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Research paper

Relapse in schizophrenia: Definitively 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.

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 previous 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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Table 1
The demographic and clinical characteristics of patients. CGI: Clinical Global Impression Scale.

Total patients			51
			Mean (SD)
Age	Male *N* = 37 (73%)		32.4 (9.0) years
	Female *N* = 14 (27%)		35.2 (8.4) years
Clinical global impression (CGI)			2.4 (1.1)
Days since enrolment in the ITAREPS program			398 (362)
			N (%)
Diagnosis	Schizophrenia		31 (60.8%)
	Schizoaffective disorder		16 (31.4%)
	Acute polymorphic psychotic disorder with schizophrenia symptoms		4 (7.8%)
Antipsychotic medication	No		4
	Yes	Atypical	44
		Classical	3

Table 2
The items of the early warning sign questionnaire (EWSQ) for patient and family member.

Item no.	EWSQ 10 Patient Version	Item no.	EWSQ 10 Family Member Version
1	Has your sleep worsened since the last evaluation?	1	Change of the sleep pattern
2	Has your appetite decreased since the last evaluation?	2	Marked behavioral changes
3	Has your concentration, e.g., ability to read or watch TV, worsened since the last evaluation?	3	Social withdrawal
4	Have you experienced fear, suspiciousness, or other uneasy feelings while being around other people since the last evaluation?	4	Deterioration in daily activities and functioning
5	Have you experienced increased restlessness, agitation, or irritability since the last evaluation?	5	Deterioration in personal hygiene
6	Have you noticed that something unusual or strange is happening around you since the last evaluation?	6	Loss of initiative, motivation
7	Have you experienced loss of energy or interest since the last evaluation?	7	Eccentric thought content, marked preoccupation with strange ideas
8	Has your capability to cope with everyday problems worsened since the last evaluation?	8	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?	9	Irritability, restlessness, agitation, aggressivity
10	Have you noticed any other of your individual early warning signs since the last evaluation?	10	Have you noticed any other individual early warning signs since the last evaluation?

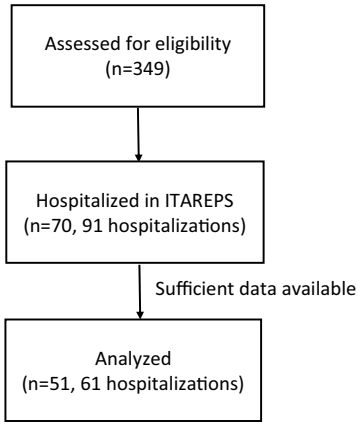

Fig. 1. Study flowchart.

criteria can be seen in Fig. 1. The data set that entered analysis consisted of the SMS history of 61 hospitalizations from 51 patients (Table 2) and 31 family members (family member-reported history was available for 35 hospitalizations). Nine patients experienced multiple hospitalizations: eight patients were hospitalized twice and one was hospitalized three times. The data set consisted of 1283 patient SMSs and 722 family member SMSs. The mean duration of pre-hospitalization follow up was 124 days (median = 140 days, SD = 27 days).

2.5. Data analysis

Data handling and exploratory data analysis was performed in Matlab (Matlab 2012b, The MathWorks, Inc., Natick, Massachusetts, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). The latter was also used for the bootstrap tests and generalized linear models.

2.5.1. Analysis of EWSQ inner structure

We used principal component analysis (PCA) [5] to analyze the structure of the EWSQ. PCA finds orthogonal components (linear combinations of the original items) that explain the highest possible proportion of the variance in data. Exploration of the variance accounted for by each principal component and the components' influence on the questionnaire items provides information about underlying variables and their relationship to particular items.

PCA showed only one dominant component, which accounted for 66% of the overall variance in EWS scores, to which all of the subscores contributed similarly. None of the remaining nine principal components accounted for more than 7% of variance explained in EWS scores. Based on these results, we decided to include the sum of all EWSQ item scores in our data set.

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The sum score was used as the main indicator of change in patient state in the analysis of prodromal onset time point and was analyzed together with individual EWSQ items in all remaining analyses

2.5.2. Detection of prodromal onset time point

To identify the earliest point at which an increase in specific EWSQ parameters was detectable we used a one-sided test with a non-parametric bootstrap. The sample mean for each parameter was compared with the mean of the bootstrap distribution obtained by multiple random temporal resampling of the preceding time series.

To control for bias due to multiple comparisons (testing for increases at multiple points before hospitalization) we used a sequential testing strategy. A difference in a parameter at a given time point was considered significant if and only if the elementary tests for this and all subsequent time points were significant at the 5% level. This approach controlled the familywise error rate in the strong sense at the predefined level of 5%, as amounted to a closed testing procedure [23].

2.5.3. Analysis of inter-subject differences in prodrome dynamics

After identifying a robust mean onset time for prodrome at the group level using the procedure described above we investigated the dynamics of prodromal changes and inter-subject variability in prodrome using a general linearized mixed effects model [25]. Owing to the nature of the data we used a negative binomial regression analysis model (see details in the Supplementary material). An exponential progression in symptoms after onset was assumed, with variable baseline and progression parameters. The component of changes in EWSQ scores that was common to all subjects was thus modeled as fixed effects; whereas the component that varied between subjects (baseline level of symptoms, rate of symptom progression) was captured as random effects.

2.5.4. Analysis of the temporal dynamics of prodrome

Visual inspection of weekly means for individual EWSQ parameters indicated a steady, continuous increase long before hospitalization. To exclude the possibility that the occurrence of this pattern of a long gradual increase in symptoms (GIP) just before hospitalization was due to chance we assessed the prevalence of such patterns in randomly temporally reshuffled data.

All pre-hospitalization data were analyzed in smoothed (moving three-week averages) weekly mean values for both EWSQ sum score and item scores. In the bootstrap testing procedure duration of the GIP was compared with the distribution of pre-hospitalization GIPs in a simulated population generated by randomly shifting each subject's history, computing weekly averages and smoothing the result. A positive result on this test would indicate that the length of the observed GIP is exceptional, given the natural properties of the data.

3. Results

3.1. Detection of prodromal onset time point

A bootstrap test on 10,000 resamples revealed that there was a change in patients' EWSQ sum scores 5 weeks before hospitalization. The observed mean of sum scores and the 95th percentile of the null hypothesis distribution are shown in Fig. 2. Estimated change points for all parameters are presented in Table 3A.

3.2. Analysis of inter-subject differences in prodrome dynamics

Owing to very high variability in individual EWSQ item scores, the generalized linear mixed effects model was only applied to sum

Table 3
Results of the prodromal onset time point detection bootstrap (A—maximum length of pre-relapse increase in symptoms) and the temporal dynamics of prodrome bootstrap analysis (B—length of gradual increase pattern, points at which the increase in symptoms was significant are marked with an asterisk).

		1 sleep	2 food	3 concentration	4 fear	5 restlessness	6 paranoia	7 loss of interest	8 coping with chores	9 voices	10 individual symptoms	SUM
PATIENT	(A) onset time (wks. to relapse)	3	2	4	6	5	2	5	5	2	2	5
	(B) dynamics (GIP length in wks.)	6*	5*	6*	2	8*	2	5*	8*	9*	2	8*
		1 sleep	2 changes in behavior	3 social withdrawal	4 coping with daily chores	5 hygiene	6 loss of motivation	7 preoccupation	8 poverty of speech	9 restlessness	10 individual symptoms	SUM
FAMILY MEMBER	(A) onset time (wks. to relapse)	1	1	1	1	1	2	1	1	1	4	1
	(B) dynamics (GIP length in wks.)	1	1	1	1	1	6*	4*	1	4*	9*	8*

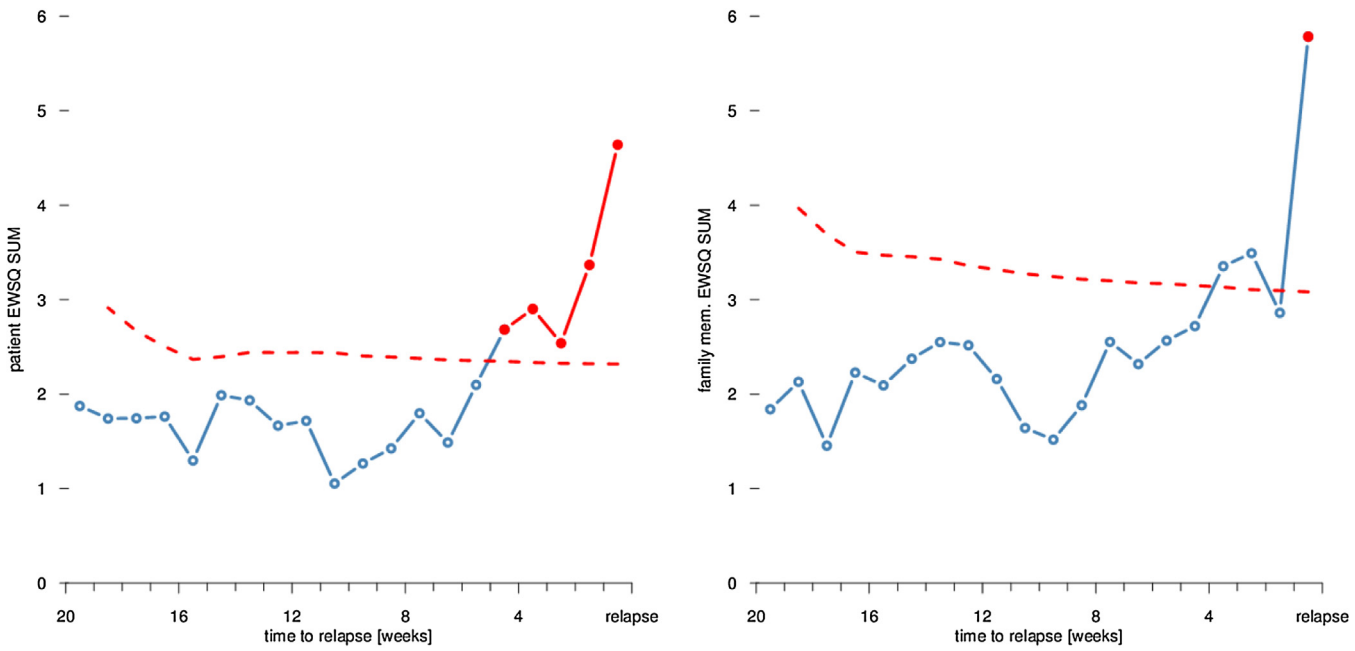

Fig. 2. Simple visualization of prodromal onset time point detection results for mean EWSQ sum score for patients (left) and family members (right). The solid line represents weekly population mean (significant region in red), the dashed line indicates the 95th percentile of the resampled bootstrap population means.

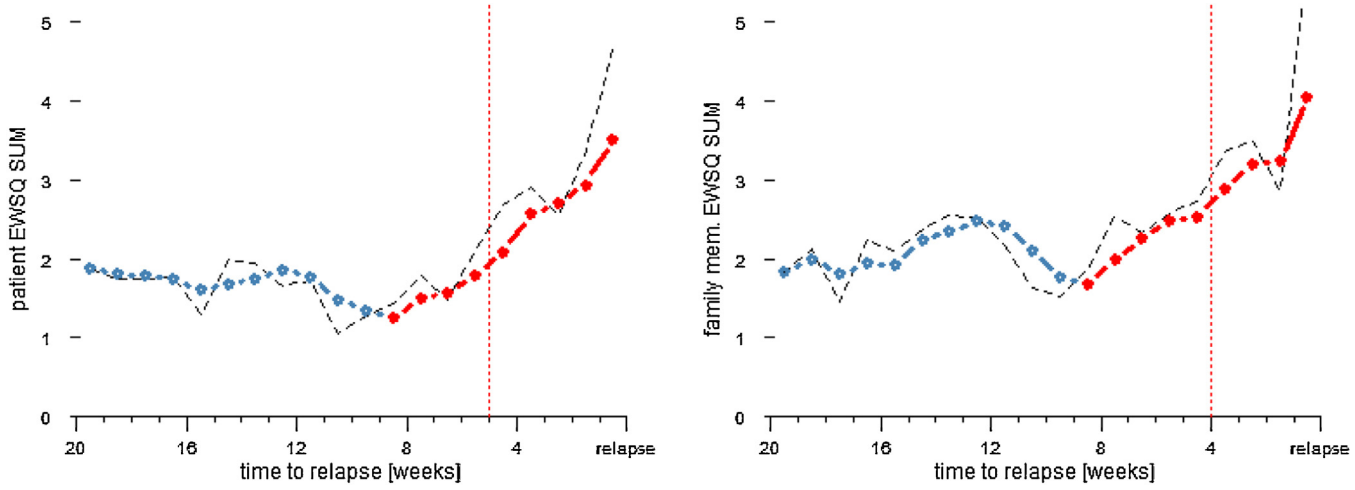

Fig. 3. Trend in mean EWSQ sum score in the real population (solid blue line). The GIP segment is marked in red in patient (left) and family reports (right), respectively. The start of last rising segment in the bootstrap (B) null distribution that exceeds the upper 95% confidence boundary is shown as a dotted vertical line. Unsmoothed weekly means are shown with a black dashed line.

score. In family reports there was a very short period between prodrome onset and hospitalization (1 week) and so further modeling was limited to patient-reported data. The results for the mixed-effects model can be divided into two main components: (i) the fixed effects, corresponding to the population mean trend and (ii) the random effects, corresponding to the additional between-subject variability.

The fixed effects in our model predicted exponential growth after the change point given by the weekly multiplication factor 1.143 ($p = 0.0005$, bootstrap with $N = 50000$). In other words, after the estimated break point (5 weeks before relapse—see previous subsection for details) the patient-reported EWSQ sum score increases by approximately 14% every week. Over the five-week prodromal period this amounts to a roughly twofold increase in population mean response ($1.143\hat{5} = 1.951$).

Both random effects in the model proved significant ($p < 0.00002$). This provides strong evidence that there are individual differences in baseline symptoms and in the rate at which symptoms worsen after the break point.

Although there was significant inter-subject variability in both the baseline symptom level and progression speed, in the majority of re-hospitalizations (50 out of 61 cases) the model estimated a steady increase in symptoms after the break point.

3.3. Analysis of the temporal dynamics of prodrome

The bootstrap analysis performed on 10,000 resamples revealed a GIP which began 8 weeks before relapse in the smoothed data for patient- and family-reported EWSQ sum scores (Fig. 3). The same steady increase pattern (the duration varied between 1 and 9 weeks) was detected in most of the individual items (Table 3B).

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4. Discussion

We analyzed the dynamics of EWSQ with respect to 61 schizophrenic relapses in hospitalization on the basis of weekly patient and family reports delivered via a telemedicine system. We sought to determine the earliest time point at which subjective signs of prodrome can be robustly detected at a group level. We also attempted to describe the dynamics of prodrome and the inter-individual variability in prodrome.

On population level, an increase in patient-reported EWSQ sum score was detected as early as 5 weeks before hospitalization. This finding is in line with previous prospective studies reporting an average four-week detectable prodrome in schizophrenia [2,7,16,22,30].

Our subsequent analysis showed significant inter-subject variability in prodrome with most, but not all, relapses being preceded by an increase in EWSQ sum score.

Further visual inspection of the mean EWSQ subscore trajectories revealed that prodrome appears to start much earlier than our initial analysis indicated. In particular, the plot of mean EWSQ sum scores shows an almost monotonic increase in symptoms, starting 10 weeks before hospitalization. This was preceded by a small dip in symptom scores, which may be why the longer prodrome was not identified in the statistical analysis as this effectively compared the EWSQ score at a given time point with all previous values, not just the immediately preceding time point.

To quantify this observation we conservatively smoothed the data, using a three-week moving average to remove noise-related fluctuations. This revealed a gradual, monotonic increase 8 weeks before relapse. The duration of the pre-hospitalization GIP was shown to be statistically significant by a nonparametric bootstrap testing procedure (Table 3B, Fig. 3).

Our results suggest that at population level the pathophysiological processes presumed to underlie overt relapse may be reflected in signs and symptoms over a much longer period than was previously thought.

The GIP seen for the whole group became even more pronounced when EWSQ items were considered separately (Table 3B). This finding may be useful in the development of novel preventive strategies for schizophrenia as three out of the ten items in the patient version of EWSQ are suitable for continuous objective monitoring. Item no. 3 (worsening in concentration, e.g. inability to read a longer text, problem remembering long texts or following the plot of a film or a TV show, problems following conversations among groups of people) seems particularly promising in this respect. The steady, incremental loss of concentration emerged 6 weeks before relapse in our sample (Table 3, also Supplementary A). Further studies to assess the predictive utility of this particular cognitive measure are warranted. It should be noted that use of mobile phone-administered assessment tools is growing area and is technically, financially and practically feasible [17]; this method of data capture may therefore be suitable for transmitting data about longitudinal changes in cognition.

Similarly, a significant and sustained GIP was observed in item no. 5, 'restlessness' (increased compulsion to walk up and down; inability to stay in one place; feelings of inner tension without any obvious cause) and item no. 1 'sleep disturbance' (insomnia; frequent awakening during the night; early morning awakening, difficulty falling asleep). The GIP was started 8 and 6 weeks before relapse for item no.s 5 and 1, respectively. These variables could potentially be tracked using wearable actigraphic sensing systems combined with remote data capture solutions capable of almost real-time analysis of motor behavior and sleep/wake cycle disturbances. Such objective approaches are promising means of extending the prodromal time window during which preventive treatment may be initiated perhaps much further than is possible using psychiatrists', patients' or family members' subjective assessments.

Generally, our findings suggest that there is a continuous and—in contrast to previous reports—protracted period during which the pathophysiological processes presumed to precede relapse are reflected in subjective changes in cognitive, emotional and behavioral indicators that represent the bulk of current early warning signs. Presynaptic hyperdopaminergia is the most commonly reported final common pathway in episodes of psychosis [13,14] and thus represents a candidate underlying mechanism for these changes; in fact levels of catecholamines and their metabolites can be used to predict symptom exacerbation [9,18,31,32]. Overactivity of the dopaminergic system is related to early signs including sleep disturbance [24] and agitation [6]. Elevated dopamine synthesis capacity is clearly related to the occurrence of prodromal symptoms in ultra-high risk clinical subjects who go on to develop a psychotic disorder [6,15]. Taken together this evidence supports the view that early warning signs preceding relapse are related to neurochemical abnormalities.

Our results must be understood in the context of the methodological limitations stemming from the fact that the EWSQ only quantifies deterioration in a given parameter relative to the baseline from the previous week and both improvements and lack of change are coded as a zero score. EWSQ thus provides only asymmetrical information about changes in clinical status. For this reason we can not reconstruct exact time courses for the development of prodromal signs. The GIP before relapse seen in the sample as a whole should be interpreted merely as continuous period of increased density of deteriorations measured by using EWSQ in subjects with schizophrenia.

5. Conclusions

In summary, despite the relatively small sample size, our findings suggest that prodrome may occur over a much longer period than previously reported, and that during this period development of underlying pathophysiological abnormalities which ultimately produce a schizophrenic relapse may be reflected in EWS.

Using patient's subjective reports we were able to retrospectively detect, at group level, the onset of a period of continuous change in EWS as early as two months before relapse.

Continuous monitoring of objective indicators or biomarkers one might achieve even better early detection of impending relapse and hence be able to offer more effective early intervention. Improved understanding of the dynamics of EWS and the phenomenology of prodromal biomarkers may open up new opportunities for developing innovative, personalized, technology-driven tools for continuous monitoring and consequently better relapse prevention strategies in psychotic disorders.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2016.04.044.

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