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

Hideki Komatsu a,⁎, Yoshimoto Sekine b, Naoe Okamura b, Nobuhisa Kanahara a,b, Kyoji Okita a, Saburo Matsubara c, Toyoaki Hirata d, Tokutaro Komiyama e, Hiroyuki Watanabe f, Yoshio Minabe g, Masaomi Iyo a

a Department of Psychiatry, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuou-ku, Chiba 260-8670, Japan
b Division of Medical Treatment and Rehabilitation, Center for Forensic Mental Health, Chiba University, 1-8-1 Inohana, Chuou-ku, Chiba 260-8670, Japan
c Matsubara Hospital Neuropsychiatric Institute, 4-3-5 Ishibiki, Kanazawa-shi, Ishikawa 920-8654, Japan
d Department of Psychiatry and Neurobiology, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, Kanazawa-shi, Ishikawa 920-8640, Japan
e Shizuoka Psychiatric Medical Center, 4-1-1 Yoichi, Aoi-ku, Shizuoka 420-0949, Japan
f Department of Neuropsychiatry, Iida Hospital, 1-15 Odori, Iida, Nagano 395-8505, Japan
g Department of Neuropsychiatry, Asahi General Hospital, 1326 Ino, Asahi-shi, Chiba 289-2511, Japan
h Department of Psychiatry and Neurobiology, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, Kanazawa-shi, Ishikawa 920-8640, Japan

A R T I C L E   I N F O
Article history:
Received 20 December 2012
Received in revised form 21 July 2013
Accepted 10 August 2013
Available online 31 August 2013

Keywords:
Schizophrenia
Relapse prevention
Information technology
Visiting nurse
ITAREPS

A B S T R A C T
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 (88.8 days) (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.

© 2013 The Authors. Published by Elsevier B.V. Open access under CC BY-NC-SA license.

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
been developed and is reported to be highly effective (Spaniel 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 (Spaniel 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 (Spaniel 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 psychosocial educational 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

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

ITAREPS = Information Technology Aided Relapse Prevention Programme in Schizophrenia. SD = standard deviation.

- a Fisher’s exact test.
- b Mann–Whitney U test.

**Fig. 1.** Enrollment, randomization, and follow-up of the study patients.
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 \( (p = 0.049; 95\% \text{ CI}, 0.04–0.99)\) 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.

### 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.

Role of funding source
This study was supported by a Grant-in-Aid for Scientific Research, of the Ministry of Health, Labour and Welfare, Japan, 2009 (Grant No. 09158491). The Ministry had no further role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the manuscript for publication.

Contributors
Conception and design: Y.S., and M.I.
Administrative support: Y.M.
Collection and assembly of data: H.K., N.K., K.O., S.M., H.T., K.T., H.W., and M.I.
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.

Acknowledgment
The authors would like to thank the patients, visiting nurses, clinicians, and researchers who have contributed to this study. We also acknowledge the supervision of Ms. Masumi Mori for the visiting nurses, and the database management of Ms. Miwa Okuda.

References
Gleeson, J.F., Alvarez-Jimenez, M., Cotton, S.M., Parker, A.G., Hetrick, S., 2010. A systematic review of relapse measurement in randomized controlled trials of relapse prevention in first-episode psychosis. Schizophr. Res. 119 (1–3), 79–88.
Ho, B.C., Andreasen, N.C., Ziebell, S., Pierson, R., Magnotta, V., 2011. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch. Gen. Psychiatry 68 (2), 128–137.
Keith, S., 2006. Advances in psychotropic formulations. Prog. Neuropsychopharmacol. Biol. Psychiatry 30 (6), 996–1008.
Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., Davis, J.M., 2012. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet 379 (9831), 2063–2071.
Mathalon, D.H., Sullivan, E.V., Lim, K.D., Pfefferbaum, A., 2001. Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. Arch. Gen. Psychiatry 58 (2), 148–157.
McEachern, T.H., 1988. A selective review of recent North American long-term followup studies of schizophrenia. Schizophr. Bull. 14 (4), 515–542.
Robinson, D., Woerner, M.G., Alvir, J.M., Bilder, R., Goldman, R., Geisler, S., Koveen, A., Sheitman, B., Chakos, M., Mayerhoff, D., Lieberman, J.A., 1999. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch. Gen. Psychiatry 56 (3), 241–247.
Španiel, F., Hrdlička, J., Novák, T., Kozený, J., Höschl, C., Mohr, P., Motlová, L.B., 2012. Effectiveness of the information technology-aided program of relapse prevention in schizophrenia (ITAREPS): a randomized, controlled, double-blind study. J. Psychiatr. Pract. 18 (4), 269–280.
Španiel, F., Hrdlička, J., Kozený, J., Novák, T., Motlová, L., Čermák, J., Bednarík, J., Novák, D., Höschl, C., 2008a. ITAREPS: Information Technology Aided Relapse Prevention Programme in Schizophrenia. Schizophr. Res. 98 (1–3), 312–317.
Španiel, F., Vohlídková, P., Hrdlička, J., Kozený, J., Novák, T., Motlová, L., Čermák, J., Bednarík, J., Novák, D., Höschl, C., 2008b. The Information Technology Aided Relapse Prevention Programme in Schizophrenia: an extension of a mirror-design follow-up. Int. J. Clin. Pract. 62 (12), 1943–1946.
Tiihonen, J., Haukka, J., Taylor, M., Haddad, P.M., Patel, M.X., Korhonen, P., 2011. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am. J. Psychiatry 168 (5), 693–699.
Volavka, J., 2008. ITAREPS relapse prevention in schizophrenia. Int. J. Clin. Pract. 62 (12), 1824–1825.
Wiersma, D., Niemhuis, F.J., Sloor, C.J., Giel, R., 1998. Natural course of schizophrenia disorders: a 15-year followup of a Dutch incidence cohort. Schizophr. Bull. 24 (1), 75–85.
Xia, J., Merinder, L.B., Belgamwai, M.R., 2011. Psychoeducation for schizophrenia. Cochrane Database Syst. Rev. (6), CD002831.