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ITAREPS: Information Technology Aided Relapse Prevention Programme in Schizophrenia

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Abstract

ITAREPS presents a mobile phone-based telemedicine solution for weekly remote patient monitoring and disease management in schizophrenia and psychotic disorders in general. The programme provides health professionals with home telemonitoring via a PC-to-phone SMS platform that identifies prodromal symptoms of relapse, to enable early intervention and prevent unnecessary hospitalizations. Its web-based interface offers the authorized physician a longitudinal analysis of the dynamics and development of possible prodromes.

This work presents preliminary findings from a one-year mirror-design follow-up evaluation of the programme's clinical effectiveness in 45 patients with psychotic illness. There was a statistically significant 60% decrease in the number of hospitalizations during the mean 283.3±111.9 days of participation in the ITAREPS, compared to the same time period before the ITAREPS entry (sign test, $p<0.004$). Variables significantly influencing the number of hospitalizations after the ITAREPS entry (medication compliance along with factors intrinsic to the ITAREPS, i.e. adherence to the programme and involvement of a family member) suggest a critical role of the programme in controlling the number of relapses and subsequent hospitalizations in psychosis.
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Keywords: Psychotic disorders; Schizophrenia; Relapse prevention; Hospitalizations

1. Introduction

Schizophrenia is a major psychotic disorder that has devastating effects on the lives of patients and their caregivers.

The illness is accompanied by high rate of relapses and readmissions. An overview of studies investigating long term outcomes has shown that people with schizophrenia have a one-year relapse rate of 15 to 35%, rising to 80% at five years after the onset of first-episode, despite maintenance medication (Robinson et al., 1999). Achievement of full remission becomes less likely after each relapse (Wiersma et al., 1998). In addition, an increased number of relapses positively correlate with subsequent

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social decline and reduced treatment response in patients with schizophrenia (Lieberman et al., 1996; Shepherd et al., 1989). Needless to say, these patients as well as their caregivers experience extremely high levels of burden related to the dramatic consequences of relapse and hospitalization.

Studies published so far suggest that the prediction of relapse appears to be an achievable goal for a substantial proportion of patients with schizophrenia. The successful prediction of relapse using new technologies e.g. telemedicine capabilities will most likely require a combination of components built into an integrated programme. These components may include monitoring of non-specific and specific prodromal symptoms, frequent assessments and an involvement of both patients and caregivers (Fitzgerald, 2001). Crisis interventions such as increasing the dose of antipsychotic medication, based on early detection within a relapse prevention programme, may reduce relapse and readmission rates compared to a treatment-as-usual group. Timely review of patient mental status with close to real-time feedback has been shown as a critical success factor in the management of psychosis (Herz et al., 2000).

The future wide availability of high bandwidth public wireless networks will give rise to new mobile health care (or M-Health) services. These approaches allow for home-based telemedicine ensuring the direct and prompt communication between the clinician and the patient or their caregiver.

The ITAREPS project (Information Technology Aided Relapse Prevention Programme in Schizophrenia) developed at the Prague Psychiatric Centre represents a step towards a highly customizable prodromal signs monitoring M-Health service platform.

1.1. The ITAREPS programme design

Participants enrolled in the ITAREPS programme (the patient and her/his family member) were instructed to complete a 10-item Early Warning Signs Questionnaire (EWSQ) by a Short Message Service (SMS) request sent weekly (on Thursdays) by an automated system to their mobile phones. Attendance of a family member at the ITRAEPS was highly recommended, albeit optional.

There were two versions of EWSQ, one for patients (EWSQ-10P) and the other for their family members (EWSQ-10FM). Full reporting on psychometric properties of EWSQ has been published elsewhere (Spaniel et al., 2007).

Nine of the EWSQ items covered the most common early non-specific warning sings of the relapse. The tenth item instructed patients and carers to list three specific symptoms which had individually preceded previous relapse or relapses in the given patient and which were not included under items 1–9 (Table 1). In case of more than one specific symptom occurrence, the most pronounced sign was selected and scored under item 10.

The EWSQ was designed to detect proportional worsening (or a new onset) of symptoms compared to the baseline (the previous week's completed questionnaire). Each item score ranged from 0 (no worsening or improvement of symptoms) to 4 (extreme worsening).

Table 1
Early warning sings questionnaire, patient and family member version

Item no.	EWSQ 10 Patient Version	EWSQ 10 Family Member Version
1	Has your sleep worsened since the last evaluation?	Change of the sleep pattern.
2	Has your appetite decreased since the last evaluation?	Marked behavioral changes.
3	Has your concentration, e.g., ability to read or watch TV, worsened since the last evaluation?	Social withdrawal.
4	Have you experienced fear, suspiciousness, or other uneasy feelings while being around other people since the last evaluation?	Deterioration in daily activities and functioning.
5	Have you experienced increased restlessness, agitation, or irritability since the last evaluation?	Deterioration in personal hygiene.
6	Have you noticed that something unusual or strange is happening around you since the last evaluation?	Loss of initiative, motivation.
7	Have you experienced loss of energy or interest since the last evaluation?	Eccentric thought content, marked preoccupation with strange ideas.
8	Has your capability to cope with everyday problems worsened since the last evaluation?	Marked poverty of speech and content of thoughts.
9	Have you experienced hearing other people's voices even when nobody was around since the last evaluation?	Irritability, restlessness, agitation, aggressivity
10	Have you noticed any other of your individual early warning signs since the last evaluation?	Have you noticed any other individual early warning signs since the last evaluation?

Completion of the questionnaire took approximately 5 min. Individual EWSQ scores were sent by participants back to the ITAREPS as a SMS message, presented as a string of ten digits (i.e. 0001202001). The information was then processed automatically. If the total score (and/or given score in prepsychotic sub items of the EWSQ) exceeded a given score threshold, an immediate ALERT was declared and the psychiatrist was notified of this by an e-mail message.

The e-mail ALERT message contained the code number of the patient and an Early Intervention Algorithm (EIA). The EIA was a key factor allowing for early crisis intervention. It consisted of five consecutive steps in which immediate phone contact with the patient and prompt evaluation of his/her current status was recommended.

The presence of early warning signs warranted an immediate 20% increase from baseline maintenance dose of antipsychotic within the next 24 h. The effectiveness of this particular intervention has been confirmed previously (Herz et al., 2000). To achieve the most appropriate 20% fractional dose increase, splitting or dividing of the tablets was to be done in the most suitable way according the relevant antipsychotic's Product Information. The fifth item of EIA emphasizes the importance of doctor–patient face-to-face contacts during the treatment, pointing on the fact that the program is not intended to reduce the number of visits.

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 physician via e-mail along with recommendation concerning subsequent tapering down the medication to the pre-ALERT doses. During the ALERT PERIOD, participants were to return questionnaires twice-weekly upon SMS request (on Thursdays and Mondays).

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.

Admissions to the hospital and discharge dates were announced to the system by either and/or both patient and family member by SMS message. In order to record the event in the system, SMS had to follow a predefined form. This information was automatically integrated into line graphs accessible to clinicians. Information about hospital admissions were subsequently confirmed by the outpatient psychiatrist for the purpose of this clinical evaluation.

The patient data entering process was operated exclusively on the internet using standard browsers. In order to access the ITAREPS (www.itareps.com), participating psychiatrists needed a username and a password. Subsequently, his/her personal page was created in which his/her patients were registered and assigned a specific code number. The subject number and patient initials were recorded on a patient assignment log, which was kept exclusively by the outpatient psychiatrist.

During each personal web page visit, the physician could easily check the current medical status of his/her patient. Longitudinal score values (both from the patient and his/her carer) were available in a graphic form (line graphs) and in a detailed written description which was converted from the completed questionnaires returned as SMS messages from patient and his/her carer. In this way the psychiatrist could easily review the dynamics and development of possible prodromes.

All stored data contained no patient identifiers. The data were rendered unreadable to unauthorized persons. Data processing and security measures addressed all known security vulnerabilities including encryption of transmission and storage of information across the internet.

No specific training has been provided for ITAREPS participants. According to the clinical experience with ITAREPS program, ITAREPS User Manual distributed to the program participants provided a firm basis for appropriate management and system operation.

2. Methods

2.1. Subjects

A total of 45 patients and 39 family members were enrolled in the one-year, longitudinal, mirror-design evaluation of the ITAREPS clinical effectiveness since its implementation in clinical practice in the Czech Republic in September 2005. These subjects were recruited by their psychiatrists through 14 outpatient mental health facilities in the Czech Republic. Direct advertising in Czech peer-reviewed journal Psychiatrie was used for the purpose of out-patient facilities recruitment. No financial or other incentives were given to any participant to take part in this clinical evaluation.

Patients fulfilled ICD-10 criteria for diagnosis of schizophrenia, schizoaffective disorder, or acute polymorphic psychotic disorder with or without symptoms of schizophrenia, and were aged between 18 and 65 (Table 2).

Mean illness duration (time since occurrence of the first psychotic symptoms) was 6.9 (SD 4.8) years in the participants, resulting in 134 hospitalizations during a total of 256 patient/years. Thus, cumulative hospitalization

Table 2
The demographic and clinical characteristics of the patients

			Mean (SD)
Age	Male $N=27$ (60%)		31.3 (7.6) years
	Female $N=18$ (40%)		29.6 (5.8) years
CGI			2.6 (1.2)
			N
Diagnosis	Schizophrenia		29 (64.4%)
	Schizoaffective disorder		11 (24.4%)
	Acute polymorphic psychotic disorder with schizophrenia symptoms		4 (8.9%)
	Acute polymorphic psychotic disorder without schizophrenia symptoms		1 (2.3 %)
Antipsychotic medication	No		22 (48.8%)
	Yes	Atypical	19 (42.2%)
		Classical	4 (9%)

incidence in our patient group was 0.51 patient/years before the ITAREPS entry.

Because this follow-up used only clinical information without specific patient identifiers and the procedures required no deviation from standard clinical practice, informed consent was not obtained from participants. The protocol of ITAREPS programme was approved by the Ethics Committee of the Prague Psychiatric Center.

2.2. Measures

The following baseline measurements were obtained from outpatient psychiatrists: demographic data; diagnosis; illness history; CGI and current medication. Compliance was evaluated by therapists using a questionnaire with a 5-point scale (1 = always and 5 = never taking antipsychotic medication (Herz et al., 2000)). The adherence to the ITAREPS programme was measured as a percentage difference (PD) between the number of messages the patient/family member were supposed to send according to the ITAREPS programme and the number actually sent by both participants. Patients and family members were divided into two groups according to PD. Subjects with a PD of less than 30% undelivered SMS messages containing EWSQ scores were designated as "Cooperative" and "Uncooperative" if they had a PD of more than 30% SMS messages missing.

2.3. Statistics

Statistical analysis was performed using the sign test, the Mann–Whitney *U* test and the Fisher's exact test. The

Table 3
Relationship of patient variables to hospitalization status after the ITAREPS entry

Variable	Non-hospitalized during ITAREPS ($n=38$)		Hospitalized during ITAREPS ($n=7$)[a]		Difference between non-hospitalized and hospitalized during ITAREPS	
	Median	Minimum–maximum	Median	Minimum–maximum	Mann–Whitney *U* (*z* scores)	*p*
CGI	2.0	1–5	3.0	1–5	−1.064	0.3
Illness duration (days)	2178.5	51–3910	3489.0	2203–4940	−1.535	0.13
No. of hospitalizations before ITAREPS	2.0	0–13	6.0	1–15	−1.558	0.12
Medication compliance	1.5	1–3	2.0	1–5	−1.969	0.04[b]
No. of Alert states	0.0	0–26	0.0	0–1	−0.538	0.64
No. of days in ITAREPS	291.0	5–565	300.0	76–412	−0.047	0.97
		N		*N*		*p*[c]
Medicated/unmedicated		19/19		4/3		0.69
Inclusion of a family member Yes/No		35/3		4/3		0.05[b]
Patient cooperation Yes/No[d]		32/6		3/4		0.03[b]
Family member cooperation Yes/No[d]		21/17		1/6		0.09

[a] Two subjects were hospitalized twice during the follow-up period.
[b] Statistical significance at $p \leq 0.05$, exact significance, two-sided.
[c] Fisher's exact test.
[d] Cut off point of cooperativeness defined as more or less then 30% undelivered SMS messages.

criterion for statistical significance was set at $p \leq 0.05$ exact significance, two-sided to have adequate power to detect differences with the small number of subjects.

3. Results

In total 1540 EWSQs were completed and returned as a SMS message by patients along with 1020 EWSQs from family members during a total follow-up period of 34.7 patient/years.

The ITAREPS system announced the onset of early warning sings in 88 cases based on EWSQ scores sent by patients and in 47 cases based on family members' reports, during the follow-up period.

The overall patient drop-out rate during the evaluation period was 10%. The drop-out was defined as any discontinuation of participation in ITAREPS programme for more than 10 weeks.

There were 9 hospitalizations in the 45 patients participating in the ITAREPS programme (Table 3) for a mean of 283.3 ± 111.9 days follow-up, compared with 27 hospitalizations during the same length of time before entering the programme, resulting in a statistically significant 60% reduction in the number of hospitalizations during ITAREPS programme participation (sign test, $p < 0.004$). There was 100% decrease in the number of hospitalizations (from 13 to 0) in highly cooperative patients ($N = 21$, 47%, family member included, more than 70% SMSs returned by both participants) during the follow-up. Those subjects showed cumulative hospitalization incidence 0.42 patient/year before the ITAREPS entry.

In a second step, Mann–Whitney or Fisher's exact tests were performed to search for variables influencing the number of hospitalizations after ITAREPS enrolment (Table 2). No significant differences between hospitalized and non-hospitalized patients in the ITAREPS programme were found regarding the duration of illness, number of hospitalizations before entering ITAREPS, CGI ratings during initial visit, number of ALERT states during ITAREPS, medication status (on or off antipsychotic medication at the entry of the ITAREPS programme) or duration of the ITAREPS programme participation.

However, univariate comparisons showed that non-hospitalized patients were significantly more compliant with their medication, more adherent to the ITAREPS programme and had a family member significantly more frequently involved in the programme compared to subjects hospitalized after ITAREPS entry. A similar but non-significant trend related to higher family member adherence to the ITAREPS programme was found in non-hospitalized compared to hospitalized patients.

4. Discussion

The prevention of relapse and readmission has high priority in the treatment of patients with a psychotic disorder. There is an urgent need to develop effective relapse prevention programmes that are applicable in routine clinical practice.

The use of telemedicine capabilities to monitor chronically ill patients is becoming more clinically relevant and economically cost effective.

The novel M-health management package, ITAREPS, by means of a simple, interactive communication based on user–server interactivity between healthcare professional and project participants, can timely report prodromal symptoms of relapse and promote appropriate measures that can be taken for early pharmacological intervention.

This one-year mirror-design follow-up was carried out to evaluate the impact on outcome of early intervention enabled by the ITAREPS system in 45 patients with psychotic illness. Significantly fewer hospitalizations were shown in patients enrolled in the ITAREPS programme compared to the follow-up period before the programme entry. Among several variables that were considered to be potentially associated with the rate of hospitalizations after ITAREPS entry, only medication compliance, adherence to the ITAREPS programme and involvement of a family member in the project showed statistical significance. Those preliminary findings suggest that the parameters intrinsic to the ITAREPS programme, along with compliance, as a crucial factor in project efficiency resulted in a reduction of the number of relapses and subsequent hospitalizations in psychosis.

The results of this pilot clinical evaluation must be interpreted in light of its methodological limitations including absence of a control group and relatively small numbers of patients.

In addition, although a specific procedure was recommended according to Early intervention algorithm (EIA), the exact nature of the intervention during the Alert states could not be documented in this clinical evaluation. This is of particular importance in medication-free subjects ($n = 22$, 49%) in which antipsychotic readministration corresponds EIA during the ALERT state.

Therefore, a prospective, double-blind, randomized trial with the ITAREPS programme is warranted to confirm our preliminary findings.

5. Conclusions

The ITAREPS programme presents a novel approach towards relapse prevention which according to our

knowledge has not been used before. The programme offers affordable solution to face the challenges of frequent rehospitalizations and relapses in patients with schizophrenia and psychotic disorders in general. Besides this primary effect, one of the main goals of the program is implementing continuous quality improvement in the doctor–patient relationship resulting in the strengthening and positive interference with the rapport between physician and patient. Furthermore, ITAREPS user-friendly, web-based data capture system enables international large-scale naturalistic studies to be conducted, aimed at the evaluation of long-term outcomes, dynamic fluctuations of the course of psychotic illness and the rate of relapses related to the particular antipsychotic medication.

Role of funding source

Eli Lilly Czech Republic supported financially the project. This company had no further role in the collection, analysis and interpretation of data.

Contributors

Filip Španiel developed ITAREPS system, designed the study, wrote the protocol and manuscript. Pavel Vohlídka co-worked on study concept and design and drafting of the manuscript. Jan Hrdlička made substantial contributions to the manuscript in terms of data acquisition and analysis. Jiří Kožený undertook the statistical analysis and interpretation of the data. Lucie Motlová and Jan Čermák managed the literature searches, analyses and technical support of the study. Daniel Novák contributed to analysis and interpretation of the data. Josef Bednařík and Cyril Höschl were responsible for critical revision of the manuscript for intellectual content.

Conflict of interest

Pavel Vohlidka and Josef Bednařík are employees of Eli Lilly CR, s.r.o. which has provided a unrestricted grant for ITARERPS development. All other authors declare that they have no conflicts of interest.

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ITAREPS is operating under the auspices of the Psychiatric Society CLS JEP of Czech Republic and Psychiatric Society SLS, Slovak Republic.

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