Prodromal Symptoms vs. Early Warning Signs and Clinical Action in Schizophrenia

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Abstract

The term "prodromal symptoms" has traditionally referred to pre-psychotic changes in thought, affect, and cognition that precede the initial onset of schizophrenia. Recently, however, the term has been extended into a clinical action context to refer to the early warning signs (EWS) of impending relapse in patients already diagnosed as having schizophrenia. However, recent reports reviewed by Norman and Malla (1995, this issue) use a narrow definition of prodromal symptoms and question their use in the clinical action context. We argue that the dual use of the term "prodromal symptoms" has led to conceptual confusion and to the impression that EWS cannot be used effectively for clinical action. The ability to base clinical action on EWS is central to schizophrenia therapeutics and is the cornerstone of pharmacological strategies based on early intervention. Our review of the evidence suggests that the effective clinical use of EWS depends on (1) the inclusion of both psychotic and nonpsychotic symptoms as EWS; (2) the use of clinician judgment in combination with predefined symptom changes to define the occurrence of EWS; (3) frequent clinical visits; and (4) the use of family or caregiver informants. We therefore suggest that, in the clinical action context, the terminology "early warning signs of impending relapse" should be used instead.


The concept of prodromal symptoms in schizophrenia has traditionally referred to the subtle pathological deviations in thought, affect, and behavior that precede the initial onset of overt psychosis. Such deviations are typically subclinical forms of thought disorganization, psychosis, and negative symptoms. Individuals may express various unusual or odd beliefs that are not of delusional proportions; their speech may be generally understandable but regressive, vague, or overly abstract or concrete; and their behavior may be peculiar. In addition to these positive-like symptoms, individuals may lose interest in activities and become socially withdrawn, less talkative and inquisitive, and/or less affectively expressive. Such negative-like symptoms are often the first signs that something is wrong; family members may ultimately report that the individual seemed to be "gradually slipping away" (American Psychiatric Association 1994). The occurrence and nature of prodromal symptoms is particularly clear in patients with an insidious onset of illness, for whom such symptoms may emerge gradually over many years.

In recent years, the use of the term "prodromal symptoms" has been extended into a clinical action context to refer to the early warning signs (EWS) of impending relapse in patients already diag-
nosed as having schizophrenia (Docherty et al. 1978; Herz and Melville 1980; Carpenter and Heinrichs 1983). Several studies have suggested that the identification of these EWS can be used to quickly redirect clinical care and effectively interrupt the relapse process (Carpenter et al. 1987, 1990; Jolley et al. 1989, 1990; Herz et al. 1991; Pietzcker et al. 1993; Marder et al. 1994). Although such use would apparently be less effective than continuous medication, it could be tremendously beneficial in treating schizophrenia, particularly in community-based settings. For example, if exposure to particular stressors gives rise to EWS in part precipitating a relapse, the identification of these signs would allow the clinical care team to intervene by decreasing environmental demands, providing closer monitoring, offering more support, and increasing pharmacological protection.

Additionally, where clinical care is attempting to minimize drug exposure, it should be anticipated that low-dose, continuous medication strategies will require periodic temporary increases in medication to ensure maximum protection at times of increased risk or impending relapse. This is especially relevant for patients who are off medication. Patients may be off medication for clinical reasons (e.g., emerging dyskinesia, pregnancy) or as part of research participation or a placebo-controlled clinical trial, or they may be using experimental medication that may prove ineffective. The most common reason for schizophrenia outpatient to be off medication, however, is patient noncompliance. Many noncompliant patients intensely dislike the experience of medication during periods of stability, and some will therefore comply with rapid neuroleptic intervention on a temporary basis to reduce risk at times of impending relapse. Here too, then, the early detection of a relapse process can enhance the effectiveness of therapeutic interventions (Heinrichs et al. 1985).

Given the clinical importance of using an early detection/rapid intervention clinical strategy to minimize symptom exacerbation, the appearance of recent reports questioning the specificity, sensitivity, and predictive value of prodromal symptoms (Norman and Malla 1995, this issue) is of considerable concern. Herein we offer an alternative view to Norman and Malla’s conclusion that prodromal symptoms are of limited clinical value in the clinical action context, and we argue for a broader definition, which includes nonpsychotic and psychotic symptoms under the concept of EWS.

**Predictive Power**

The controversy over the clinical utility of EWS revolves around two major issues: (1) Whether EWS have sufficient predictive power to facilitate effective clinical intervention, and (2) how best to define EWS used in the clinical action context.

The predictive power of EWS is related to their sensitivity and specificity. Sensitivity refers to the proportion of exacerbations that are actually preceded by EWS (true positive rate), whereas specificity refers to the proportion of nonexacerbated patients who do not exhibit EWS (true negative rate). The positive predictive value (PPV) is the probability that observed EWS will actually be followed by an exacerbation. Effective intervention will deflate estimates of PPV. The negative predictive value (NPV) represents the probability that a patient who is not exhibiting EWS will not proceed to exacerbation. A high NPV simply means that the absence of EWS today is validly reassuring about exacerbation in the immediate future. For clinical intervention, the clinician needs good sensitivity, but a high PPV is crucial.

**Predictive Power of Narrowly Defined Prodrome**

Norman and Malla (1995, this issue) reviewed six studies (Birchwood et al. 1989; Jolley et al. 1990; Tarrier et al. 1991; Gaebel et al. 1993; Malla and Norman 1994; Marder et al. 1994) that formally assessed the predictive power of prodromal symptoms. Because effective interventions will alter predictive power, we have selected for further comment the three studies (Jolley et al. 1990; Gaebel et al. 1993; Marder et al. 1994) in which treatments were controlled variables. These are also more comparable, as they are 2-year longitudinal studies in which clinicians rated nonpsychotic prodromal symptoms.

In the context of a double-blind comparison of placebo versus low-dose maintenance neuroleptic treatments in which all patients received targeted oral neuroleptic at prodrome, Jolley et al. (1989, 1990) report a first-year sensitivity rate of prodromal symptoms of 73 percent and a 2-year rate of 53 percent. The PPV was only 16 percent for the 2 years. However, the authors note that effective treatment interventions may prevent
progression to relapse and may thereby falsely reduce the PPV to an undetermined extent. Although it is the natural course following prodromal symptoms that is crucial in evaluating the PPV, altering the natural course is exactly the point of treatment interventions.

Gaebel et al. (1993) evaluated nonpsychotic prodromal symptoms in their three treatment groups (maintenance, early intervention, and crisis intervention) during a 24-month observation period and report sensitivities of 7.7, 14.4, and 10.3 percent; PPVs of 21.4, 15.3, and 42.9 percent; and specificities of 90.3, 70.4, and 93.0 percent, respectively. The maintenance and crisis intervention groups provide the best estimates of the PPV, given that the early intervention group received the most active intervention when prodromal symptoms were observed. The treating/rating psychiatrists were not blind to treatment condition and may have had a lower threshold for judging the presence of prodromal symptoms in the early intervention group in order to facilitate the initiation of treatment. The higher rate of relapses predicted by prodromal symptoms and the lower PPV in the early intervention group as compared with the other two groups is consistent with this proposition. However, the reported sensitivities and PPVs are too low for meaningful clinical application.

Marder et al. (1994) recently published the only double-blind comparison of placebo with neuroleptic add-on for the treatment of nonpsychotic prodromal symptoms. All patients were stabilized and maintained on low-dose neuroleptics and were monitored for prodromal symptoms, which were diagnosed according to an individualized severity “cutoff” for each patient. When prodromal symptoms were observed, patients were randomly assigned to receive more neuroleptic or placebo. These investigators found a 37-percent sensitivity and a 43-percent PPV. However, they noticed that the PPV changed as the patients were evaluated longer. For the group randomized to placebo, the PPV increased from 29 to 63 percent between the first 6 months and the last 18 months of the study. For the patients treated with neuroleptics, the PPV decreased from 50 to 29 percent during the same time periods. This decrease was interpreted as an improvement over time in the ability of clinicians to predict when a patient was on the verge of exacerbation and as evidence of the effectiveness of intervention. Such an interpretation is plausible and supports the utility of clinical action based on prodromal symptoms. However, the sensitivity of these symptoms is too low for clinicians to rely on nonpsychotic prodromal symptoms as part of a general treatment strategy for relapse prevention.

Prodromal Symptoms Versus EWS

These three studies suggest that there are significant problems in the predictive power of narrowly defined nonpsychotic prodromal symptoms, that the sensitivity and the PPV of these symptoms are unacceptably low, and that such symptoms are therefore not practical guidelines for clinical application (Gaebel et al. 1993). Clinicians treating patients with chronic and exacerbating illnesses are concerned that worsening in any component of the illness may signal an exacerbating process. This is particularly true for schizophrenic patients, who are not usually completely symptom free between illness episodes. Concern for illness exacerbation is heightened when baseline symptoms begin to worsen and/or when prodromal or other new symptoms emerge. The clinician is concerned not with the conceptual problem of whether the observed change precedes exacerbation or is merely the first indication of this process, but rather with detection and intervention. Thus, restricting the definition of EWS to nonpsychotic phenomena relates to a conceptual distinction that is irrelevant to clinical action. In fact, Malhi and Norman (1994) have found evidence to suggest that “much of the predictive usefulness of the non-psychotic symptoms may be because they themselves are related to early and subtle signs of psychosis” (p. 490).

The Jolley et al. (1990), Gaebel et al. (1993), and Marder et al. (1994) studies, through their demonstration of the limited utility of restricted definitions of EWS, provide indirect support for the need to include both psychotic and nonpsychotic symptoms.

The theoretical question of the architecture of relapse is not adequately addressed in action-oriented clinical trials that deal with clinical care delivery questions. In the clinical action context, the issue is whether some change in clinical status predicts symptom exacerbation, enabling a change in clinical care that can effectively reduce the probability of significant symptom progression. Clinicians who follow patients presume that they can detect signs of worsening and respond clinically. Indeed, when the definition of EWS is
broadened to include both psychotic and nonpsychotic symptoms, Carpenter et al. (1987) have found this presumption to be valid.

In contrast to Jolley et al. (1990), Gaebel et al. (1993), and Norman and Malla (1995; this issue), we find that the clinical trials data support the hypothesis that EWS of relapse can be detected and met with prompt, effective clinical action. Most studies examining the efficacy of targeted versus continuous prophylactic medication approaches (Carpenter et al. 1990; Jolley et al. 1990; Herz et al. 1991; Gaebel et al. 1993; Schooler et al. 1993) have found continuous approaches to be more effective in preventing relapse. However, the rate of severe relapse and hospitalization in patients whose treatment was targeted appears less than would be expected had not EWS triggered a rapid neuroleptic intervention. It was not prudent to establish actual contemporaneous, no-treatment base rates for relapse in these studies, but two Maryland studies nonetheless provide direct evidence that targeted intervention based on the presence of EWS was efficacious. In the first study (Carpenter et al. 1987), a targeted drug strategy was combined with enhanced psychosocial clinical care aimed at facilitating early detection and rapid intervention. This approach was compared with continuous medication administered in the context of a standard treatment paradigm. Although the standard treatment paradigm represented a still somewhat enriched model of clinical care (patients were seen every other week rather than weekly, as in the targeted drug group, or every 4–8 weeks, as in the clinics that would ordinarily have provided care to these patients), no differences emerged over the course of 2 years in rates of relapse, attrition, or rehospitalization. It was in the second Maryland study (Carpenter et al. 1990), when continuous medication was similarly enhanced with a clinical care emphasis on close monitoring, early detection, and medication increase, that continuous medication proved superior to targeted medication for relapse prevention. Even here, however, most global measures of clinical course did not differentiate the two treatments during 2 years.

Despite their finding that a continuous medication approach is more effective in preventing relapse, Gaebel et al. (1993) also provide direct evidence of the efficacy of the targeted approach. They found that the relapse rate was significantly lower for those receiving early intervention response to narrow prodromal symptoms compared with those receiving crisis intervention, even though the former group did not receive more total neuroleptic dosage or more clinical support. Taken together, these studies suggest that detecting EWS (the Maryland studies: Carpenter et al. 1987, 1990) or nonpsychotic prodromal symptoms (the German study: Gaebel et al. 1993; Pietzcker et al. 1993) and providing an active intervention is an effective relapse prevention strategy that is superior to no treatment even if inferior to continuous medication.

Recently, Herz et al. (1994; Lamberti, personal communication, May 1994) presented preliminary data on the clinical advantage of an early intervention psychosocial program for schizophrenia outpatients that includes active monitoring of nonpsychotic and mild psychotic EWS, weekly group therapy, and biweekly family education. The standard treatment group includes biweekly individual supportive therapy and family intervention as needed. Antipsychotic medications are not controlled. During the first 6 months of treatment, the early intervention group required significantly fewer days in the hospital with a trend toward fewer patients hospitalized and fewer hospitalizations per patient.

Other Factors Related to the Usefulness of EWS

Additional methodological issues are important for understanding the results of the studies reviewed by Norman and Malla (1995, this issue). The number of patient visits, the level of involvement of family members, and judgments about the clinical significance of symptom exacerbations may all enhance the clinical utility of EWS. The 2-year London study (Jolley et al. 1990) raises the most significant challenge to the clinical utility of EWS, but the absence of close clinical monitoring and the reliance on strict prodromal symptom definitions rather than on usual clinical criteria may have significantly hindered optimal clinical care. The German study, in fact, demonstrated that defining prodromal symptoms from rating scale data that are devoid of clinical judgment of significance generates little in the way of a relationship between prodromal symptoms and relapse. Prediction improved (although sensitivity was still low) when clinical judgment was combined with rating scale data.

Further, the London and German studies provided infrequent
observation, usually once a month. Gaebel et al. (1993) found that incorrect predictions of relapse occurred more often when there were longer time intervals between assessments. At each monthly visit, patients were classified as prodromal (nonpsychotic), relapsed, stable, or another state, which included psychotic symptomatic worsening. The false negative rate (i.e., relapse without prodromal symptoms) was high. However, it is likely that broadening the definition of prodromal symptoms to include psychotic “worsening states” would increase the sensitivity and the PPV without remarkably reducing the high specificity rates observed. This would be consistent with ordinary clinical reasoning in which intervention is based on any valid predictor without regard for strict criteria or semantic distinctions.

Linking EWS to effective intervention also involves using as informants family members or other caregivers who maintain intimate contact with the patient. Jolley et al. (1990), explaining the marked loss of sensitivity from the first to the second followup years, noted that “a single teaching session at the beginning of the study does not provide patients and families with an adequate grasp of the paradigm of the intermittent treatment strategy” (p. 839). In optimal clinical care, clinicians will see patients often enough to prevent a substantial time gap between EWS manifestation and detection. The longer the time between the actual emergence of EWS and their clinical detection, the more time the relapse phenomenon has had to progress. Any such delay is expected to undermine the treatment intervention, and this effect is robust (Heinrichs et al. 1985). Use of the patient’s insight and of observations of informed family members, however, can extend the clinician’s capacity to detect change beyond the formal clinic visits.

**EWS in a Controlled Treatment of Relapse Prevention**

The importance of these methodological issues is underscored by the preliminary results of a study in which we test the hypothesis that diazepam, administered to nonmedicated patients at the first appearance of EWS, can prevent relapse progression. If this hypothesis is correct, it would enhance clinical care by providing an effective alternative to initiating or increasing neuroleptic treatment when minor signs of worsening are present. This may be especially important if the PPV is low and clinicians are hesitant to increase neuroleptic dosage unless they are confident that the patient is truly deteriorating. Placebo and fluphenazine are the comparative treatments. The decision to implement treatment is based on a definition of EWS that combines predefined changes in Brief Psychiatric Rating Scale (Overall and Gorham 1962) ratings with a clinician’s judgment that the patient is in an early stage of relapse. Patients whose symptoms worsen despite treatment with either of the three experimental treatments and who meet predefined criteria for further exacerbation are then treated with neuroleptics at a point in the progression intended to be compatible with successful outpatient management and prevention of severe relapse. The patients are seen weekly, and they and their caregivers are educated extensively on the importance of identifying and reporting changes in the clinical condition of the patient. The presence of the placebo group provides a specific opportunity to determine the sensitivity and PPV of using EWS to detect the beginning of relapse.

In the initial 20 patients randomly assigned to receive placebo, 16 progressed to the second stage of the relapse process, suggesting a PPV of 80 percent (i.e., 80% of the patients identified as beginning a relapse phenomenon actually gave evidence that this was a valid judgment). The 80-percent figure will underestimate the PPV to the extent that placebo was effective (which it is more often than is no treatment) and that psychosocial intervention mitigated against progression. All patients reaching the criteria for the second stage of the relapse process were previously detected at the initial stage (100% sensitivity).

These data support the utility of monitoring for EWS with a clinical treatment plan designed for rapid intervention. From a clinical care perspective, it is not reasonable to implement such a treatment strategy in circumstances that preclude frequent patient observation, that fail to allow for relevant information from other observers, that rely on rating scale data to the exclusion of clinical judgment, or that neglect signs of clinical worsening that do not fit a narrow concept of EWS.

**Conclusions**

The term “prodrome” has come to have two prominent meanings in schizophrenia: the early, morbid,
nonpsychotic behavioral changes that occur before onset of schizophrenia psychosis, and, in the clinical action context, the early changes in clinical state that presage relapse. These dual meanings have led to confusion and an arbitrary restriction in the type of symptoms used in the clinical action context. Norman and Malla (1995, this issue) propose restricting the defining criteria for prodrome to nonpsychotic symptoms. This change may improve the architectural study of the phenomenology of relapse, but it is ill applied in the clinical action context. The clinician's task is to identify any change that suggests impending relapse without conceptual consideration as to whether it is an emergence or an intensification of a baseline psychotic symptom or the emergence of nonpsychotic warning signs, such as agitation and insomnia. In fact, it is common in schizophrenia treatment to have patients in partial remission whose psychotic symptoms are less intense and more stable than during periods of exacerbation. In clinical care, it is the action-oriented EWS concept rather than the phenomenologically refined prodrome concept that is operative. The Maryland group has contributed to this semantic confusion by sometimes using the term "prodrome" when discussing the EWS concept. As an alternative, we suggest the terminology "early warning signs of impending relapse." This wording appears far more appropriate in light of the problems reflected in the studies reviewed by Norman and Malla (1995, this issue) and discussed in this article. If we are correct in our argument, the doubt cast on the clinical utility of prodromal symptoms by applying a strict definition is eradicated by applying a clinically valid approach to EWS.

References


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