Perspective

Relapse Risk Assessment in Early Phase Psychosis: The Search for a Reliable and Valid Tool

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A significant advance in the field of mental health during the past 2 decades has been the recognition that early and optimal, phase-specific treatment of mental illness results in better clinical and functional outcome.[1–4] A framework for SEI services for psychosis, focused on the critical period of the first 5 years following the onset of illness,[5] and comprised of pharmacological and psychosocial interventions,[6–9] has been shown to have superior effectiveness in comparison with routine care.[10–12] Importantly, relatively high rates of symptomatic remission rates in response to early intervention and treatment have been reported.[13] However, there is considerable variation in remission rates (24% to 82%), which may be attributed to variation in the criteria used for remission (for example, inclusion of remission of negative symptoms),[14] duration of follow-up period,[15] aspects of the multi-component treatments used,[16] and possible pharmacological treatment options[17] (for example, oral, compared with long-acting injectable) used.

While remission of symptoms is an important early goal of treatment, the principal objective of treatment of early phase of psychosis should be to promote full recovery. Recently, there has been a more optimistic outlook on recovery generated from SEI services, as it is assumed that patients in the early phase are likely to have retained greater motivation and skills to engage in a process that could lead to full recovery in all dimensions.[18, 19] Although recovery is defined on multiple dimensions,[20–23] remission of symptoms still remains an important part of the road to recovery, whether guided by clinical, functional,[14] or a patient's subjective perspective.[23] However, one clinical barrier toward remission, and thus recovery, is the high rate of relapse and the lack of an assessment tool for identification of risk of relapse at this early phase of illness.

Relapse in Early Phase Psychosis

While remission rates are high and recovery is more tangible in early phase psychosis, a sobering statistic that clinicians, patients, and their families face is the relatively high rate of relapse during the first 5 years following initial treatment. In fact, in regular care, 80% of patients with a diagnosis of a first episode of schizophrenia have been reported to experience relapse, often multiple, within 5 years of treatment or remission from their index episode.[24,25] Rates of relapse in SEI services are lower than that reported in regular care,[26,27] but still remain a substantial barrier to recovery. These lower rates (20% to 30% during 2 years) may be, at least partly, associated with the better medication adherence rates[27] achieved in these programs through

better engagement in the multiple components of treatment provided. The significantly high risk of relapse, even with enhanced treatment offered in SEI services, exposes our lack of capacity to predict relapse with any degree of confidence. A reliable prediction of risk for relapse would ensure early intervention and thereby reduce the associated negative effects of relapse and improve overall outcomes.

Why Is Relapse of Psychosis an Important Concern for Clinicians?

Relapse in early phase psychosis can have significant consequences for patients and their families. The most obvious consequence of relapse is its relation to functional outcome through interruption of sustained remission. Indeed, length of remission of both positive and negative symptoms has recently been shown to be by far the most significant predictor of functional outcome (employment, school, and social relationships) at 1 and 2 years follow-up of patients with early phase psychosis.[28] In the latter study, conducted on a large sample of patients with early phase psychosis in an SEI service, length of remission of negative symptoms contributed most to functional outcome at 1 year, while length of positive symptom remission played an even more significant role at 2 years. In addition, relapses undermine a sense of hope and optimism toward their future for young people with psychotic disorders, many of whom are at the age of planning careers, entering post-secondary education, solidifying healthy relationships, and becoming independent. These feelings can be amplified when, as is often the case, relapse follows a period of improvement. Clinically, relapse may potentially elicit behaviours that are dangerous for the individual and others, may lead to future decreases in responses to treatment, and duration of relapses may even be associated with grey matter loss as indicated by a recent report of a prospective longitudinal magnetic resonance imaging study.[29]

Reducing risk of relapse remains one of the greatest challenges in the treatment of psychosis in the early phase and in counteracting the consolidation of negative long-term impacts of the illness during the critical period. Building a method to predict relapse with adequate accuracy could help implement interventions to minimize or prevent relapses, as well as their consequences.

Can We Learn From Other Disciplines in Medicine?

Is it possible to conceptualize relapse risk assessment in early phase psychosis in the manner of the Framingham risk analyses—a simple questionnaire that evaluates one's

Abbreviations

ESS	Early Signs Scale
FEP	first-episode psychosis
SEI	specialized early intervention

risk, the probability of getting coronary heart disease? As this scoring system gives an indication of risk of developing cardiovascular disease, it also identifies people who would benefit the most from prevention strategies, both in lifestyle modifications and pharmacologic treatment (an important point as well in early phase psychosis relapse prevention). Treating patients in this context, who had high Framingham risk scores, has led to a decrease in mortality—an obvious important outcome of the use of such a tool. Another important consideration is that while the Framingham algorithm was developed to predict a first event, not recurrent events, new risk models are being developed and tested for recurrent events that include not only predefined classical risk factors but also markers of vascular damage and disease (and thus many end points).[30] Oncology may be another area of medicine that is relevant to this discussion. Most areas of oncology have developed risk assessment tools, some of which have moved to online prognosis calculators. These fields tend to use multiple factors to determine the risk for cancer recurrence and the likelihood of successful treatment.[31] Here, we argue that a similar conceptual framework and methodology could be used for mental disorders. As in the case of cardiac and cancer care, there will be patients who may not have a relapse after an FEP (estimated at 15% to 20%), while others will have a very high risk of relapse. If we can identify people at varying risks of relapse with the use of an instrument, which is relatively easy to administer in a clinical setting, patients would benefit from more focused treatment and follow-up for managing their risk of relapse. This has been accomplished, at various levels, for risk prediction of depression, but not for early phase psychosis.[32]

How Can We Design an Adequate Assessment Tool to Assist in Early Identification of Risk for Relapse?

A relapse risk assessment tool for early phase psychosis has to consider the current understanding of predictors of relapse risk, based on well-designed cohort studies using multivariate regression techniques for analyses of the data.

A recent systematic review and meta-analyses of the literature specific to relapse in early phase psychosis indicated that, of the 20 predictors that could be used for analyses, 4 independent factors significantly increased the risk for relapse. Medication nonadherence, persistent substance use, care givers' criticism (not expressed emotion), and poorer premorbid adjustment increased the risk of relapse 4-, 3-, 2.3-, and 2.2-fold, respectively.[33] A different line of investigation has also attempted to identify a set of nonpsychotic symptoms and other behaviours as prodromal to a relapse.[34,35] Based on the latter, other investigators have designed a list of behaviours as early warning signs to be used while monitoring patients for relapse during follow-up.[36] In addition, clinicians have often observed that patients tend to show behaviours prior to each relapse that are similar to the prodromal symptoms or behaviours that preceded the FEP. However, little is known about how

patients and their families experience early signs of relapse, and what they regard as particularly important predictors or early signs, and their value in predicting relapse.

An important process in the development of this tool is the consideration of known risk factors for relapse in early phase psychosis, generic early warning signs, and perspectives of patients and families to inform risk in a given individual. External validation in multiple geographic areas of the country and in different settings (community and academic clinics) will be an important step in the development of a tool that would have high clinical utility. This can be accomplished with the collaboration among sites involved in the Canadian Consortium for Early Intervention in Psychosis. This collaboration around validation will also be beneficial to ensure consensus about its eventual uptake. Once this tool has been validated, it will be equally important to evaluate the impact that the use of this tool has in the clinical setting. This can take on various forms, including randomized trials (for example, comparing relapse rates in cohorts exposed to the tool with cohorts not exposed) or observational (for example, relapse rates or severity in time period prior to use of scale, compared with after). Potential impact of prognostic tools, while important, has been lacking in the development of other similar tools,[37] even though the overall end goals are to improve patient outcomes and cost-effective care.

Currently, available tools for relapse assessment are not inclusive of all identified risk factors, nor are they necessarily illness-phase specific. A review of 15 quantitative scales relevant to preventive interventions for influencing the course of schizophrenia[38] reported on the inability of these scales to be sensitive and specific in identifying people at high risk for developing psychosis. Additionally, these authors posited that these instruments were developed for people with psychotic disorders of longer duration and were subsequently applied to early phase psychosis, with resulting measurement issues. To illustrate this, the ESS,[39] used to identify relapse in schizophrenia, can identify a particular state putatively preceding a relapse of psychotic symptoms with modest predictive validity; however, it was not developed for assessing relapse in early phase psychosis. It does not ask about known predictors of relapse in early phase psychosis, such as adherence and substance use. In its application to an FEP group, the ESS reached adequate sensitivity, but poor specificity and positive predictive validity for relapse.[40] Numerous instruments exist to help identify and quantify the specific relapse predictors reported in the literature (for example, Premorbid Adjustment Scale, Chemical Use, Abuse and Dependence Scale, Expressed Emotions). However, these rating scales or interviews are research instruments, each assessing a specific domain, and would have very poor use in a clinical setting.

An assessment tool for evaluation of risk of relapse during the critical period following onset of psychosis should incorporate currently established risk factors, behaviours regarded as early warning signs derived from literature, and

from historical accounts of each individual patient's history, covering the period leading to the initial onset of psychosis. This would potentially be supplemented by information gathered from qualitative studies involving focus groups, with patients and families to obtain an in-depth experiential perspective on relapse from them. The themes derived from the qualitative work could be added to enhance the assessment tool prior to establishing its psychometric properties, validation, use, and impact in a clinical setting.

Summary

To prevent negative consequences of an illness, such as a psychotic disorder, the first step is to be able to identify early the event that needs to be prevented. It would seem obvious that given the enormity of potential personal, family, and societal problems associated with relapse in psychosis, and its high frequency during the first few years of illness, that a tool to identify the risk for relapse early in the course is very likely to have a positive influence on eventual outcomes. Currently, this tool does not exist, but its development would be welcomed.

Acknowledgements

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