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# Psychiatrist's adherence: a new factor in relapse prevention of schizophrenia. A randomized controlled study on relapse control through telemedicine system

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## Accessible summary

- Exposure to psychotic states has detrimental effects on the long-term outcome of schizophrenia and brain integrity. Therefore, improving relapse prevention is a key component of long-term management of schizophrenia. Previous studies using continuous monitoring of an individual's early signs of relapse and adopting preventative pharmacological interventions, when early signs are detected, showed promising clinical results in terms of relapse risk reduction.
- This 18-month multi-centre parallel randomized controlled, open label, trial with telemedicine relapse prevention programme ITAREPS failed to show superiority of maintenance plus prodrome-based targeted medication strategy over treatment as usual. The study, marked by low investigator's adherence, confirmed that absence of pharmacological intervention at early stage of prodrome, critically influenced the risk of relapse.
- This and previous randomized controlled trials with telemedicine programme ITAREPS suggested that substantial improvement in relapse prevention in schizophrenia is likely to be unattainable under current clinical settings.
- Future preventive strategies in schizophrenia would require rapid pharmacological intervention upon occurrence of subclinical prodromal symptoms that are undetectable under conventional outpatient practice. Studies with ITAREPS suggested that integration of telemedicine relapse prevention systems and visiting nurse service might together represent practical solution capable to address those requirements.

## Abstract

The Information Technology Aided Relapse Prevention Programme in Schizophrenia (ITAREPS) presents a telemedicine solution for weekly monitoring and management of schizophrenia. This study aims to evaluate the effectiveness of the programme in reducing the number of hospitalizations during the 18-month multi-centre parallel randomized controlled, open label, trial. Outpatients with schizophrenia or schizoaffective disorder were randomized to the active ($n = 74$) or control group ($n = 72$). In the active arm, investigators increased the antipsychotic dose upon occurrence of prodrome announced by the system. Intention-to-treat analysis showed no

between-group difference in the hospitalization-free survival rate [Kaplan–Meier method; hazard ratio (HR) = 1.21, 95% confidence interval (CI): 0.56–2.61, $P = 0.6$). In a post hoc multivariate Cox proportional hazards model, out of 13 potential predictors, only ITAREPS-related variables (number of alerts without pharmacological intervention/HR = 1.38, $P = 0.042$/ and patient non-adherence with ITAREPS /HR = 1.08, $P = 0.009$/) increased the risk of hospitalization. In this trial ITAREPS was not effective. The results in context with previous ITAREPS studies suggest non-adherence of both psychiatrists and patients as the main reasons for the failure of this preventive strategy. Tertiary prevention in schizophrenia have to be regarded a major challenge, warranting the need for implementation of strategies with more active participation of both patient and treating psychiatrist.

## Introduction

Patients with schizophrenia are prone to a substantially high risk of relapse. In total, more than 80% of those who achieve a remission from their first episode experience a relapse within 5 years, with comparable percentages of relapsed patients going on to have second and third relapses (Robinson *et al*. 1999). Even under conditions of clinical trials, the 1-year relapse rate in subjects adjusted on antipsychotic medication reaches 27% (Leucht *et al*. 2012).

This fact becomes specifically alarming in light of the emerging evidence that the active psychosis may affect the brain in a 'toxic' fashion, thus determining long-term illness outcome (Shepherd *et al*. 1989, Lieberman *et al*. 1996, Wiersma *et al*. 1998, Harrison *et al*. 2001).

Structural and functional brain changes may provide a pathophysiological basis for these detrimental effects of relapse. Available evidence suggests that, in schizophrenia, extended periods of relapse (Andreasen *et al*. 2013) and exposure to overt psychotic symptoms after the first episode (Cahn *et al*. 2009) have a negative effect on brain integrity. The findings from studies focused on the effects of duration of untreated illness lend additional support to the notion that a psychotic state is toxic per se. Meta-analytic evidence suggests an association between a longer duration of untreated psychosis and poorer long-term outcome (Marshall *et al*. 2005, Perkins *et al*. 2005) and development of structural brain changes in the form of grey matter reduction (Haijma *et al*. 2013).

With these factors in mind, there is an urgent need to test clinical efficacy of proactive tertiary preventive measures that may avert relapse in schizophrenia and thus effectively reduce exposure to a psychotic state. Those strategies involve continuous monitoring of an individual's early signs of relapse and adopting preventative pharmacological interventions when early signs are detected. Studies evaluating early signs interventions employ two different approaches: (1) maintenance plus targeted medication strategy (MTM); and (2) prodrome-based intermittent targeted medication (PBIM).

The MTM strategy was previously tested in two randomized controlled trials. In the first of them, patients with schizophrenia were maintained on a low-dose depot medication and monitored weekly with regards to occurrence of early warning signs (Marder *et al*. 1994). If early signs emerged, the participant was randomly allocated to receive either a targeted oral antipsychotic or targeted placebo. At the end of 2-year follow up, there was no significant advantage of the active targeted medication over placebo in terms of symptom exacerbation. In a second randomized controlled trial (RCT) employing MTM strategy, schizophrenia outpatients were randomly assigned to receive either programme for relapse prevention (PRP; $n = 41$) or treatment as usual ($n = 41$) and were followed up for a 18 months (Herz *et al*. 2000). In this study, antipsychotic intervention based on early signs detected by PRP reduced relapse and rehospitalization rates.

Prodome-based intermittent targeted medication techniques involve service users' antipsychotic medication being withdrawn and then targeted medication being used if ongoing monitoring reveals early signs of relapse.

Out of seven PBIM studies conducted so far, continuous medication was superior to targeted intermittent pharmacological treatment in preventing decompensations and hospitalizations in four trials (Jolley *et al*. 1989, 1990, Carpenter *et al*. 1990, Schooler *et al*. 1997), whereas three studies revealed a non-significant difference between those two treatment strategies (Carpenter & Heinrichs 1983, Carpenter *et al*. 1987, Herz *et al*. 1991).

Those findings generally attest to the promising potential of MTM strategy based on improved early signs detection in the improvement of relapse outcomes (Eisner *et al*. 2013).

Three randomized controlled trials also determined the effectiveness of non-pharmacological interventions to prevent relapse in patients with psychosis. Meta-analysis of psychosocial interventions vs. treatment as usual involving 679 patients demonstrated the former to be more effective in preventing relapse (Alvarez-Jiménez *et al*. 2011).

Novel Mobile Health (mHealth) technologies, providing health services via mobile phones, represent in combination with MTM a pragmatic strategy in relapse prevention applicable in normal clinical settings. While this fast-growing, technology-driven health-care segment has its main domain in industrialized world, a recent rapid rise of mobile phone penetration opens a new avenue towards its employment in low-income countries as well.

The Information Technology Aided Relapse Prevention Programme in Schizophrenia represents an mHealth platform enabling early pharmacological intervention in psychosis by the identification of prodromal symptoms of relapse using home telemonitoring via a phone-to-PC short message service (SMS) interface. The project has been developed and subsequently integrated into clinical practice in the Czech Republic since 2005.

The ITAREPS showed very promising results using a mirror-image design, comparing the number of hospitalizations occurring during participation in the study with the number during the equivalent amount of time prior to entry (Spaniel *et al*. 2008a, 2008b). However, this methodological approach has inherent weaknesses, including the inability to account for the effect of regression to the mean on hospitalizations.

For these reasons, two 1-year randomized controlled trials with ITAREPS has been conducted separately in the Czech Republic (Spaniel *et al*. 2012) and Japan (Komatsu *et al*. 2013). However, these studies have produced conflicting results without obvious differences in the study designs, except for strong control over adherence factors in the later Japanese RCT, in which visiting nurses achieved full cooperativeness of patients in parallel with antipsychotic dose increase in all prodromes detected by the programme. Therefore, in the subsequent research reported here, we tested the ITAREPS programme in a randomized, open, controlled prospective study over a longer study period of 18 months, focusing on adherence issues related to both users (patients) and psychiatrists (investigators). The trial was designed to test the effectiveness of early pharmacological intervention upon the occurrence of early warning signs detected by ITAREPS in patients with schizophrenia or schizoaffective disorder in 25 outpatient psychiatric facilities in the Czech Republic. The study was conducted among national representatives and most common samples of state, county, and private outpatient facilities.

The main hypothesis was that ITAREPS would be superior to treatment as usual at decreasing the number of hospitalizations. The primary end point was the difference between the active and control groups in the 1.5-year hospitalization-free survival. No changes to eligibility criteria or other methods were made after trial commencement (Clinicaltrials.gov NCT01885923).

## Subjects and method

### Participants

Inclusion criteria:

1. Men and women, ages 18 to 60 years. Elderly subjects were excluded in order to constitute a relatively young study population with higher risk of relapse.
2. A diagnosis of schizophrenia or schizoaffective disorder according to International Classification of Diseases-10.
3. Having more than one psychiatric hospitalization for psychosis before the study enrolment.
4. Severity (CGI-S) ≤3 (i.e. mildly ill – clearly established symptoms with minimal, if any, distress or difficulty in social and occupational function) at baseline. (Forkmann *et al*. 2011).
5. All patients were required to be on stable doses of antipsychotic medication for at least 3 months prior to taking part in this study.

Exclusion criteria:

1. Current or previous diagnosis of organic mental disorder.
2. Mental disorder due to psychoactive substance use and/or mental retardation.
3. Baseline Hayward compliance rating scale (Kemp *et al*. 1998) score <2 (i.e. subjects completely or partially refusing their medication were excluded).
4. Participation in another relapse prevention programme.

The trial protocol was reviewed and approved by local independent ethics committees according to the regulatory requirements in both participating countries. Informed consent was obtained from each patient and a family member before enrolment in the study. The study was conducted through Good Clinical Practice guidelines.

### Randomization

Upon entering the study, all patients were randomized in a 1:1 ratio into the active and control groups via a centralized computer-based dynamic random allocation method (minimization) that represents a randomization procedure in which the allocation of subjects to treatment groups is influenced by the current balance of pre-specified factors (Scott *et al*. 2002). The web-based randomization system

**Table 1**
Summary of patient demographic and baseline characteristics

| | Active (n = 74) | Controls (n = 72) | $\chi 2^1$ | *P** |
|---|---|---|---|---|
| Age, yrs: Mean (SD) | 36.2 (9.3) | 36.7 (9.7) | | 0.76 |
| Female (%) | 44.6 | 43.1 | 0.04 | 0.85 |
| Diagnosis (schizophrenia/schizoaffective) | 50/24 | 52/20 | 0.38 | 0.54 |
| Illness duration prior to inclusion, months (Mean, SD) | 88.8 (72.8) | 85.2 (86.4) | | 0.79 |
| Age at the onset of illness (Mean, SD) | 28.8 (7.8) | 29.6 (10.0) | | 0.60 |
| Number of hospitalizations prior to inclusion (Mean, SD) | 3.0 (2.6) | 2.6 (1.7) | | 0.25 |
| Education, yrs (Mean, SD) | 12.4 (2.8) | 12.1 (2.1) | | 0.24 |
| Hayward medication compliance (Mean, SD) | 6.3 (0.9) | 6.2 (0.9) | | 0.51 |
| Baseline GAF (Mean, SD) | 68.0 (14.0) | 67.9 (12.6) | | 0.97 |
| Baseline CGI (Mean, SD) | 2.3 (0.8) | 2.3 (0.7) | | 0.71 |
| Baseline depot medication (%) | 10.8 | 19.4 | 2.13 | 0.14 |

**t*-test.
[1]Chi-square test.

was part of ITAREPS data capture system accessible by use of common Internet browsers. The system gave investigators the option of uploading all baseline data and factors for randomization. Subsequently, the randomization process was initiated in the remote ITAREPS central database, in order to balance the treatment groups across the following variables: age, gender, level of education, duration of illness, Clinical Global Impression Scale (CGI) score, score on the Global Assessment of Functioning scale (Jones *et al*. 1995), Hayward Medication Compliance Scale score, number of previous hospitalizations, current medication (oral or depot) and age at the onset of illness (Table 1). Investigators received an email message containing ID generated by the system and to which group they belong (active or control).

## Study design

After randomization, patients allocated to the active arm, along with their family members, were involved in the ITAREPS programme. On a weekly basis, they, together with their family members, completed the 10-item Early Warning Signs Questionnaire reporting proportional change (worsening) in the patient's symptoms compared to last week's baseline. There were two versions of Early Warning Signs Questionnaire (EWSQ), one for patients (EWSQ-10P) and the other for their family members (EWSQ-10FM) (Spaniel *et al*. 2008a). The completion was prompted upon an SMS automatically sent to the receiver's mobile phone. The questionnaire was forwarded back to the system as a 10-digit SMS. If the severity of patient's symptoms exceeded a preset mathematical algorithm, an email message was automatically sent to the treating psychiatrist. Default thresholds triggering an alert were calculated from the results of mathematical data mining in 300 patients enrolled in the programme since 2005. Thus, the maximum predictive validity of the instrument was achieved.

According to the protocol, the alert email message warranted an obligatory 20% dose increase in the current antipsychotic medication within the next 24 h (Spaniel *et al*. 2008a). The effectiveness of this particular intervention has been confirmed previously (Herz *et al*. 2000). Antipsychotic dose escalation was then carried out arbitrarily with the following exceptions only: (1) If the minimal time lag between the previous and current alert would increase the risk of inappropriately rapid dose escalation contrasting with current clinical recommendations that potentially would lead to an increase in the risk of side effect occurrence. In this case, a 20% increase should be realized during an appropriately longer period of time, in accordance with the clinical recommendations; (2) If persistent side effects or the current somatic state potentially would increase the overall risk resulting from a dose increase in a given patient; (3) In the case of patient refusal of the pharmacological intervention; (4) If either the patient and/or the investigator were not contactable during the alert announcement; and (5) If the patient was already adjusted on the maximum doses of prescribed antipsychotic.

Seventy-two hours following each alert announcement, investigators were prompted via email to complete an unscheduled post-alert visit to either (1) confirm per protocol dose increase, or (2) state the reason for potential pharmacological non-intervention (listed above under 1–5), so that the exact nature of the non/intervention and the investigator's adherence to the protocol could be documented. If protocol-based exceptions for non-intervention were not applicable, option (6) 'Other reasons' was chosen. A web-based interface offered an authorized physician a user-friendly method of entering patient data from both study arms.

In the control group not involved in the ITAREPS, the investigators detected and reacted to potential signs of

psychotic relapse during regular outpatient visits and also on the basis of carer's reports, as they would have done prior to patient enrolment in the study.

All controls received routine clinical and medication management with their normal frequency of visits to their usual outpatients departments.

Two study visits were scheduled after screening: at baseline and month 18 (the end-of-study visit). All collected data were web based, and investigators were prompted to perform data input via an automatic email containing a direct link to the web page with the relevant case report form.

### Measures

Study assessments including the CGI-I, the Hayward 7-item Medication Compliance Rating Scale and Global Assessment of Functioning, along with demographic data and the history of illness were captured at baseline. Dates of hospitalization, doses of antipsychotic medication and any changes in medication during the study period were recorded at the end-of-study visit.

### Statistical analyses

Group sample sizes of 60 subjects (60 patient/family member pairs) in the active group, and 60 patients in the control group were a priori estimated to achieve 80% power to detect at least 20% between-group differences in the survival rate (18 months hospitalization-free survival) using the Kaplan–Meier analysis ($\alpha = 0.05$, two-tailed model, active group/control group size = 1). To calculate this power analysis, variation in the response variable reflected as the standard deviation of the principle variable was adopted from previous research (Spaniel *et al*. 2008a). Considering an average 20% drop-out rate in clinical studies, the intention was to enroll a total 150 of patient/family member pairs.

To compare the clinical and demographic characteristics between both groups unpaired *t*–test, or Mann–Whitney test for continuous variables, and chi-square test for categorical variables were used.

In the intention-to-treat analysis, the cumulative probability of remaining free of hospitalization due to relapse was estimated using the Kaplan–Meier survival analysis and compared this variable with log-rank statistics. An overall risk difference and risk ratios were calculated at the end of the study using 95% confidence intervals (CIs).

To assess the effect of pharmacological intervention upon alert occurrence, in a post hoc analysis we focused on patients from the active arm in which the system had detected at least one alert during the study period. Post hoc Cox regression models were constructed, with the first occurrence of relapse during the study period as the event variable. Hazard ratios and associated confidence intervals for selected potential predictors of relapse were obtained based on the model for each individual variable. In total, 13 potential predictors were selected. Two of them were closely related to ITAREPS itself: (1) patient non-adherence to ITAREPS (the number of SMSs sent to the system as a proportion of the total number of planned SMS); (2) number of alerts without consequent pharmacological intervention in a given patient. Remaining factors were identified in the literature as being relevant relapse predictors in schizophrenia: (3) age (Doering *et al*. 1998); (4) sex (Geddes *et al*. 1994, Doering *et al*. 1998, Grossman *et al*. 2006), education (Geddes *et al*. 1994); (5) age at the illness onset (Doering *et al*. 1998, Olfson *et al*. 2011); (6) diagnosis (Hui *et al*. 2013); (7) duration of illness (San *et al*. 2013); (8) baseline severity of symptoms (CGI) (Olfson *et al*. 2011); (9) medication adherence (Valenstein *et al*. 2002, Lang *et al*. 2010, Xiang *et al*. 2011, Hui *et al*. 2013); (10) baseline level of functioning (Global Assessment of Functioning) (Olfson *et al*. 2011); (11) number of previous hospitalizations (Doering *et al*. 1998, Olfson *et al*. 2011, Ascher-Svanum *et al*. 2013, San *et al*. 2013); and (12) drug administration (oral/depot) (Grimaldi-Bensouda *et al*. 2012). All computations were carried out using Statistica version 9.0 (Statsoft, Inc., Tulsa, Oklahoma, USA) and MedCalc Statistical Software version 14.12.0 (MedCalc Software, Ostend, Belgium).

## Results

### Study population

We screened 304 eligible patients between April 2012, and July 2012 (Figure 1) in 25 outpatient study centres. In 154 cases, patients refused to participate in the study. In total, 150 patients were randomly assigned to one of two study groups. Four of these subjects withdrew consent early in the study. Therefore, the total number of patients in the study (intention-to-treat population) was 146 (74 in the active and 72 in the control group). Both groups were similar in terms of baseline variables (Table 1).

During the 18 months, participants in the active arm sent a total of 9927 SMS (6023 SMS were sent by patients and 3904 by family members). Overall, the return rate was 70.6% in patients from the active arm. The Information Technology Aided Relapse Prevention Programme in Schizophrenia detected and announced a total of 160 alerts in the active group.

Since important events that may jeopardize the subject or may require intervention should be regarded as serious,

all 42 hospitalizations due to relapse occurring in this trial were considered as serious adverse events.

## Adherence to the protocol

*Patient adherence to ITAREPS*

Twenty-six patients from the active arm (35%) met predefined criteria for non-adherence to ITAREPS (i.e. they responded to fewer than 70% of SMS prompts) (Spaniel *et al*. 2012).

*Investigator protocol adherence*

Despite protocol-directed therapy, the antipsychotic dose was not increased in response to 50 out of 160 alerts (31.2%) in the active group. Investigators reported the following reasons for their failure to perform the required pharmacological intervention in the case of the alert announcement: other reasons (48%), patient refusal of the pharmacological intervention (24%), risk of inappropriately rapid dose escalation (8%), persistent side effects or current somatic state precluding dose increase (8%), patient and/or investigator not in reach (6%) and maximum dose already attained (6%). Unjustified absence of dose increase in nearly half of all non-interventional alerts suggests generally low adherence of investigators to the protocol.

The Information Technology Aided Relapse Prevention Programme in Schizophrenia identified early warning signs of relapse at least once during the course of the study in 52% of patients in the active arm of the study ($n$ = 43). Seventy-four per cent of those subjects elicited more than one alert, median = 3, range = 10.

## Primary endpoint: hospitalization-free survival rate

In the intention-to-treat analysis ($n$ = 146), 12 of the 74 patients in the active group (16.2%) were hospitalized due to psychosis relapse compared with 14 of the 72 patients (19.4%) in the control group (Table 2). No statistically significant differences were found in patient survival between the active and the control groups using the Kaplan–Meier method plus the log-rank test ($\chi 2 = 0.32$, df = 1, p = 0.57, hazard ratio [HR] 1.21, 95% CI 0.56–2.61, $P = 0.6$).

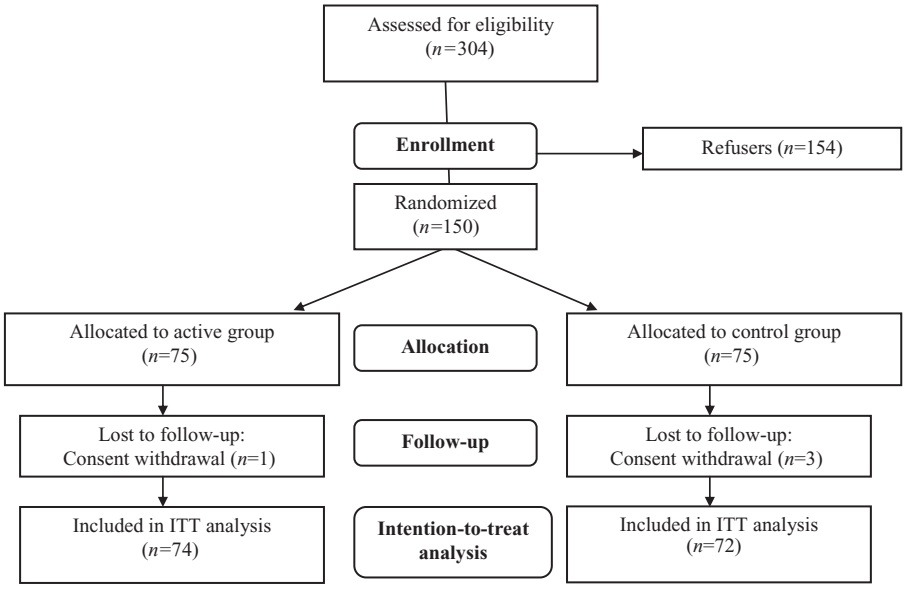


**Figure 1**
Trial profile
ITT, intention to treat.

**Table 2**
Results

| | Intention-to-treat | | | |
|---|---|---|---|---|
| | Active (n = 74) | Controls (n = 72) | Z** | *P** |
| Patient adherence, % (Mean, SD) | 70.6 (34.9) | na | | |
| Alerts with pharmacological intervention (%) | 67.0 | na | | |
| Number of hospitalizations | 19 | 23 | | |
| Inpatient days (Mean, SD) | 11.3 (27.6) | 13.4 (43.3) | | |
| Direct inpatient costs in EUR (Mean, SD) | 537.9 (1313.9) | 637.9 (2066.2) | | |

*$P < 0.05$.

**Mann–Whitney *U*-test.

### Secondary end point: inpatient days

There were no differences in the number of inpatient days between active [mean 11.3 days, standard deviation (SD) 27.6] and control group, respectively (mean 13.4, SD 43.3; Mann–Whitney *U*-test, Z = 0.34, *P* = 0.73).

### Predictors of hospitalization

A post-hoc Cox proportional hazards regression analysis was carried out to determine independent predictors of hospitalization due to relapse during the 18-month study in patients from the active arm in which the system recognized at least one alert during the study period (*n* = 43).

This analysis revealed that, out of 13 factors that entered the model, only two variables were significantly associated with the risk of hospitalization: (1) number of Alerts without pharmacological intervention (HR = 1.38, 95% CI 1.01–1.89, *P* = 0.042). Each additional alert with absence of consequent pharmacological intervention was associated with a 38% increased hazard of hospitalization during the study period; (2) Patient non-adherence to ITAREPS (HR = 1.08, 95% CI 1.02–1.14, *P* = 0.009). Each increment of 1% patient non-adherence with ITAREPS was associated with an 8% increased hazard of hospitalization during the study.

## Discussion

This study comprised a multi-centre randomized controlled trial using the telemedicine mHealth programme to prevent relapse in schizophrenia by use of maintenance plus targeted medication strategy.

The present study builds on sparse longitudinal research with conflicting results that directly investigated preemption strategies in the management of schizophrenia, i.e. antipsychotic medication dose increase early enough at the occurrence of early warning signs to prevent ongoing relapse (Eisner *et al*. 2013).

In the primary intention-to-treat analysis (ITT), our results showed no difference in the 18-month hospitalization-free survival rate between the active and the control groups. The current study replicated negative findings obtained from the first RCT with ITAREPS carried out in the Czech Republic in 2008 (Spaniel *et al*. 2012), in which ITT analysis also failed to confirm significant differences in 1-year hospitalization-free survival rate between active and control groups.

Interestingly, both studies suffered from a noticeably high proportion of absence of pharmacological intervention upon alert release in the active group (61% out of all announced alerts in the previous study and 31% in the current study, respectively), even though this factor represents the essential strategy of the programme. As a consequence, an unexpectedly high rate of investigator protocol deviations was observed in both studies (65% of non-interventional alerts in the previous RCT and 48% in the current trial, respectively). In contrast to this, patient acceptance of the programme was relatively high, with 3% and 7% drop out rate along with 70% and 80% SMS return rate in the current and previous RCT, respectively.

To identify predictors of hospitalization, a post hoc Cox proportional hazard regression analysis was performed in a previous Czech RCT (Spaniel *et al*. 2012). The strongest predictor was the absence of antipsychotic dose increase after alert, which increased nearly 11 times the risk of hospitalization. Gender and education were also statistically significant in terms of inpatient admission risk, which is consistent with previous reports (Geddes *et al*. 1994, Grossman *et al*. 2006).

Since non-cooperation in psychiatrists and users might have obscured the clinical effectiveness of ITAREPS, the authors of a subsequent Japanese randomized, controlled trial virtually excluded the effect of patient and physician adherence to the ITAREPS requirements (Komatsu *et al*. 2013). Visiting nurses were involved in the study and they ensured a 100% return rate of EWSQ from patients randomized into the active arm of the study. Furthermore, by visiting the patient's home directly, nurses verified that the patient had increased his or her oral medication following all alerts announced by the system. Under conditions of ensured full adherence of both patients and psychiatrists, the effectiveness of the programme became evident. Kaplan–Meyer survival analysis showed statistically significantly reduced risk of re-hospitalization down to one-fifth in the ITAREPS group in comparison to controls.

Similar results were obtained from a previous Czech study carried out in 2008 in which the direct effect of intervention upon alert occurrence was separately tested in a post hoc survival analysis. The 'intervention positives' (dose increase upon all announced alerts) showed, in comparison to 'intervention negatives' (no pharmacological intervention upon alert occurrence), a substantially reduced hazard ratio of hospitalization down to one tenth (Spaniel *et al*. 2012).

Coming back to the current study, when assessing hazard ratios for re-admission during the trial of subjects from the active arm in which the system detected at least one alert, a Cox regression analysis revealed among 13 relevant factors only two variables to be statistically significant prognostic predictors of hospitalization, both implicitly related to the ITAREPS programme: (1) patient

non-adherence with ITAREPS; and (2) number of alerts without pharmacological intervention in a given patient.

The latter result may call into question the canonical view that risk factors related to re-hospitalizations with psychosis are largely, if not solely, patient centered.

Improving relapse prevention has been emphasized as key component of the management of schizophrenia (Kane 2007). However, to accomplish this goal, we have to understand crucial specifics related to predictors of relapse. Primarily, early warning signs show generally very small mean elevations of objective psychopathology measures and may be largely beyond the resolution capability of the physician (Marder *et al*. 1984, Subotnik & Nuechterlein 1988, Birchwood *et al*. 1989, Gaebel & Riesbeck 2007). Second, proper detection of precursors of relapse require frequent assessments with the use of specific instruments tailored to detect prodromal signs (Birchwood & Spencer 2001). Recommended sampling frequency is equal or higher than once every 2 weeks (Van Meijel *et al*. 2004). Almost needless to say, standard clinical practice precludes this possibility due to a restricted number of outpatient visits. In this sense, telemedicine solutions can be the best approach to attain this goal.

Even when these requirements are met, another and equally important aspect emerges as a fundamental obstacle, as studies using ITAREPS suggest that psychiatrists are generally reluctant to use a rapid pharmacological response to considerably subtle prodromal symptoms. This factor, however, might be the main barrier to achieving effective relapse prevention. This was well illustrated in the present study where absence of antipsychotic dose increase ensuing alert announcement was associated with nearly 40% increase in the risk of rehospitalization.

We can speculate that a proactive approach at the very early stages of prodrome contrasts sharply with traditional clinical lore and psychiatric practice as psychiatrists tend to use pharmacological intervention largely in response to overt clinical decline in the patient. After all, psychiatrists bear substantial responsibility for potential side effects of the prescribed medicines and the dangers related to dose increase in de facto clinically stable cases. From the perspective of current level of scientific and clinical knowledge, this attitude is fully justified.

The power of these clinical habits was so strong in our two RCTs that they influenced psychiatrists to engage in frequent violations of the study protocol. As previous studies have confirmed, this factor precludes conducting of non-failed clinical trials unless investigators could be strongly relied upon to implement the necessary pharmacological interventions, as in the Japanese trial.

Clinically apparent deterioration as the only trigger for taking action was clearly demonstrated in the 2008 Czech RCT in which interventional Alerts in the active arm attained significantly and robustly higher CGI-I scores from investigators when compared to non-interventional ones ($P = 0.00005$, $Z = 4.07$) even though, the latter case fulfilled the criteria for protocol deviation (Spaniel *et al*. 2012).

In addition, low psychiatrist acceptance of the programme may generally reflect psychiatrists' lack of confidence in warning methods based on information technology. In this respect, investigators are, in all likelihood, loath to surrender their authority to an impersonal machine-like procedure.

Exposure to psychotic states has detrimental effects on the long-term outcome of schizophrenia and brain integrity (Andreasen *et al*. 2013). Nevertheless, primary prevention in schizophrenia is probably impossible, whereas secondary preventive approaches have so far met with disappointing results (Andrade *et al*. 2012). Thus, the therapeutic effort should be focused mainly on tertiary prevention. Whereas antipsychotics substantially reduce the risk of relapse (Leucht *et al*. 2012), there is a major concern related to medication issues that poses a substantial clinical dilemma. Greater intensity of antipsychotic treatment also influences progressive morphological changes in schizophrenia (Ho *et al*. 2011, Andreasen *et al*. 2013, Fusar-Poli *et al*. 2013). These factors involve making trade-off decisions, in that relapse prevention should be sustained using the lowest possible medication dosages that will control symptoms (Ho *et al*. 2011).

All these factors underline the importance of widespread implementation of effective relapse prevention programmes allowing patients to be maintained on the lowest dose of medication with ad hoc intensification of pharmacotherapy upon occurrence of subtle predictive signals. However, from a clinical care perspective, it may be that substantial reductions in relapses and re-hospitalizations in schizophrenia are likely to be unattainable unless substantial changes are made in the medication management of schizophrenia in a manner that is profoundly different from the way we have treated this illness for the past half century. The current lack of biomarkers makes standard care based on cross-sectional brief clinical assessments during outpatient visits inadequate for proper control of patient relapse risk. The results of previous Japanese RCT with ITAREPS programme show that the future of successful management of schizophrenia may lie in the integration of telemedicine relapse prevention systems within community mental health care with prominent role of visiting nurse service.

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