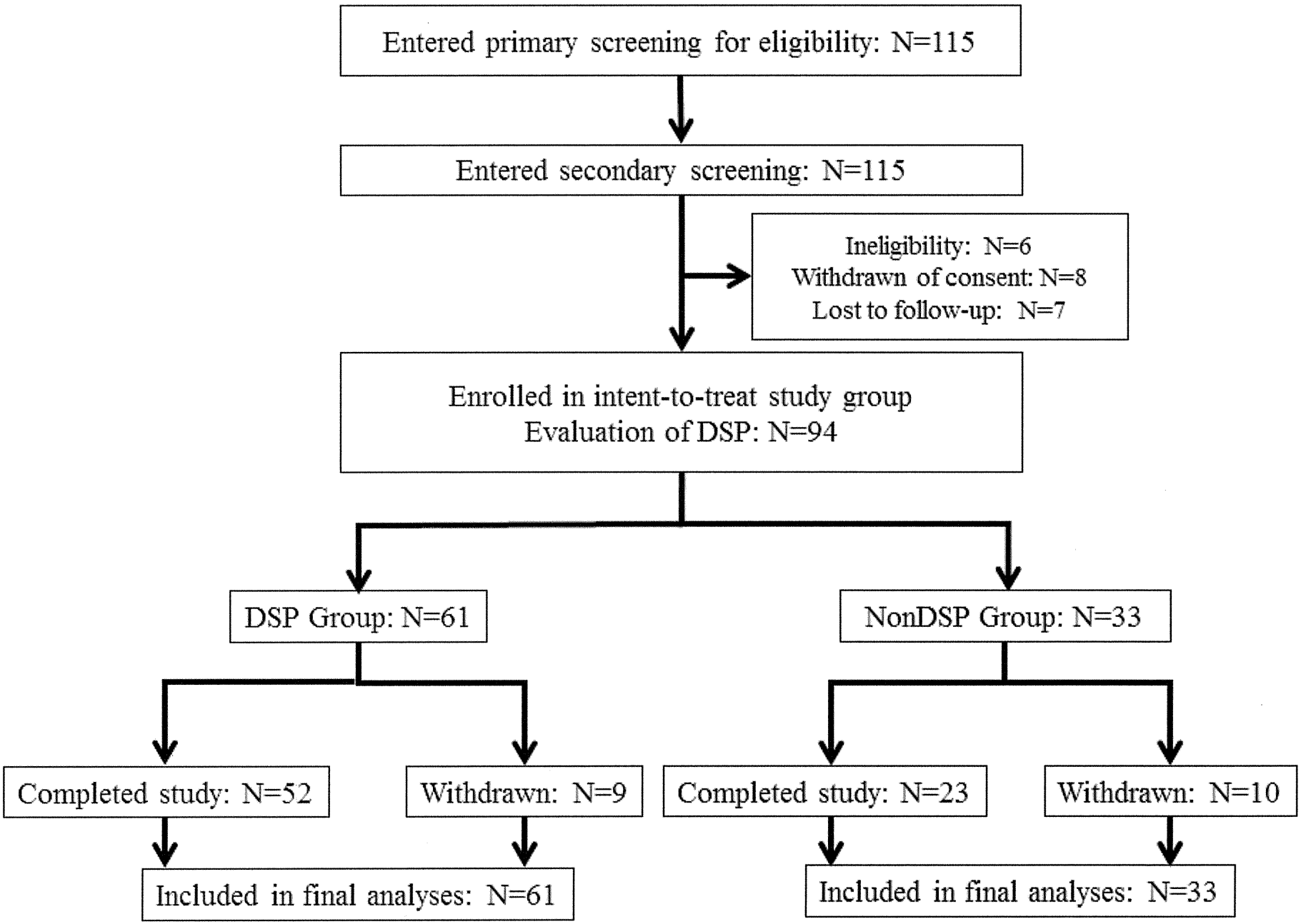
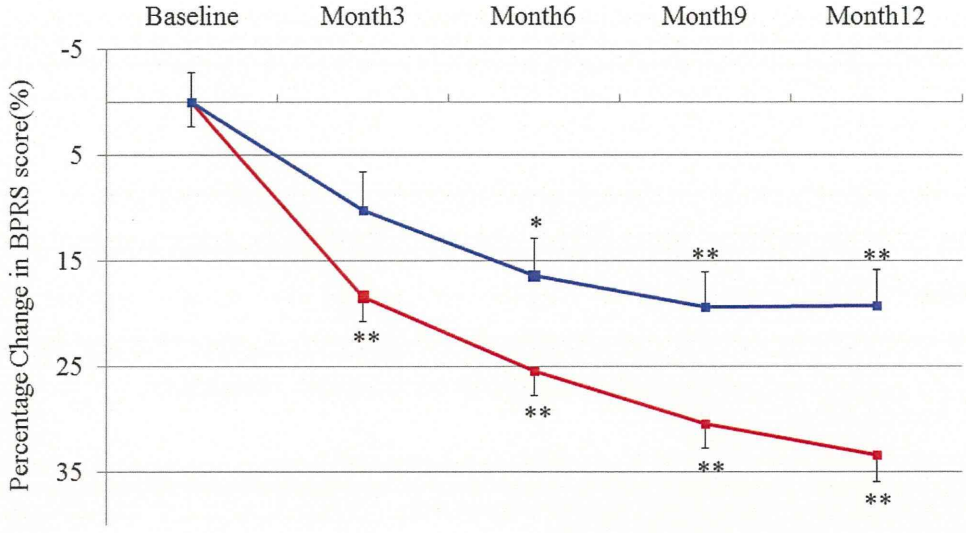

Entered primary screening for eligibility: N=115
Entered secondary screening: N=115
Ineligibility: N=6
Withdrawn of consent: N=8
Lost to follow-up: N=7
Enrolled in intent-to-treat study group
Evaluation of DSP: N=94
DSP Group: N=61
NonDSP Group: N=33
Completed study: N=52
Withdrawn: N=9
Completed study: N=23
Withdrawn: N=10
Included in final analyses: N=61
Included in final analyses: N=33

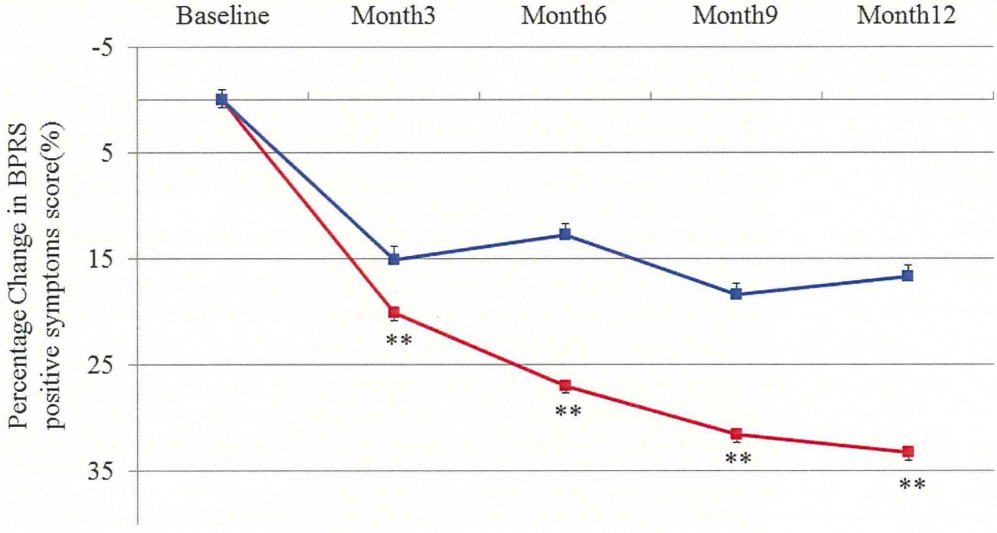
Number of Subjects

	Baseline	Month3	Month6	Month9	Month12
DSP group	61	60	56	54	52
NonDSP group	33	31	25	24	23

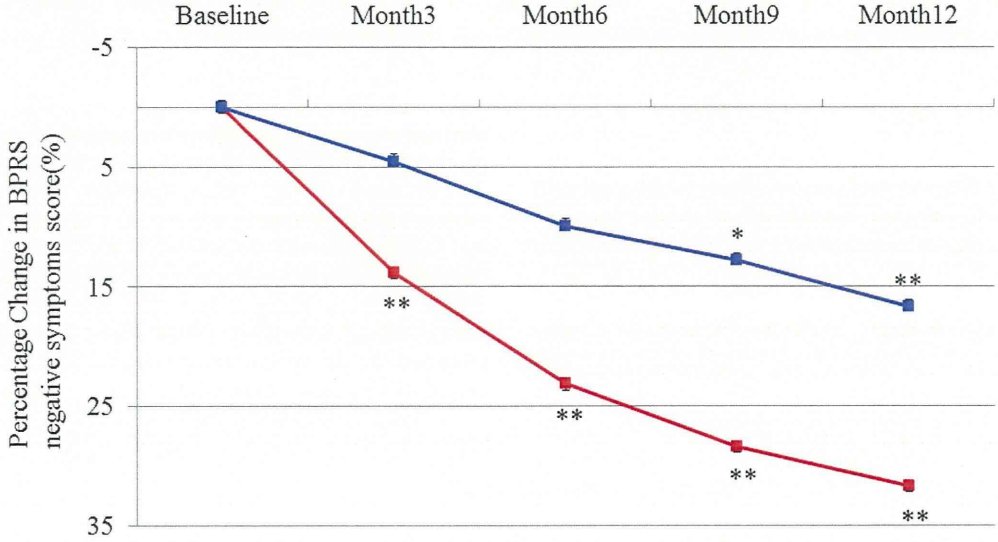
A) BPRS Total Score



B) BPRS Positive Symptoms Score



C) BPRS Negative Symptoms Score



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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, $p = 0.033$)

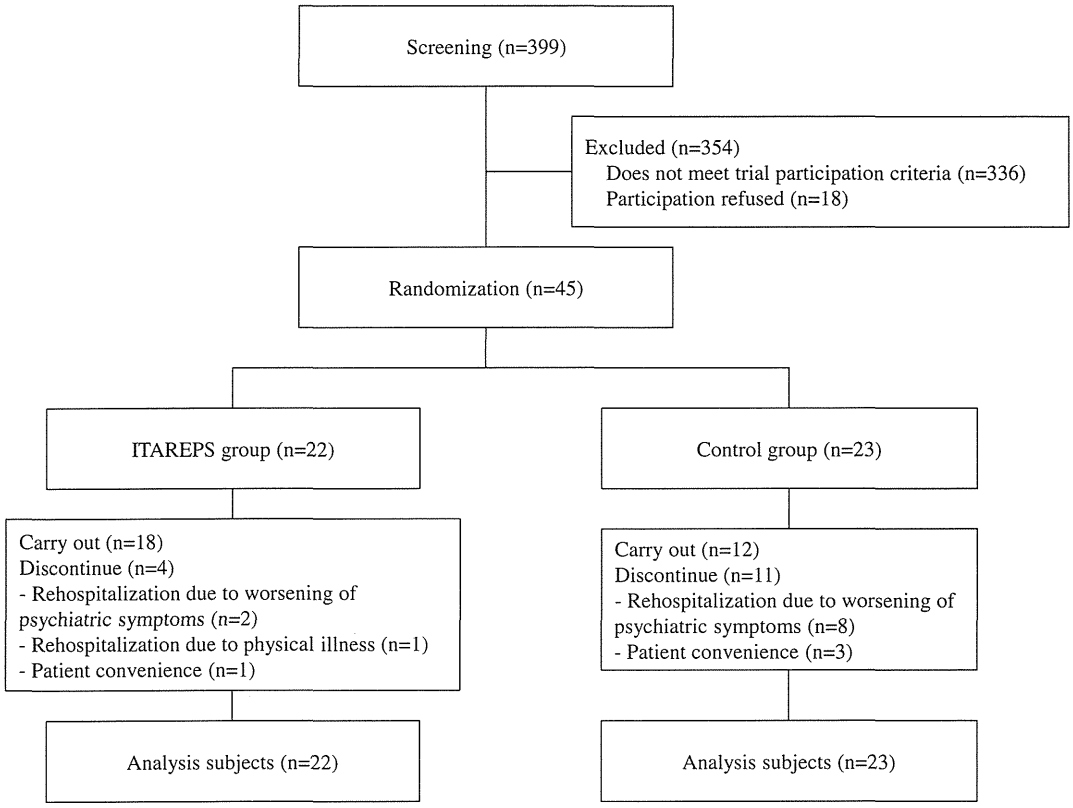

Fig. 1. Enrollment, randomization, and follow-up of the study patients.

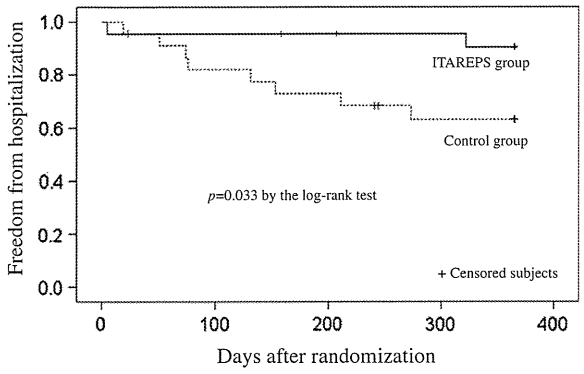

Fig. 2. Time to rehospitalization after randomization.

(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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Contributors

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Data analysis and interpretation: Y.S., N.O., and M.I.
Manuscript writing: H.K., Y.S., N.O., and M.I.
Final approval of manuscript: All authors.

Conflict of interest

The authors declare no conflict of interest.

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PLOS ONE

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-

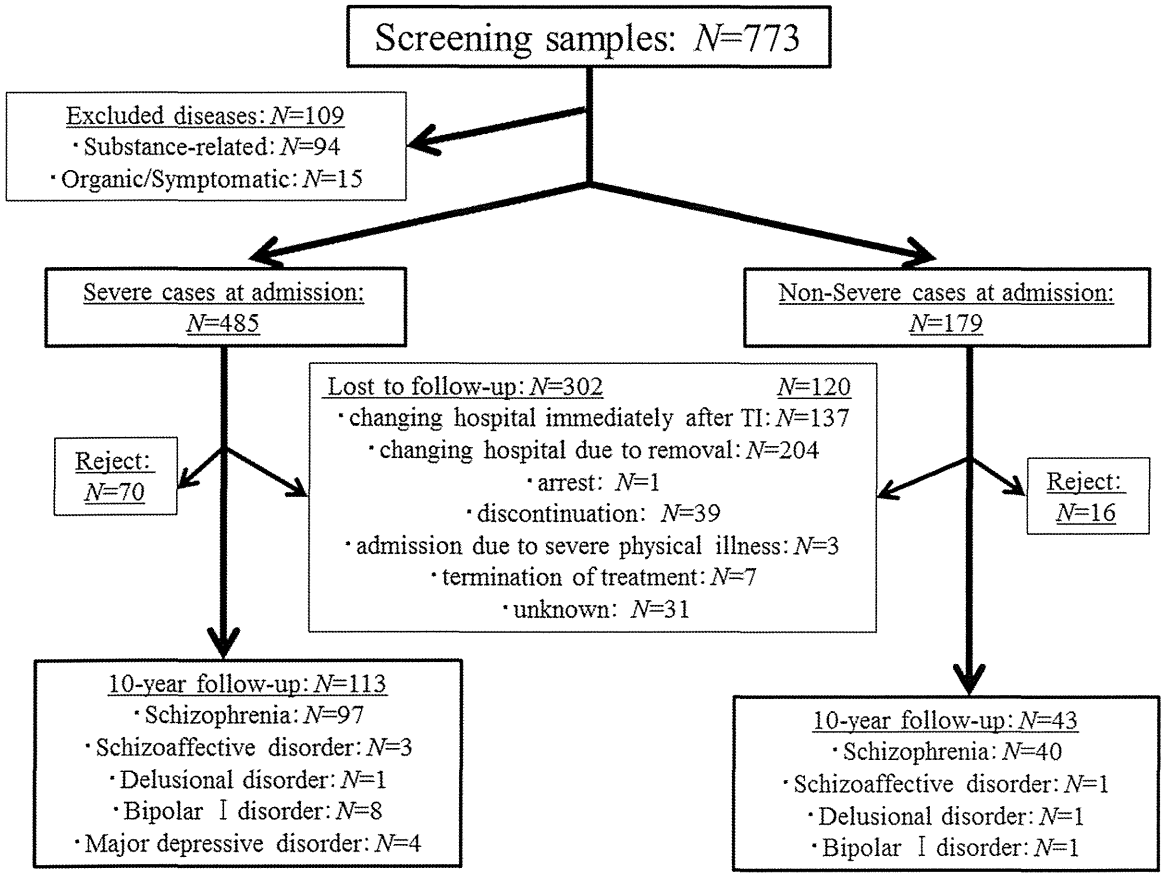


Figure 1. Flow chart of the present study.
doi:10.1371/journal.pone.0067273.g001

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.
doi:10.1371/journal.pone.0067273.t001

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**).

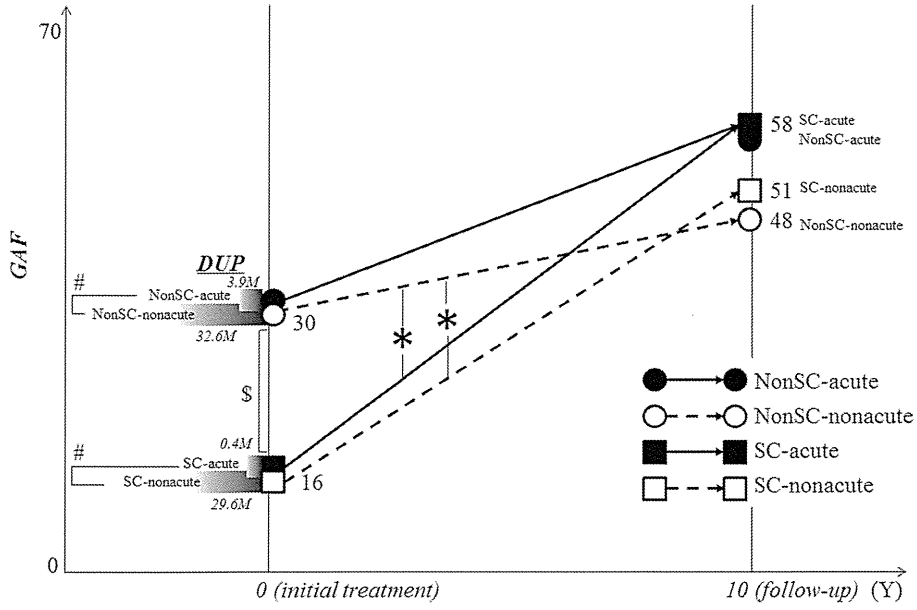
When the change in GAF (follow-up GAF minus baseline GAF) was calculated, the value in the NonSC-nonacute-group was

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.
doi:10.1371/journal.pone.0067273.t002

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)

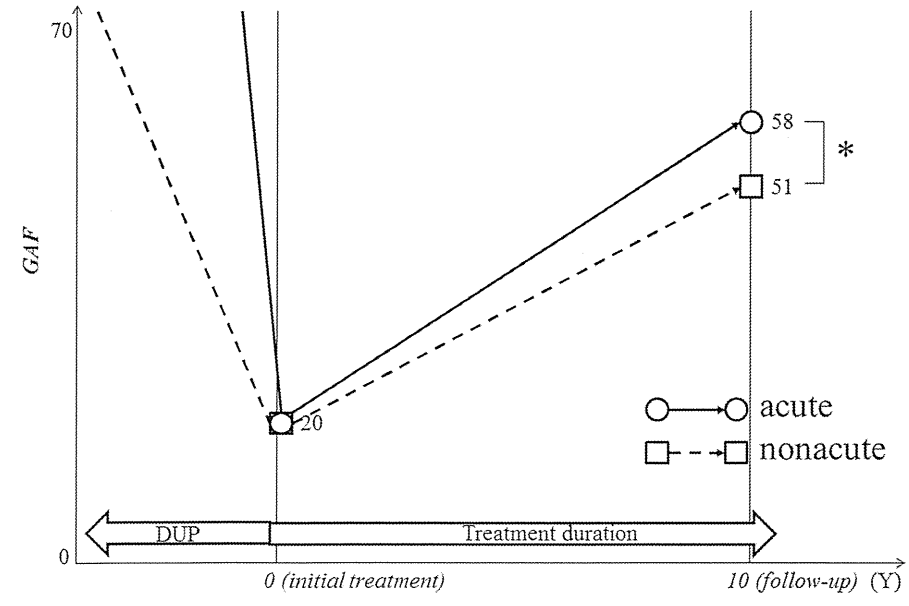


Figure 2. Change in the GAF from treatment intervention to 10-year follow-up point in the 4 subgroups. A)*$P<.05$ by ANCOVA, indicating lesser increase of GAF in the NonSC-nonacute-group than those in the SC-acute and SC-nonacute groups. # $P<.05$, indicating significant difference in DUP between the 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.
doi:10.1371/journal.pone.0067273.g002

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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特集―統合失調症の退院支援の進め方―17の視点と工夫―

非定型持効性注射剤による統合失調症難治例への取り組み

金原　信久[1)]　宗岡　克政[2)]　木村　大[3)]　伊豫　雅臣[3)]

抄録：入院統合失調症患者の退院に際して，服薬アドヒアランスの維持は大きな問題となり得る。また再発・再入院を繰り返す患者においては過剰な抗精神病薬治療になりがちであり，結果的にドパミン過感受性状態を形成し，再発準備性を高めてしまう可能性もある。非定型持効性注射剤は，このアドヒアランスの問題とドパミン過感受性状態の両者にとってメリットのある戦略であり，退院促進において一考に値する治療である。

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Key words：*adherence, dopamine supersensitivity, long-acting injectable form, schizophrenia, relapse*

はじめに

統合失調症患者へのデポ剤の導入は，従来は服薬アドヒアランス不良状態の患者に対して検討される手段であった。しかし多くの調査・報告により，部分アドヒアランスの状態にある患者の割合は，医療スタッフの想像を大きく越えているものと示唆されている。入院患者の退院の判断に際し，服薬アドヒアランス維持の可否は，長期入院患者・難治性患者においてより一層大きな問題となる。

一方入院患者のある一定の比率を占める治療抵抗性統合失調症患者（treatment-resistant schizophrenia：TRS）はその治療経過において，ドパミン過感受性精神病（dopamine supersensitivity psychosis：DSP）を呈していることが指摘されている。すなわち再発・再燃を繰り返す過程において抗精神病薬の用量が増大していき，その結果不安定な病状を呈す疾患経過である。これは高用量の抗精神病薬治療が再発準備性を高めるという一見逆説的な状況でもある。

非定型持効性注射剤は，過剰な内服抗精神病薬による治療よりも，その半減期の長さを利点に，ドパミン過感受性状態の防止に寄与する可能性がある。部分アドヒアランスの問題の解決に止まらず，難治性統合失調症の病態の，ある部分に即した治療手段であるとも言え，長期入院患者に対して検討すべき有力な手段と言える。本稿では服薬部分アドヒアランスの問題とDSPの視点の両者から非定型持効性注射剤の導入の考え方を考察してみたい。

A treatment approach with atypical antipsychotics of long-acting injectable form for treatment refractory patients with schizophrenia.

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Ⅰ．服薬アドヒアランスの実態

統合失調症の入院患者の退院に際し，服薬アドヒアランスの問題をクリアできるかどうかは，最も重要な問題の一つであろう。入院中に形成された規則正しい服薬習慣が，退院後には不規則となり，その結果病状不安定となる症例はしばしば経験される。服薬アドヒアランス不良の原因として，疾患への認識欠如のみならず，服薬に関連した不快な副作用，認知機能障害に基づく不注意による飲み忘れなどが，数々の報告で指摘されてきた[12,16]。またこの問題の解決困難な側面として，外来診療でアドヒアランスの実態について判断がつかないという問題もある。

実際に多くの調査によって，部分アドヒアランスの患者の割合がきわめて高いことが報告されている。その定義は報告により若干の相違はあるものの，多くの報告で40～90％と高率に見積もられている[8,18,23]。また患者の自己申告と処方医の服薬予想が大きく異なることも示されており[21]，処方医は服薬アドヒアランスを楽観的に捉えがちである。一方で部分アドヒアランスは糖尿病や高血圧などの慢性身体疾患にも共通する問題でもあることも知られている。すなわち精神症状や病識，向精神薬特有の副作用など精神疾患に特異的な問題とは限らない。このことからアドヒアランス向上のためには，一般的に推奨される服薬指導の限界についても認識する必要があるかもしれない。

しかし統合失調症患者の治療において服薬アドヒアランスの問題がきわめて重要である理由は，再発頻度の高さのみならず，それが疾患の経過に大きな影響を与えるからである。6万人以上の外来患者を対象とした大規模調査において，担当医の薬剤処方日数と患者の通院間隔日数の比から算出される medication possession ratio（MPR）が0.8以上の群とそれ未満の群を比較すると，1年間の観察期間で，後者は再入院率が2.4倍高く，また入院期間も長期化するとされる[26]。また米国国内の病院調査で，不規則な通院の統合失調症患者は定期的に通院する患者よりも再入院率で約2倍，入院日数で約4倍に増大することが示されている[17]。このような結果から，従来，定型薬のデポ剤は，部分アドヒアランス患者によい適応として使用され，実際に多くの試験で再発予防の効果が示されてきた[9]。

Ⅱ．治療抵抗性症例とドパミン過感受性精神病

服薬アドヒアランスの問題が再入院・長期入院のリスクとなる一方で，幻覚妄想などの陽性症状が通常の抗精神病薬治療に十分な反応を示さず，病状が安定しないため，退院できない患者も相当数いるものと推測される。この中でも異なるクラスの抗精神病薬を2種類（少なくともそのうちの1種類は非定型抗精神病薬であること），chlorpromazine 換算量でそれぞれ600mg/日以上，4週間使用しても，十分な改善が見られず，結果としてGAF（機能の全体的評定）が41点以上まで到達しない治療状況にある患者を，本邦においてはTRS の反応不良群と定義される。

このようなTRS の基準は，1988年に Kane らによって初めて定義された[11]。そして clozapine の対象患者を選別するという視点と切り離すことのできない概念ともなった。本邦における同薬の導入は2009年であり，実臨床における TRS 患者の評価・診断はごく最近の概念である。それまで難治性症例に対しては，一般の抗精神病薬による多剤併用療法・多剤大量療法がやむを得ず，あるいは漫然と継続されてきた側面も否めない。実際に久しく本邦における大量療法の実態は国内・国外から報告がなされ[3]，有効な手立てがないまま，長期間継続されてきたことが窺われる。

1970年代よりこのような抗精神病薬治療中の患者に，治療中断直後に速やかに精神病症状の再燃を認める現象が報告されていた[4]。また tardive dyskinesia（TD）は抗精神病薬服用中に生じてくる難治性の副作用と捉えられるようになってきた[2]。これらの現象は DSP という概念として提唱され（表1）[6]，その背景に抗精神病薬によるドパミン D2受容体（DRD2）のアップレギュレーションの関与が推定されるようになった[10]。それとともに同受容体のドパミンに対する感受性は亢進

表1　ドパミン過感受性精神病の診断基準（Chouinard, 1991[6]を一部改編）

(A) 必須条件：3ヵ月以上の抗精神病薬治療歴
(B) 大基準
（1）過去5年間に薬剤減薬・怠薬の際に精神病症状が再燃―内服薬では6週以内・デポ剤では3ヵ月以内
（2）継続治療にもかかわらず頻回の再発
（3）薬剤への耐性（過去5年間に20%以上の増量）
（4）著しい耐性：増量でもコントロールできない
（5）再発時精神病症状が新しい統合失調症症状あるいは著しく重篤
（6）減薬が突然の場合にのみ再発
（7）過去に耐性の証拠があり，現在大量処方継続
(C) 小基準
（1）遅発性ジスキネジア
（2）再発時に薬剤増量で速やかな改善
（3）ストレスで容易に悪化
（4）デポ剤注射前の悪化
（5）高プロラクチン血症
(D) 除外項目
（1）初発急性期の状態
（2）抗精神病薬に無反応で持続する重篤な精神病状態

すると考えられ，臨床的には治療中断や減薬時における，速やかな再発・再燃現象やその症状の重篤性の獲得と関係する。また再燃エピソードとともに，薬効が認めにくくなる耐性現象に繋がる可能性が指摘されている。結果的に頻回の入退院エピソードや長期入院に至る重要な背景因子となる可能性が高いと思われる[10]。

定型抗精神病薬が治療の中心であった時代に，TDの出現頻度は20～40%と報告されており[5,25]，ChouinardらはこのDSPは，患者全体の約50%において認められる現象と推定し，抗精神病薬が疾患の経過に与える大きな影響を論じている[7]。実際に我々が国内の精神科医療機関において予備的に調査したところ，134人のTRS患者群において，面接および診療録の記録から，このDSPエピソードの有無については，実に67%の患者にこのようなエピソードが確認された[27]。すなわち重症患者においてドパミン過感受性状態が高率に生じている可能性が示唆される。

現在のところ，TRS患者に対して確立された治療法はclozapineによる薬物療法が唯一の方法である。しかし長期入院あるいは入退院を繰り返し難治化する患者の一部に見られるDSP現象に対するアプローチは，clozapine導入の他にも，その機序を推定することで確立できるかもしれない。

Ⅲ．非定型持効性注射剤による治療アプローチ

前節で述べたDSPのさらなる悪化を防ぐためには，DRD2の過剰遮断を防ぐことがきわめて重要である。この考え方は，例えば多くの治療ガイドラインに示されているように，維持期の治療において初発エピソードの治療よりも，やや低用量での治療が推奨されていることにも通じている。しかしながら長期経過の中でこのコンセプトに基づく薬物療法を維持させることは実際には至難の業であることも日常的に経験するところである。実際に多くの患者で観察される，繰り返される再発エピソードは，（程度の差はあれ）部分アドヒアランスに基づく薬効の消失，一方で相対的な高用量投与に関係するDRD2の過剰遮断による潜伏的なドパミン過感受性状態の形成が関係している。これらの複合的な機序を，再発エピソードの背景として認識しておく必要がある。

このような観点から，服薬アドヒアランスに難のあるドパミン過感受性状態にある患者へのアプローチとして，持効性注射剤は有効となる可能性がある。動物モデルにおいてhaloperidolにてアップレギュレートしたDRD2を，aripiprazoleによってダウンレギュレートすることが示されている[24]。これらの知見から定型注射剤よりも非定型持効性注射剤が病態に即した治療と言える。

現在（2013年10月）のところ本邦で使用できる非定型持効性注射剤はrisperidone持効性注射剤（risperidone long-acting injection：RLAI）に限られているが，同薬に対しての臨床効果の報告は豊富に集積している。RLAIの導入によって，症状の改善，また再発率の低下，再入院率の抑制などが示されている[20]。しかもrisperidoneの経口薬と比較しても同注射薬に切り替えた場合，有意な改善を示す報告もなされている[19]。しかしながらいくつかの報告では優位性が認められないとするものもある[15,22]。異なる結果を示す臨床試験の背景として，試験デザインや患者背景の違いが指

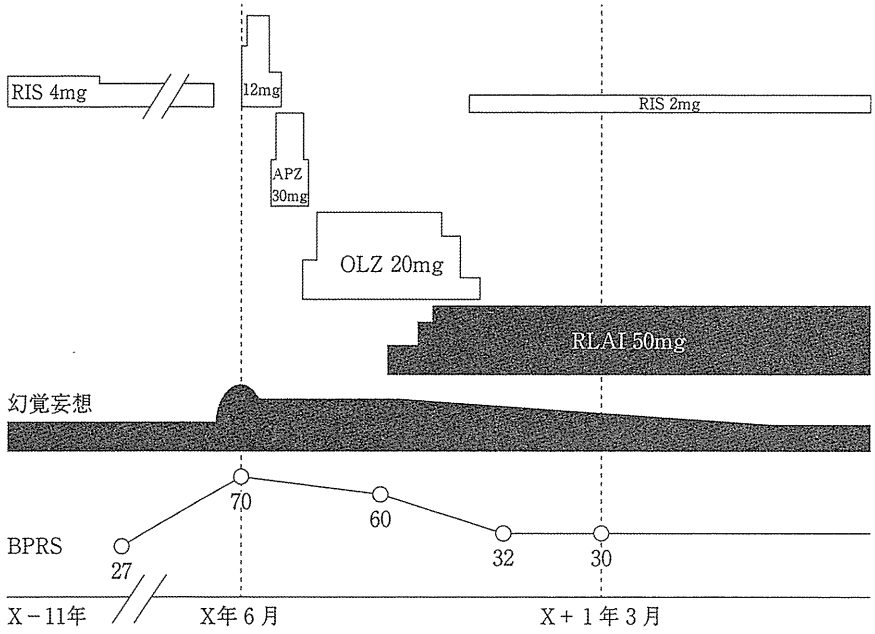

図1　症例1の治療経過
RIS : risperidone, APZ : aripiprazole, OLZ : olanzapine, RLAI : risperidone long acting injection, BPRS : Brief Psychiatric Rating Scale

摘されている[1,14]。すなわち服薬アドヒアランスの程度が異なる患者の組み込みやその評価法の違いが試験結果に影響を与えている可能性である。試験に組み込まれた患者群の重症度や治療環境（入院か外来か）によって，服薬アドヒアランスとドパミン過感受性状態の程度に影響を与えているかもしれない。同薬を検証した臨床試験のほとんどが，これらの因子に関する評価に触れられていない。そのため同薬の臨床的効果が支持されているものの，その効果を引き出す因子に患者毎に違いがある可能性を考慮する必要がある。

Ⅳ．実際の症例

我々が2010年度から実施している臨床試験においては，ドパミン過感受性状態にある患者へ同薬の効果を認めている[13]。この試験は服薬アドヒアランスが比較的良好と確認された患者を対象として，RLAIを内服抗精神病薬に上乗せ投与して1年間観察したものである。その結果DSPエピソードを認める患者群においては，それがない患者群よりも，RLAI上乗せ治療の効果が大きく観察されている。我々は服薬アドヒアランスの単なる改善ではなく，ドパミン過感受性状態に対する長半減期薬剤の効果であると推測している。ここでDSPを呈し入院治療を要し，RLAIを導入したことにより，退院可能となった2症例を提示する。

〔症例1〕（図1）

43歳男性。内気だが勤勉な性格。専門学校卒業後に5年ほど会社勤めをしていた。再就職活動がうまくいかずに，思い悩み次第に自閉的となっていった。X－11年（32歳）に滅裂思考が出現し統合失調症と診断され，治療が開始された。当初はrisperidone 8mgにて治療が行われ，改善は良好であった。以降risperidone 4mgから3mgに減量され11年間にわたり病状は安定していた。しかし父の入院を契機に怠薬し，そこから3週間ほど経過したところから電話線を切るなどの奇異な行動が出現した。X年5月（43歳）退院した父を健康器具で殴打し逮捕され，6月に入院治療となった。「クロテツの番組が何兆円も損を出して，坊さんが出てきた」などと述べ，滅裂思考を呈していた。Risperidoneを12mgまで増量したが，

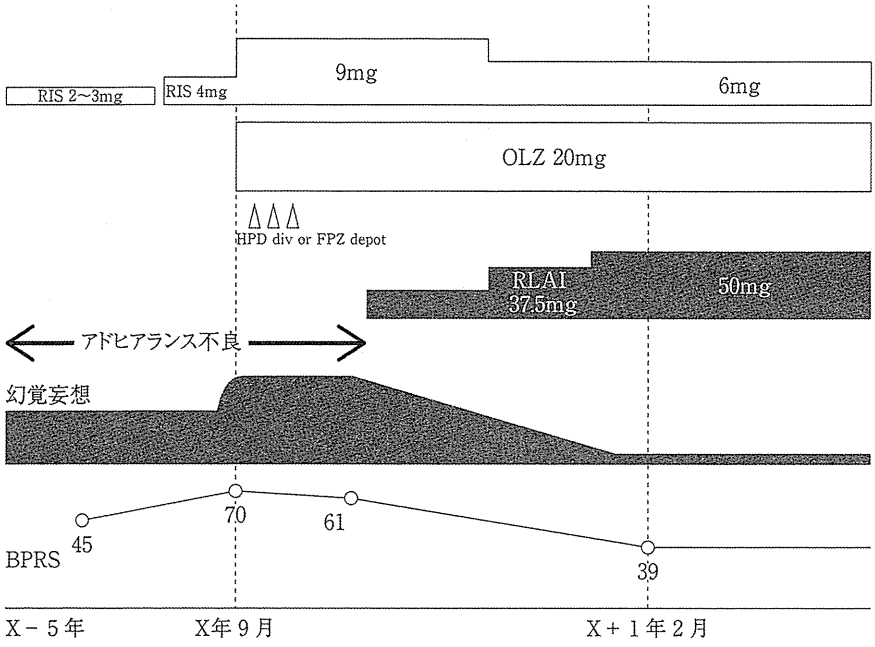

図2　症例2の治療経過
RIS : risperidone, OLZ : olanzapine, HPD : haloperidol, FPZ : fluphenazine, RLAI : risperidone long acting injection, BPRS : Brief Psychiatric Rating Scale

病状は改善せず，aripiprazoleに置換し30mgまで増量した。病状は軽度改善したものの，激しい幻覚妄想は残存し，他の患者の部屋に侵入するなど病棟内でも適応できない状態であった。さらにolanzapineに置換し，20mgまで増量したが症状は改善せず，10月RLAIを導入することとなった。25mgで幻聴から距離をとれるようになり，2ヵ月で50mgまで増量していくと，疎通も改善を見せ，日常会話に応じられるようになった。X＋1年1月隔離処遇解除され，内服抗精神病薬もrisperidone 2mgのみとなった。3月グループホームへ退院となった。現在退院して2年以上経過するが安定した経過を辿っており，単身生活を続けている。

〔症例2〕（図2）

24歳男性。中学までは運動部に所属し，社交的な性格であった。高校生になると「考えがまとまらず，集中できない」と訴え退学した。X－5年（19歳）に近医クリニックを受診し，統合失調症と診断され，risperidone 2～3mgで加療されていた。その後A病院に転通院した。自宅では怯えた様子で自室にひきこもる生活が続いていたが，自ら幻聴体験を語ることはなかった。服薬を嫌がることが多く，risperidone 4mgに増量され，その都度家族が服薬させるよう努めていた。X－2年7月（22歳）B病院に転通院。服薬状況は部分アドヒアランスの状況で経過し，「人と会いたくない」「怖い」と物音に敏感となり，自閉傾向もより強まっていった。X年9月大声で叫び，壁を叩いたり，裸になるという興奮を呈し，医療保護入院となった。隔離室でolanzapine 20mgとrisperidone内用液9mgで加療したが，拒薬傾向が続いた。そのため拘束処遇でhaloperidol点滴静注やfluphenazine筋肉注射を要した。11月よりRLAI 25mgを導入，次第に穏やかとなり，今まで語らなかった幻聴に関し，「命令されていた」と内省を得られるようになった。12月に37.5mgに増量，内服はolanzapine 20mgとrisperidone内用液6mgを併用していた。素直に会話に応じられるようになり隔離・拘束を解除。X＋1年1月にRLAI 50mgまで増量し，2月には