relapse was less in the ITAREPS group, changing by 11.3 points compared with 17.2 points in the control group, with a significant difference observed using the analysis of covariance adjusted with the baseline score ($p = 0.019$) (Table 2).

4. Discussion

We obtained significantly good results in the ITAREPS group for the average period until rehospitalization and the total number of days hospitalized. No contradictions or large changes were observed in comparison with the results of previous studies reported by Španiel et al. (2008a, 2008b). No significant differences were observed for the number of rehospitalizations, but statistical power may have been low due to the insufficient sample size and short observation period. The hazard ratio was calculated to be 0.21 ($p = 0.049$; 95% CI, 0.04–0.99) in the two groups, indicating that the risk of rehospitalization was reduced by approximately one-fifth after introducing the ITAREPS. Visiting nurses were used in this study to prevent the influence of user adherence, and nurses were instructed to perform interventions using routine nursing care (checking symptoms, recommending early medical examinations, etc.) during relapses in the control group because of ethical considerations. An even larger difference may have been observed if no intervention was performed during a relapse in the control group. The risk ratio of rehospitalization prevention effectiveness was 0.71 in a systematic review that covered the effect of psychoeducation (Xia et al., 2011), and the adjusted hazard ratio in studies examining the effect of switching from oral antipsychotics to sustainable injectable formulations was 0.36 (Tiihonen et al., 2011). The relapse prevention effectiveness of the ITAREPS was relatively large compared with these other methods; however, conditions differed between studies, thus making the results difficult to compare.

Answers to questions were reliably obtained and drug interventions were performed during warning states because visiting nurses performed a part of the ITAREPS in this study. Consequently, the effects of not only patient adherence but also practitioner adherence to the protocol could be excluded. Many cases wherein medication was not increased during the warning condition occurred in randomized controlled trials recently carried out by Španiel et al. The adherence of practitioners providing treatment became a hindrance, and no differences were found in the intention-to-treat analysis (Španiel et al., 2012). In this study, the effectiveness was verified, and we excluded the effects of user adherence so that an intervention that involved early detection of signs of relapse and early medication increases confirmed the relapse prevention effectiveness of the ITAREPS. Furthermore, we believe that stable relapse and rehospitalization prevention effectiveness not influenced by user adherence can be achieved by devising methods according to the local medical resources provided, such as the visiting nurses who performed a part of the ITAREPS in this study.

We found that the number of relapses in the ITAREPS group was the same as that in the control group, but the ratio of the number of rehospitalizations to that of relapses was significantly lower in the ITAREPS group than in the control group. The mean change in total BPRS scores at relapse and the number of inpatient days on each rehospitalization were also significantly lower in the ITAREPS group. Thus, the ITAREPS detected signs of relapse and prevented aggravation during relapse by increasing medication, which shortened the relapse duration. We postulate that the ITAREPS is an effective intervention during the early stages of relapse.

Antipsychotic drug therapy causes a dilemma during the maintenance phase of schizophrenia. Although many treatment guidelines recommend continuing antipsychotic drug therapy to prevent relapses, a smaller amount of medication may be preferable considering the well-known side effects such as extrapyramidal symptoms due to antipsychotic drugs and the adverse effects of the antipsychotic drugs on the brain (Ho et al., 2011). The ITAREPS was effective in preventing relapses through a temporary increase in medication during the early relapse phase. Therefore, in the future, it may have a large effect on treatment strategies during the maintenance phase wherein the above dilemma is faced.

Table 2
Results at 12 months.

	ITAREPS group (n = 22)	Control group (n = 23)	*p*
Number of hospitalizations	2	8	0.071[a]
Total number of rehospitalization days	37	710	0.023[b, *]
Inpatient days (mean ± SD)	18.5 ± 12.0	88.8 ± 57.0	0.036[b, *]
Number of relapses	7	9	0.758[a]
Number of rehospitalizations/number of relapses	2/7	8/9	0.035[a, *]
Change in total BPRS scores at rehospitalization (mean ± SD)	9.0 ± 1.4	18.3 ± 6.1	0.135[c]
Change in total BPRS scores at relapse (mean ± SD)	11.3 ± 5.6	17.2 ± 6.5	0.019[c, *]

ITAREPS = Information Technology Aided Relapse Prevention Programme in Schizophrenia.
SD = standard deviation.
BPRS = Brief Psychiatric Rating Scale.
[a] Fisher's exact test.
[b] Mann–Whitney *U* test.
[c] Analysis of covariance.
* $p < 0.05$.

5. Conclusion

This study noted that the relapse prevention effectiveness of the ITAREPS for schizophrenia was high, and we confirmed that the ITAREPS, i.e., detecting signs of relapse and increasing medication

during the warning state, is an effective intervention during the early stages of relapse.

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Conflict of interest

The authors declare no conflict of interest.

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Onset Pattern and Long-Term Prognosis in Schizophrenia: 10-Year Longitudinal Follow-Up Study

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Abstract

Background: Although the duration of untreated psychosis (DUP) plays an important role in the short-term prognosis of patients with schizophrenia, their long-term prognosis generally is not determined by DUP alone. It is important to explore how other clinical factors in the early stage are related to DUP and consequent disease courses.

Methods: A total of 664 patients with untreated psychosis were surveyed for this study. At the first examination, we divided them into the severe positive symptoms cases (SC) or the less severe cases (NonSC) and compared the prognosis among the two groups after a 10-year follow-up. In all, 113 patients in the SC group and 43 patients in the NonSC group were follow-up completers.

Results: Whereas DUP was not different between the two groups, patients with nonacute onset in both groups had significantly longer DUP than those in patients with acute onset. For all clinical measures, there was no difference in prognosis between the two groups or among the four groups classified by mode of onset (MoO) and initial severity of positive symptoms. However, the degree of improvement of global assessment of functioning (GAF) was significantly smaller in the NonSC-nonacute group than in the SC-acute and SC-nonacute groups.

Conclusions: These results suggest that neither DUP nor MoO alone necessarily affects the initial severity of positive symptoms. Moreover, it is possible that patients with low impetus of positive symptoms onset within long DUP experience profound pathologic processes. Therefore, the current study results indicated that long DUP and nonacute onset were related to poor long-term prognosis, regardless of initial positive symptoms.

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Introduction

Schizophrenia is a highly heterogeneous disorder, and its long-term course and/or prognosis also vary significantly from patient to patient. Several studies reported that, although symptom remission could be obtained for 27% of patients within 4 weeks and 45% within 5 years following treatment initiation [1,2], 20–30% of patients reached a treatment-resistant status on the other side [3]. Even if patients reach remission once, a high relapse rate is inherent in this disorder. Actually, 35% of patients with schizophrenia experienced relapse within 2 years [4] and 74% within 5 years [5] after the onset. These findings indicate that predicting the *true* prognosis of an individual patient requires long-term observation, which exceeds at least the critical period [6].

The prediction of prognosis during the early stage is, nonetheless, importance form the viewpoint of developing the optimal treatment strategy throughout the overall disease course. The authors of previous studies have presented a variety of potential predicting factors, such as duration of untreated psychosis (DUP), mode of onset (MoO) and premorbid functioning [7,8]. DUP has been reported to have a significant negative impact on various symptoms, remission rate and social functioning in the prognosis of several years after treatment intervention [9,10]. For long-term outcome, some longitudinal studies have shown that the effect of DUP is not as great as the previously believed [11]. As regard MoO, insidious onset has been suggested to be related with unfavorable outcome [12,13]. Accumulating evidence of these two factors (DUP and MoO) indicates that their numeric values were not only clinical usefulness, but also that onset pattern could have great effects on the etiology occurring prior to treatment intervention and further consequent disease course. If these two factors already determined severity of symptoms at treatment intervention, the combined analyses based on these three factors

(DUP, MoO and initial symptom severity) might be able to anticipate reliably long-term prognosis.

Here, the present study evaluated untreated psychotic patients, who were mostly subjects with schizophrenia, with focus particular on DUP and MoO. Concurrently, we divided them into two groups based on initial severity of positive symptoms and further followed them during 10 years. The reason of selecting positive symptoms as initial severity is that positive symptoms was the most reliable and valid symptom scale among various ones, in particular for first-episode psychosis. The present study aims at clarifying the relationships among predicting factors (DUP and MoO) and initial positive symptoms and further their remote effects on prognosis.

Methods

Informed Consents

This study was approved by the ethics committees of Chiba Psychiatric Medical Center (CPMC) and Chiba University. Oral and written informed consents for study inclusion were obtained from all participants and from their family members, if possible, at the prognosis interview. The consents obtained from participants were for 1) conducting an interview with the participant, and 2) using the participant's clinical data that had been saved at CPMC, to facilitate the appropriate research. When a potential participant denied permission for study participation (even if the denial was judged to be due to his/her illness condition), we neither conducted the interview with the patient's family nor accessed the patient's medical records. On the other hand, when a potential participant could not understand our explanations or could not adequately judge whether to participate in the study due to his/her illness condition, following careful discussion by researchers and the patient's physician, we approached his/her family member (parents or spouse) to discuss the study participation. If the family member agreed to enlist the patient in the study, the interview was conducted with both the patients and the family. As a third case, when the participant agreed to participation in the study, we conducted the interview with the patient and, if possible, with his/her family members. Patients were assured both in writing and verbally that refusal to participate in the study would not have any effect on their subsequent treatments.

Subjects

For this study, we recruited patients who had received no treatment with antipsychotics or who had received antipsychotics within one week and had not reached sufficient improvement of the relevant psychotic symptoms, which we defined as absence of treatment history, from among patients who had visited CPMC from April 1, 1996 to March 31, 2001. The hospital is an emergency psychiatric center serving all of Chiba prefecture, which has 6 million residents in its catchment area. CPMC is the pioneer hospital of the super-emergency system in Japan, which commits emergency psychosis cases, collaborating with public health departments, rescue teams and police offices. The hospital provides extensive pharmacotherapy and psych-education to patients with acute-stage psychosis and their families. Based on an agreement with other psychiatric hospitals within the prefecture, any patient who lives fairly far from CPMC is treated in the hospital during the acute stage of his/her illness and then transferred into his/her local hospital after some improvement of the disease. CPMC thus manages severe psychotic cases in the most proactive manner amongst psychiatric hospitals in Chiba prefecture.

If patients were diagnosed as suffering from alcohol-related or illegal drug-related psychosis, organic brain or symptomatic psychosis, or psychosis due to any dementia at the first examination or at any time during their follow-up, they were excluded from this study. All participants were diagnosed according to the Structured Clinical Interview for DSM-IV (SCID) [14], by researchers (N.K., T.Y) and by their own physician only at the 10-year follow-up point. Thus, delusional disorder (F24), schizoaffective disorder (F25) and the like, except for schizophrenia (F20) were included in this study.

Study Design

In the present study we divided participants into two groups. Patients who were judged to be in need of involuntary admission due to profound psychotic symptoms were classified as belonging to the severe case at admission group (SC-group), while patients who received initial treatment intervention in the outpatient clinic were classified as belonging to the non-severe case at admission group (NonSC-group). Voluntary admission based on patient request was impossible, and all admitted cases were involuntary admissions, including medical protection admissions based on requests from patients' families, or involuntary admissions based on orders from the government.

MoO was assessed for the individual patients at the treatment intervention and thus in the present study we have conducted follow-up for four subgroups based on positive symptoms severity (SC-group, NonSC-group) and MoO (acute onset, nonacute onset). After patients received 10 years of treatment, we evaluated each clinical symptom as long-term prognosis as well as the SCID interview as final diagnosis.

Assessments

Data at first examination as well as information about improvements following treatment intervention were evaluated through interviews with patients and their families. We analyzed the patient data from the original data base system of CPMC, which was established when the center opened, and thus DUP, MoO and global assessment of functioning (GAF) could be extrapolated by using this system.

DUP is defined as the period between the onset of any psychotic symptom and treatment intervention for the symptom, which led to consequent continuous treatment. As regards MoO, when the patient's state, which has maintained his/her premorbid function including interpersonal relationships before the onset, deteriorates within about one month, such an onset pattern was judged to be acute onset [13,15], while other onset cases were judged to be nonacute onset. To ensure there was a clear difference in positive symptoms at the first admission between the groups, we assessed retrospectively the degree of positive symptoms at that time. Positive symptoms (disorganization, suspiciousness, delusion, unusual thought content) and psychomotor excitement at first examination were evaluated if patient symptoms rated a score of 5 or higher on the corresponding item in the Brief Psychotic Rating Scale (BPRS) [16] based on patient medical and nursing records.

To assess patient prognosis, we conducted direct interviews with patients, and when possible, their family members. To measure prognosis, we evaluated BPRS, positive symptoms [17] and negative symptoms [18] from BPRS, GAF and remission level [19]. Those who died from any cause during the follow-up were excluded from the present analysis.

Statistics Analysis

The statistical procedure was conducted with IBM SPSS Statistic ver. 19 (SPSS Inc., Chicago, IL, USA). Since DUP was extremely positively skewed, the values were transformed into natural logarithms. A chi-square test was applied for categorical

variables. For continuous variables in background data, we applied ANOVA when there was equal distribution or the Kruskal-Wallis test when there was not equal distribution. For the analysis of prognosis measurements between groups we performed ANCOVA, with potential factors having effects on prognosis, gender, age of onset, MoO and DUP as covariates.

Results

We recruited 773 patients with no treatment history. Of these, 109 patients were excluded according to the exclusion criteria. Among the remaining 664 cases, 485 (73.0%) were classified as belonging to the SC-group and 179 (27.0%) were classified as belonging to the NonSC-group (**Fig. 1**). A total of 401 patients had never been medicated, including 282 patients in the SC-group (58.1%) and 119 patients in the NonSC-group (66.5%). Two hundred forty two of the 664 cases (36.4%) received a prognosis interview at the 10-year follow-up. The reasons for dropping out of the study are shown in **Fig. 1**. There were 86 cases who rejected study participation. Therefore, 113 cases in the SC-group and 43 cases in the NonSC-group participated in the final analysis (**Fig. 1**).

Initial Measurements

1. Comparison of characteristics between the SC and NonSC groups. Gender, age at onset, MoO and DUP did not significantly differ between the SC- and NonSC- groups (**Table 1**). However, GAF in the SC-group was significantly lower than that in the NonSC-group. Furthermore, the SC-group exhibited higher rates of patients with emergency requests, sedative procedures with drug injection, 5 or greater points in positive symptoms and excitement than those of the NonSC-group.

2. Comparison between follow-up and no follow-up cases. The rate of acute MoO in dropping-out cases ($N = 302$) was higher than that in the follow-up cases ($N = 113$) ($P < .05$) in the SC-group. The other factors did not differ among the two groups. In the NonSC-group, gender rate, age at onset, MoO, GAF and DUP were similar among follow-up ($N = 43$) and drop-out cases ($N = 120$).

Measurements at 10-year Follow-up

1. Comparison in prognostic variables between the SC and NonSC groups. There were no statistical differences in any variables between the SC- and NonSC-groups, but all of these parameters indicated favoring trends for the SC-group (data not shown). When these analyses were conducted for only patients with schizophrenia, these results did not differ.

There were 12 deceased cases overall during the follow-up period, and 9 of these cases were judged to be due to suicide. All of these cases were included in the SC-group.

2. Comparison in prognostic variables based on classification of positive symptoms and mode of onset. Further analysis was conducted by classification of MoO for both the SC-group and NonSC-group (**Table 2**). Although age did not differ among the groups, DUPs of the SC-nonacute-group and the NonSC-nonacute-group were significantly longer than those of the SC-acute-group and the NonSC-acute-

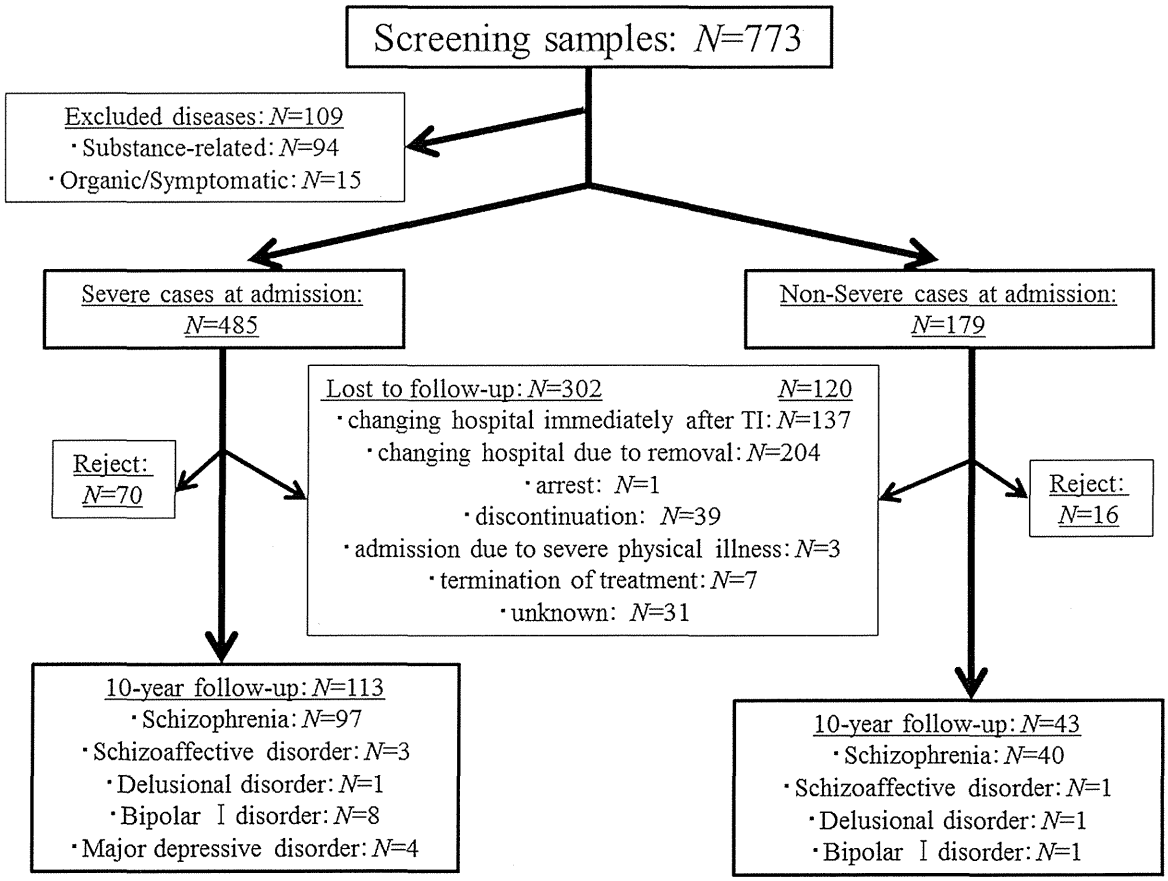

Figure 1. Flow chart of the present study.
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Table 1. Clinical characteristics at admission.

Clinical variables	Severe cases at admission (SC)	Non-severe cases at admission (NonSC)	Statistic values
sex [male/female]	113 [61/52]	43 [16/27]	N.P.#
age at onset	34.2 y (11.9)	33.3 y (12.3)	N.P.□
emergency request (%)[police/emergency]	50% [33/24]	7% [1/2]	$P<0.001$#
positive symptoms scores (≥5)[a]	95%	50%	$P<0.001$#
excitement score (≥5)[b]	53%	5%	$P<0.001$#
sedation with injectable drug[c]	65 [59%]	4 [10%]	$P<0.001$#
mode of onset [acute/nonacute]	29/84	12/31	N.P. #
GAF	16.6 (8.8)	30.7 (7.8)	$P<0.001$ □
DUP mean	22.1 m (43.3)	24.6 m (50.6)	N.P. □
DUP median	4.0 m	6.0 m	

a: Rate of the number of patients with 5 or greater points in at least one positive symptoms item within disorganization, suspiciousness, delusion and unusual thought content, among each group.
b: Rate of the number of patients with 5 or greater points in excitement item among each group.
c: Number of patients who required sedation by injected drugs, including haloperidol and/or fulnitrazepam.
#: Chi-square test, □: Student t-test, *abbreviations*: y = years; m = months; number in parentheses indicates standard deviation.
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group. Baseline GAF of the SC-acute-group and the SC-nonacute-group was lower in comparison to that of the NonSC-acute-group and the NonSC-nonacute-group.

With respect to prognostic variables, admission duration of the SC-acute-group and the SC-nonacute-group was significantly longer than that of the NonSC-acute-group and the NonSC-nonacute-group, and the admission duration in the NonSC-nonacute-group was longer than that in the NonSC-acute-group. However, for BPRS total, positive symptoms, negative symptoms, GAF and remission rate, there was no significant difference among the four groups (**Table 2**).

When the change in GAF (follow-up GAF minus baseline GAF) was calculated, the value in the NonSC-nonacute-group was

Table 2. Comparisons in baseline and 10-year prognosis between acute onset and nonacute onset in each categorical group.

Clinical variables	Severe cases at admission (SC)		Non-severe cases at admission (NonSC)		Statistic values
	Acute onset	Nonacute onset	Acute onset	Nonacute onset	
	(N = 29)	(N = 84)	(N = 12)	(N = 31)	
Baseline					
age at onset	33.1y (10.8)	34.6 y (12.3)	35.9 y (11.4)	32.3 y (12.6)	N.P. □
GAF	16.2 (8.2)	16.7 (9.0)	30.6 (6.1)	30.7 (8.5)	$P<0.000$$
					SC-Ac/SC-Nonac<NonSC-Ac/NonSC-Nonac
DUP mean	0.39 m (0.41)	29.6 m (48.1)	3.9 m (10.2)	32.6 m (57.5)	$P<0.000$$
					SC-Ac/NonSC-Ac<SC-Nonac/NonSC-Nonac
DUP median	0.25 m	8 m	0.5 m	15 m	
10-year follow-up					
duration of follow-up	553.5 d (164.7)	563.9 d (108.6)	609.6 d (79.3)	572.8 d (125.9)	N.P. □
duration of total admission	106.3 d (102.8)	129.5 d (89.3)	9.2 d (19.5)	95.6 d (183.1)	$P<0.05$$
					NonSC-Ac<NonSC-Nonac<SC-Ac/SC-Nonac
BPRS total	9.9 (8.4)	14.2 (11.3)	12.0 (11.2)	16.3 (11.5)	N.P. □
BPRS positive	3.2 (3.8)	4.2 (4.3)	3.3 (4.9)	5.2 (4.5)	N.P. □
BPRS negative	1.9 (2.3)	4.0 (4.2)	3.4 (4.4)	4.1 (3.4)	N.P. $
death cases [suicide]	5 [3]	7 [6]	0 [0]	0 [0]	
GAF	58.4 (19.1)	51.9 (17.6)	58.2 (21.8)	47.6 (15.0)	N.P. □
Remission rate	51.7%	35.7%	41.7%	32.3%	N.P.#

#: Chi-square test, □: ANCOVA, $: ANOVA *abbreviations*: y = years; m = months; d = days; number in parentheses indicates standard deviation.
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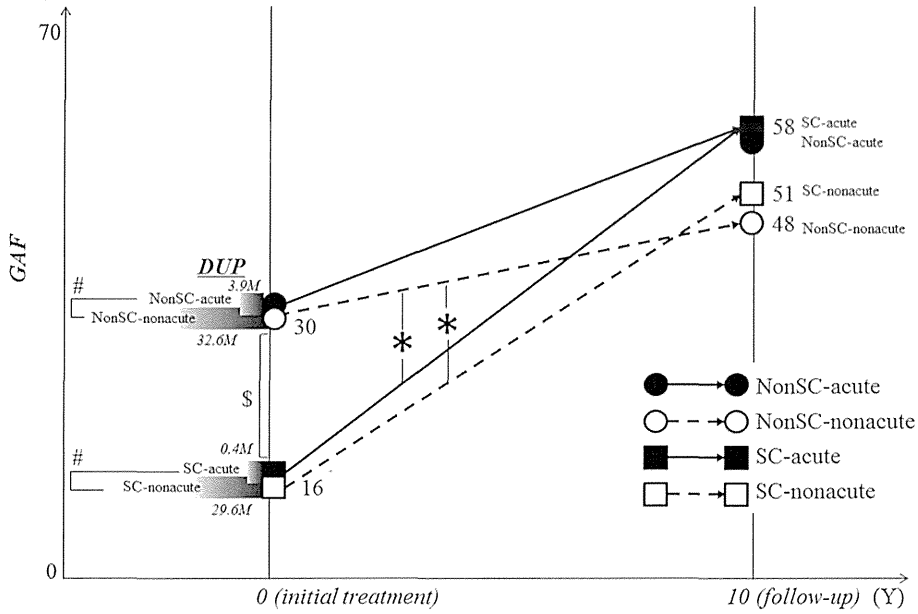
A)



B)

Group	Mode of onset	DUP Mean (M)	GAF Baseline	GAF 10-year	GAF Change	
NonSC-group	Acute	3.9	30.6	58.2	27.6	
	Nonacute	32.6	30.7	47.6	16.9	*
SC-group	Acute	0.39	16.2	58.4	42.2	*
	Nonacute	29.6	16.7	51.9	35.2	

C)

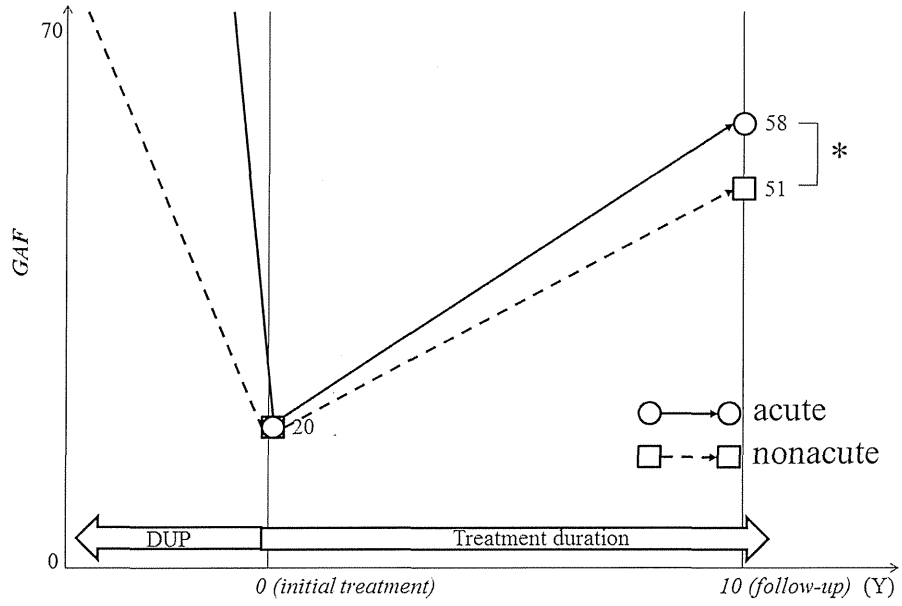


Figure 2. Change in the GAF from treatment intervention to 10-year follow-up point in the 4 subgroups. A)*$P<.05$ by ANCOVA, indicating lesser increase of GAF in the NonSC-nonacute-group than those in the SC-acute and SC-nonacute groups. # $P<.05$, indicating significant difference in DUP between the two groups. $ $P<.05$ by ANOVA, indicating a lower baseline GAF in the SC group than in the NonSC group. B) This table shows the same data as A), particular for DUP and GAF changes of participants, to support understanding of the manuscript and A). *$P<.05$ by ANCOVA. C) Comparison in GAF changes between the acute onset and nonacute onset groups. *$P<.05$ by ANCOVA.
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significantly smaller than those in the SC-acute-group and SC-nonacute-group (**Fig. 2A and 2B**).

In these analyses, however, sample sizes, in particular that of the SC-acute-group, were small, possibly causing statistical type II errors. The results in this section, moreover, demonstrated less importance of the degree of initial positive symptoms and indicated that the classification based on MoO could be more valid than the degree of initial positive symptoms in clarifying the effects of the clinical factors during the early stage on the prognosis, in addition to the validity of sample size. Thus changes in GAF in both the acute-group ($N=41$) and the nonacute-group ($N=115$) patients, regardless of whether they were the SC and NonSC groups, were additionally analyzed. The results (**Fig. 2C**) revealed that although the nonacute-group had profoundly longer DUP (30.4 months±50.6) than that of the acute-group (1.4 months±5.6), GAFs at baseline were not different between them (20.3 and 20.4, respectively). However, at the 10-year follow-up point, BPRS total (14.8±11.4), negative symptoms (4.1±3.9) and GAF (50.7±16.9) in the nonacute-group were significantly poorer than those in the acute-group (10.6±9.3; 2.4±3.2; 58.3±19.7, respectively: $P<.05$). However, BPRS positive symptoms did not differ between the two groups (acute 3.2±4.1; nonacute 4.5±4.4).

3. Relationship between DUP and prognostic valuables in the SC- and NonSC-combined group. For all follow-up participants, partial correlations between clinical variables and DUP were explored under control for gender, age at onset, MoO and premorbid adjustment. The results revealed that there were significant correlations of DUP with BPRS total ($r=0.17$, $P<.01$), negative symptoms ($r=0.21$, $P<.05$) and GAF ($r=-0.26$, $P<.001$), but not positive symptoms ($r=0.12$, $P>.05$).

Discussion

To explore the long-term effects of predicting factors prior to treatment intervention on prognosis, the initial positive symptoms severity was stood between predicting factors and prognosis in the present study. Thereby, we examined the effects of exacerbated patterns of psychosis on the following disease courses. Our examination revealed two major findings: (1) clinical processes to first admission in the patients group with relatively long DUP without early intervention could be divided according to several onset patterns, and (2) patients in the NonSC-nonacute-group had the longest DUP among our participants and further presented significantly lesser improvement, indicating that this group could experience refractoriness over long follow-up duration.

Findings from the Baseline Measurements

The present study demonstrated that longer DUP did not necessarily provide severer positive symptoms in patients with psychosis prior to treatment intervention. This finding was supported by the fact that there was no difference in length of DUP between the SC and NonSC groups, although the SC-group had more profound positive symptoms than did the NonSC-group (**Table 1**). The results suggested that there are other factors which might affect the initial severity of positive symptoms. The finding also might be related to the clinically operational characteristics of DUP; the duration of DUP was defined at its termination by treatment intervention, regardless of changes in the psychotic symptoms during the DUP. Thus we conducted further analysis to examine the effects of MoO and severity of psychosis on the DUP and GAF at the 10-year follow-up (**Table 2**). This analysis revealed that GAF scores did not differ between acute onset and nonacute onset within each SC or NonSC group, but DUP was much longer in the non-acute subgroups in both the SC and NonSC groups. These results indicated that there were several patterns in the psychopathological process from the appearance of the first psychotic symptom to treatment intervention that were dependent on at least MoO and the severity of positive symptoms. It appears that patients in the SC-acute-group who experienced rapid exacerbation of positive symptoms within a very limited period were likely to be taken to the psychiatric hospital immediately after full-brown psychosis, while patients in the NonSC-nonacute-group were likely to be left untreated for at least 2 years, partly because their behavior abnormalities were not readily apparent. These possible disease processes during the period of DUP might explain the lack of relations between DUP and the severity of positive symptoms at treatment intervention in previous studies [12,20,21,22,23].

Findings from the Prognostic Measurements

Although none of the measurements at the 10-year follow-up differed significantly among the SC and NonSC acute and nonacute subgroups in this study, all outcomes in the NonSC-nonacute-group tended to be inferior to those of the other three subgroups. In particular, these trends were clearly observed in change of GAF, and indeed the scores were significantly lower in the NonSC-nonacute-group than in the SC/NonSC-acute-groups. The former negative results might reflect the homogenous disease progression into chronicity, in which heterogeneity in symptomatology comes to be reduced gradually over time [22,24]. The lack of difference, however, in all prognostic values among the four subgroups might be simply due to a low statistical power because of the sample size. Additional analysis in which we examined the simple effect of MoO showed that nonacute mode onset could cause a significant poor total psychopathology and negative symptoms as well as GAF at 10-year follow-up, supporting the greater importance of MoO than initial positive symptoms.

Concurrently, the present study results strongly suggest that patients with acute onset had better subsequent clinical courses than did those with nonacute onset, regardless of the severity of positive symptoms at the early stage (**Fig. 2**). These results were consistent with previous reports showing that acute onset predicted better prognosis, or insidious onset predicted poorer prognosis [12,13,25]. Taken together, these results indicate that the initial positive symptoms do not act definitively as a prognosis predictor. This fact may be related to the generally accepted notion that antipsychotics provide greater beneficial effects on positive symptoms in first-episode patients than on other symptoms and/or at other subsequent stages in schizophrenia [26]. Clinical deterioration as a result of repeated relapses following the first episode, on the other hand, may be related to broader psychopathology that includes negative symptoms and cognitive function, in addition to treatment-resistant positive symptoms. In this context, in the field of early intervention for psychosis, the more essential rationale is not simply shortening DUP, leading to

attenuation of psychotic symptoms, but attenuating exposures in broader symptom domains.

Our results also showed that patients in the NonSC-nonacute group presented the worst prognosis among the four subgroups, shown by the alteration in the GAF score during the follow-up (**Fig. 2A and 2B**), indicating a greater possible effect of MoO on prognosis relative to initial positive symptoms. Considering the importance of MoO shown in the present study, we conclude that the prolongation of DUP in the NonSC-nonacute group (32.6 months) was due to low impetus of positive symptoms prior to treatment intervention, rather than simple neglect of the relevant psychosis. Thus longer DUP and nonacute onset would play important roles in predicting poor prognosis, and an evaluation of exacerbated pattern during DUP at the first visit could predict the degree of consequent improvement after treatment intervention.

Generalization of the Present Study

The termination of DUP is generally determined by the treatment intervention for the relevant psychosis, which may be affected by country or psychosocial background and/or medical facilities. This study was conducted in an emergency psychiatric hospital before the establishment of systematic intervention for early psychosis, which may explain the relatively longer DUP of about two years in the present study compared to the DUP in other similar studies. Therefore, the present results included a substantial proportion of patients with long DUP, and might rather reflect a *natural* process that occurs during the early stage of psychosis. Additionally, 5.7% (=9/156) of patients committed suicide and 32–51% of patients reached symptoms remission in this cohort, which were quite comparable to the findings reported in other studies (**Table 2**) [27,28]. When we examined partial correlation between DUP and outcomes in patients as a whole (shown in the last section of the **Results**), we found significant correlations with prognostic measurements other than positive symptoms, which was consistent with previous studies.

On the other hand, the length of DUP in the SC-acute-group was very short, and one might assume that diseases suffered by the patients in this subgroup can meet the criteria of acute and transient psychotic disorders (ATPD), rather than schizophrenia spectrum disorders. Actually, although quite a few patients in this subgroup were suspected of or diagnosed with ATPD at the first admission, most of them were finally diagnosed with schizophrenia through careful examinations. Thus these patients with very short DUP indicated clinically a representative pattern in early psychosis. Taken together, these results suggested that the patients in this study did not constitute a biased sample of patients with some peculiar characteristics, regardless of the fact that our groups included both patients with very short DUP and patients with very long DUP.

Study Limitations

This study had some limitations. The first is the relatively high drop-out rate. The reason is mainly that substantial numbers of patients were transferred into other hospitals immediately after treatment intervention in our hospital, since CPMC plays a role as an emergency care unit for a broad area. Although baseline data showed quite similar levels of each clinical symptom between the follow-up completers and non-completers, the non-completers who were transferred to other hospitals conceivably needed longer-term admission, implying severer cases. As described in the previous section, we confirmed that our follow-up cases were not substantially different from general schizophrenia patients.

The second limitation is related to study design. The present study did not assign all cases into the SC-group or the NonSC-group, based on the symptoms score at the intervention, but all cases were labeled according to clinical judgment at the patient's first admission (SC-group or NonSC-group). For example, a patient who went back to his/her home after the initial visit based on his/her family consideration, regardless of admission indication, was possibly included within the NonSC-group.

The third limitation is that clinical scores at the baseline gathered using established clinical measurements (i.e., BPRS and PANSS) were not available. Although the SC-group was surely comprised of patients with more severe illness compared to the NonSC-group, lack of evaluation using the formal scales at baseline might have slightly affected the study outcome.

Conclusions

The present study demonstrated that neither DUP nor MoO alone could explain the severity of positive symptoms at treatment intervention, but both MoO and DUP could determine several onset patterns of early psychosis. Furthermore, these factors could predict the subsequent natural course of the disease in patients with schizophrenia.

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Author Contributions

Conceived and designed the experiments: NK ES. Performed the experiments: NK TY YO HY TM HH T. Shibuya YN T. Sawa MA. Analyzed the data: NK. Contributed reagents/materials/analysis tools: NK YS. Wrote the paper: NK MI.

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