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Research paper

Relapse in schizophrenia: Definitely not a bolt from the blue

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HIGHLIGHTS

- Early warning signs (EWS) of schizophrenia relapse were analyzed using a telemedicine system.
- Previous studies demonstrated symptom increase 2–4 weeks before relapse.
- Here, the onset of continuous changes in EWS occurred 2 months prior hospitalization.
- EWS precede relapse of schizophrenia much earlier than previously suggested.

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ABSTRACT

Background: Detailed study of the period before schizophrenic relapse when early warning signs (EWS) are present is crucial to effective pre-emptive strategies.

Aims: To investigate the temporal properties of EWS self-reported weekly via a telemedicine system.

Method: EWS history was obtained for 61 relapses resulting in hospitalization involving 51 patients with schizophrenia. Up to 20 weeks of EWS history per case were evaluated using a non-parametric bootstrap test and generalized mixed-effects model to test the significance and homogeneity of the findings.

Results: A statistically significant increase in EWS sum score was detectable 5 weeks before hospitalization. However, analysis of EWS dynamics revealed a gradual, monotonic increase in EWS score across during the 8 weeks before a relapse.

Conclusions: The findings—in contrast to earlier studies—suggest that relapse is preceded by a lengthy period during which pathophysiological processes unfold; these changes are reflected in subjective EWS.

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1. Introduction

The majority of patients with schizophrenia experience multiple relapses during the course of the illness. Even under clinical trial conditions where there is substantial control over use of medication the one-year relapse rate approaches 30% [20]. Relapses, which are characterized by exacerbation of acute psychotic symptoms, have serious consequences. In general, exposure to psychotic states has a detrimental effect on the long-term outcome of schizophrenia and on brain integrity [1,4,21,26,33]. Exposure to overt psychotic

symptoms in the two years after the first episode of schizophrenia predicts a wide range of functional indices 15 years later [10]. Treatment guidelines therefore emphasize the role of tertiary prevention in the management of schizophrenia [8]. All these factors underline the importance of widespread implementation of pre-emptive strategies in the management of schizophrenia, i.e. intervening early enough in the relapse prodrome to prevent manifestation of the serious effects of the disease associated which are associated with progression.

Current standard care based on brief clinical assessments during outpatient visits is insufficient for monitoring risk of relapse. Continuous monitoring of changes in non-specific symptomatology with sampling frequency of at least once in two weeks [3] represents the minimum monitoring required to enhance our ability to pre-empt development of a relapse.

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To prevent schizophrenic relapse or minimize its severity we need to have a better understanding of the predictors. The crucial question that remains unanswered in this regard is the length of the prodrome i.e. the period between emergence of detectable early warning signs (EWS) and the onset of overt relapse. This determines the time window in which effective pharmacological intervention may occur. Both prospective studies using objective measures of psychopathology and retrospective reports from patients with psychosis and their relatives suggest that symptoms increase 2–4 weeks before relapse into psychosis [2,11,12,29,30]. To gain more detailed insight into this particular issue we analyzed weekly reports of prodromal signs before 61 hospitalizations in 51 patients with schizophrenia who were enrolled in the ITAREPS telemedicine program [19,27,28].

ITAREPS represents an attempt to move the field of psychiatry forward in the direction of “P4” medicine—a discipline that is predictive, personalized, preventive and participatory. The program takes the form of a PC-to-mobile phone platform for remote monitoring and management of patients with psychotic disorders. ITAREPS uses SMS (Short Message Service) to collect weekly patient- and family member-reported clinical data. The data are used to provide clinicians with an automatic warning if there is a severe worsening in reported symptoms. The aim for the future is that the program will provide accurate and early detection of prodromal symptoms of relapse. We believe that careful weekly monitoring and detailed analysis of multiple subjective variables could substantially extend the period during which prodromal signs are detectable and thus extend the time-window in which early intervention can take place.

The aim of this study was to investigate the dynamics of prodromal symptoms, in order to augment tertiary preventive strategies in schizophrenia. The primary focus was on identifying the onset of changes in the pattern of a relatively rich regular chronological data set, including variables related to functional health and well-being, behavioral symptoms and pre-psychotic symptoms, before relapse, herein defined as rehospitalization.

2. Materials and methods

2.1. Subjects

The patients attended outpatient psychiatric facilities cooperating with the ITAREPS program that was introduced into clinical practice in the Czech Republic in 2008. There were no qualifying criteria for inclusion except a diagnosis of psychotic illness. Patients fulfilled International Classification of Diseases (ICD-10) criteria for schizophrenia, schizoaffective disorder or acute polymorphic psychotic disorder with or without symptoms of schizophrenia.

The following baseline patient data were recorded by psychiatrists: demographic data; diagnosis; illness history; Clinical Global Impression Severity Scale (CGI-S) and current medication (Table 1).

As this analysis used clinical information without specific patient identifiers and the procedures involved no deviation from standard clinical practice, informed consent was not obtained from participants. The protocol for the ITAREPS program was approved by the Ethics Committee of the Prague Psychiatric Centre.

2.2. Description of ITAREPS

Participants enrolled in the ITAREPS program (the patient and a member of his/her family) were instructed via an automated, weekly SMS request sent to their mobile phones to complete a 10-item Early Warning Signs Questionnaire (EWSQ, patient and family member version). The EWSQ is designed to detect worsening (or onset) of symptoms (Table 2) relative to a baseline—the previ-

ous week's completed questionnaire. Item scores range from 0—no change in symptoms to 4—dramatic worsening of symptoms. Individual EWSQ scores were sent back to the ITAREPS by participants as an SMS message, presented as a string of ten digits. The information is then processed automatically. If the patient's symptoms exceed a predetermined severity threshold an e-mail alert message is automatically sent to the treating psychiatrist. The universal thresholds were previously determined to maximize the hospitalization predictive value by evaluating pooled patient data that had been collected in the ITAREPS database since the introduction of the program in clinical practice in 2005 [27]. Alert messages warrant a 20% increase in dose of antipsychotic medication within 24 h 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. Once an Alert has been declared it remains active for a 3-week Alert period during which the subject is prompted to submit a EWSQ message twice a week. If EWSQ scores during this period show no further worsening in symptoms the Alert is withdrawn and the treating outpatient psychiatrist is informed via an e-mail including a recommendation about subsequent tapering of medication to the pre-Alert baseline. If EWSQ scores exceed the severity thresholds despite the pharmacological intervention the Alert period is extended for a further 3 weeks.

The additional patient data (diagnosis, demographic variables etc.) were entered and collected exclusively through the ITAREPS program web portal at www.itareps.com. Information about hospital admissions was confirmed by the outpatient psychiatrist for the purpose of this clinical evaluation.

2.3. Selection criteria

We considered only data from patients who had experienced rehospitalization whilst participating in ITAREPS. The primary data were weekly EWSQ scores reported as SMS messages consisting of a ten-digit string (values ranging from 0 to 4) by both patients and family members during the 20-week period before a hospitalization. To ensure that the period of observation was sufficient to capture the emergence of prodromal signs we excluded sequences of SMSs shorter than six weeks and sequences with dropout, defined as lack of any SMS in the four-week period immediately prior to relapse.

2.4. Data summary

Outpatients with psychotic disorders were enrolled between July 2005 and January 2015 by their psychiatrists through 36 outpatient facilities in the Czech Republics for routine clinical use of the program. 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. During the period of observation there were 349 patients enrolled in the program, out of which 70 experienced rehospitalization—91 hospitalizations in total. The result of applying consecutive steps of the selection

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