Prodromal Symptoms and Relapse Prevention in Schizophrenia

by Marvin I. Herz and J. Steven Lamberti

Abstract

The value of monitoring for prodromal symptoms in patients with schizophrenia has been questioned by some investigators who point out that their positive predictive value, sensitivity, and specificity can be low in relation to relapse. This article focuses on methodological and conceptual issues which should be considered in evaluating the usefulness of prodromal symptoms and behaviors as part of the relapse process. The article presents the following conclusions: Many relapses are preceded by the appearance of prodromal symptoms and behaviors which may last from a few days to a few weeks or more. The presence of prodromal symptoms often does not predict impending relapse since the probability of progression to relapse depends on the complex interaction of many personal and environmental factors including the availability of prompt and effective psychiatric intervention. Finally, studies have shown that monitoring for prodromal symptoms and early intervention when they emerge is effective in reducing the likelihood of relapse in individuals with schizophrenia.


Webster's dictionary defines “prodrome” as a warning symptom indicating the onset of a disease (Guralnik 1980). In psychiatry, while relatively little attention has been given to prodromal symptoms, most of the attention has focused on prodromal symptoms in schizophrenia. Controversy has arisen recently regarding the clinical significance of these symptoms and their usefulness in predicting relapse in schizophrenia. The purpose of this article is to present a clinical and conceptual perspective of prodromal symptoms based on a review of the literature and the authors’ own clinical experiences.

Early conceptualizations of prodromal symptoms in schizophrenia focused on their occurrence before the initial onset of diagnosable illness. Kraepelin wrote of the existence of “noticeable prodromata,” consisting of insidious personality changes that preceded the onset of dementia praecox (Kraepelin 1919/1971). The concept of an early “prodromal phase” of schizophrenia remains in DSM-IV (American Psychiatric Association 1994), described as “the slow and gradual development of a variety of signs and symptoms (e.g., social withdrawal, loss of interest in school or work, deterioration in hygiene and grooming, unusual behavior, outbursts of anger)” (p. 282). Because it is important to differentiate a prodromal phase in the onset of first-episode schizophrenia from one in the onset of relapse in patients with established schizophrenia, we will use the term “prodromal symptoms” to refer to those symptoms that have reportedly occurred before relapse in schizophrenia.

Studies of prodromal symptoms in schizophrenia have addressed three basic questions:

1. Is relapse usually preceded by prodromal symptoms? If so, what are the typical prodromal symptoms?
2. Does the presence of prodromal symptoms predict relapse? If not, what are possible reasons?

3. Is monitoring for prodromal symptoms and intervening early when they occur effective in preventing relapse?

**Is Relapse Usually Preceded by Prodromal Symptoms?**

Docherty et al. (1978) reviewed the literature on the process of relapse in schizophrenia, which consists primarily of detailed case reports based on retrospective observations by clinicians. Despite the lack of empirical data, the authors observed a "remarkable consistency" in descriptions of the relapse process. They noted that relapse is a gradual process that can be divided into five stages, with the first two being characterized by nonpsychotic symptoms. The five stages are as follows:

1. Overextension. In this phase, characterized by a feeling of being overwhelmed and of having to "run faster and faster just to keep up," (Docherty 1978, p. 426) anxiety, irritability, and distractibility are common.

2. Restricted consciousness. Boredom, apathy, and listlessness are characteristic features, as a person's range of thought narrows, and social withdrawal and decreased movement occur.

3. Disinhibition. Relatively unmodulated expression of impulses begins to appear and may resemble hypomania.


5. Psychotic resolution. Anxiety is decreased as psychotic organization occurs in the form of systematized delusions or massive denial.

Although subsequent retrospective and prospective empirical studies of the relapse process have not validated the presence of the first three stages as distinct entities, some symptoms and behaviors described in the first two stages have reportedly occurred in the prodromal phase of relapse. It is possible that these stages are more relevant to first-break patients.

**Empirical Studies: The Duration of Prodromal Symptoms Before Relapse.** Seeking to determine the feasibility of conducting an intermittent drug study that would involve taking stable outpatients off medication and resuming it only when early signs of relapse appear, the senior author noted that there was no large-scale empirical study of early signs and their duration before relapse. He and a colleague subsequently developed a structured rating scale (the Early Signs Questionnaire), which they used to examine a large sample of patients and family members from two locations over a 2-year period (Herz and Melville 1980). The authors interviewed 99 stable outpatients and 80 family members in Atlanta, Georgia, and 46 inpatients in Buffalo, New York, who were recovering from a psychotic episode. Patients and family members were asked whether there were any changes in the patient's thoughts, feelings, or behaviors before the most recent episode of acute psychosis, and how long before relapse these changes were noticeable. Approximately half of all patients and 68 percent of all family members stated that the interval between noticeable changes and relapse lasted at least 1 week. However, approximately 15 percent of Buffalo patients and 8 percent of Atlanta patients and their families noted that the interval lasted only 1 to 3 days, while 7 to 8 percent of patients and 11 percent of family members stated that it was less than 1 day.

In a prospective study of 50 outpatients, Subotnik and Nuechterlein (1988) reported significantly higher Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) ratings during a 6- to 8-week period before psychotic relapse. Similarly, in their prospective study of 56 outpatients using the Psychiatric Assessment Scale (PAS; Krawiecka et al. 1977) Tarrier et al. (1991) reported significantly increased symptoms during a 1-month period before relapse. In another prospective study, Birchwood et al. (1989) reported that 75 percent of relatives noted increased symptoms more than 2 weeks before relapse using the Early Signs Scale (Birchwood et al. 1989). And in a recent retrospective study, Henmi (1993) reported that 64 percent of patients had increases on their Psychiatric Rating Scale 4 weeks before relapse; interestingly, however, these same patients showed no detectable changes over the same period on a coarser measure, the Global Assessment Scale (GAS; Endicott et al. 1976). These studies demonstrate that relapse is a gradual process for most patients and is usually preceded by a variety of noticeable changes, which may last from a few days to several weeks or more.
Empirical Studies: What Are the Typical Prodromal Symptoms?

In the Herz and Melville (1980) study using the Early Signs Questionnaire, patients and their family members were asked, “What were the earliest symptoms to either appear or worsen before the patient became so sick that hospitalization was necessary?” The responses are summarized in Table 1. It is noteworthy that there was a high rank-order correlation of symptoms reported between the two different groups of patients ($r = 0.85, p < 0.001$) and between patients and their family members ($r = 0.78, p < 0.001$). The changes most often reported by respondents were symptoms of dysphoria that nonpsychotic individuals experience under stress, including tension and nervousness, eating less, difficulty concentrating and remembering, trouble sleeping, and depression. Mild psychotic symptoms were also reported, but not as often.

A number of retrospective and prospective studies have since reported symptoms very similar to those found in the Herz and Melville study.

### Table 1. Prodromal symptoms reported by patients and families

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Buffalo group $(n = 46)$</th>
<th>Patients $(n = 99)$</th>
<th>Families $(n = 80)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tense and nervous</td>
<td>1  80.4</td>
<td>1  70.7</td>
<td>1  83.3</td>
</tr>
<tr>
<td>Eating less</td>
<td>2  71.7</td>
<td>10 49.5</td>
<td>17 52.5</td>
</tr>
<tr>
<td>Trouble concentrating</td>
<td>3  69.6</td>
<td>5  56.6</td>
<td>3  76.3</td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td>4  67.4</td>
<td>3  61.6</td>
<td>7  68.8</td>
</tr>
<tr>
<td>Enjoy things less</td>
<td>5  65.2</td>
<td>8  52.5</td>
<td>8  67.5</td>
</tr>
<tr>
<td>Restlessness</td>
<td>6  63.0</td>
<td>4  58.6</td>
<td>2  78.8</td>
</tr>
<tr>
<td>Can't remember things</td>
<td>6  63.0</td>
<td>14 46.5</td>
<td>10 60.0</td>
</tr>
<tr>
<td>Depression</td>
<td>8  60.9</td>
<td>2  63.6</td>
<td>3  76.3</td>
</tr>
<tr>
<td>Preoccupied with one or two things</td>
<td>9  59.6</td>
<td>12 48.5</td>
<td>9  65.0</td>
</tr>
<tr>
<td>Seeing friends less</td>
<td>9  59.6</td>
<td>7  54.5</td>
<td>18 50.0</td>
</tr>
<tr>
<td>Am being laughed at, talked about</td>
<td>9  59.6</td>
<td>9  51.5</td>
<td>14 53.8</td>
</tr>
<tr>
<td>Loss of interest in things</td>
<td>12 56.5</td>
<td>5  56.5</td>
<td>6  73.8</td>
</tr>
<tr>
<td>More religious thinking</td>
<td>13 54.3</td>
<td>10 49.5</td>
<td>19 47.5</td>
</tr>
<tr>
<td>Feeling bad for no reason</td>
<td>13 54.3</td>
<td>19 40.4</td>
<td>22 37.5</td>
</tr>
<tr>
<td>Feeling too excited</td>
<td>15 52.2</td>
<td>25 30.3</td>
<td>14 53.8</td>
</tr>
<tr>
<td>Hear voices, see things</td>
<td>16 50.0</td>
<td>17 42.4</td>
<td>10 60.0</td>
</tr>
<tr>
<td>Feeling worthless</td>
<td>17 48.8</td>
<td>15 44.5</td>
<td>12 56.3</td>
</tr>
<tr>
<td>Talking in nonsensical way</td>
<td>18 45.6</td>
<td>13 47.5</td>
<td>3  76.3</td>
</tr>
<tr>
<td>Believe someone else is controlling</td>
<td>18 45.6</td>
<td>18 41.4</td>
<td>21 38.8</td>
</tr>
<tr>
<td>Bad dreams</td>
<td>18 45.6</td>
<td>21 38.4</td>
<td>23 33.8</td>
</tr>
<tr>
<td>Too aggressive (pushy)</td>
<td>18 45.6</td>
<td>24 32.3</td>
<td>20 40.0</td>
</tr>
<tr>
<td>Feeling angry at little things</td>
<td>22 41.3</td>
<td>22 33.3</td>
<td>14 53.8</td>
</tr>
<tr>
<td>Not caring about way I look</td>
<td>22 41.3</td>
<td>19 40.4</td>
<td>12 56.3</td>
</tr>
<tr>
<td>Having trouble with spouse, mate</td>
<td>24 30.4</td>
<td>26 29.3</td>
<td>29 20.0</td>
</tr>
<tr>
<td>Thoughts of hurting, killing self</td>
<td>24 30.4</td>
<td>22 33.3</td>
<td>26 31.3</td>
</tr>
<tr>
<td>Frequent aches, pains</td>
<td>26 28.3</td>
<td>27 28.3</td>
<td>23 33.8</td>
</tr>
<tr>
<td>Fear of going crazy</td>
<td>26 28.3</td>
<td>15 44.5</td>
<td>23 33.8</td>
</tr>
<tr>
<td>Thoughts of hurting, killing others</td>
<td>28 23.9</td>
<td>29 10.1</td>
<td>27 27.5</td>
</tr>
<tr>
<td>Drinking more, using drugs</td>
<td>29 21.7</td>
<td>28 20.2</td>
<td>28 25.0</td>
</tr>
</tbody>
</table>

Note.—Spearman rank-order correlation for Buffalo patients and Atlanta patients = 0.85, and for Atlanta patients and families = 0.78 ($p < 0.001$). Reprinted with permission from Herz and Melville (1980). Copyright © American Journal of Psychiatry, 1980.
those found by Herz and Melville (1980) before relapse (Marder et al. 1984; Heinrichs and Carpenter 1985; McCandless-Glimcher et al. 1986; Subotnik and Nuechterlein 1988; Jolley et al. 1989, 1990; Kumar et al. 1989; Herz et al. 1991; Marder et al. 1991; Tarrier et al. 1991; Henmi 1993). Despite using different rating scales and methods, these studies have consistently demonstrated the presence of typical dysphoric and mild psychotic symptoms before relapse. Such symptoms either emerged for the first time or were more pronounced than they had been at baseline. Some patients and families also noticed changes in observable behaviors before relapse; these included social withdrawal, wearing makeup in excessive or bizarre ways, and wearing dark sunglasses inappropriately.

**Does the Presence of Prodromal Symptoms Predict Relapse?**

A number of recent studies have examined the power of prodromal symptoms in predicting relapse in schizophrenia (Birchwood et al. 1989; Jolley et al. 1990; Marder et al. 1991, 1994; Tarrier et al. 1991; Gaebel et al. 1993; Malla and Norman 1994). Specifically, these investigators examined the sensitivity and specificity of prodromal symptoms. As noted by Bustillo et al. (1995, this issue) sensitivity refers to the proportion of relapses that are actually preceded by prodromal symptoms (true positive rate), whereas specificity refers to the proportion of nonrelapsed patients who do not experience prodromal symptoms (true negative rate). In these studies, the sensitivity of prodromal symptoms ranged from approximately 8 percent (Gaebel et al. 1993) to 63 percent (Birchwood et al. 1989; Tarrier et al. 1991), while the specificity ranged from approximately 60 percent (Marder et al. 1991) to approximately 90 percent (Gaebel et al. 1993; Malla and Norman 1994).

To assess the ability of prodromal symptoms to predict relapse, investigators calculated the positive predictive value (PPV) of prodromal symptoms (Jolley et al. 1990; Gaebel et al. 1993; Marder et al. 1994). The PPV represents the likelihood that prodromal symptoms will be followed by a relapse. This figure was reported to range from a low of 15.3 percent in the early intervention group during a 2-year study of intermittent medications (Gaebel et al. 1993), to a high of 48 percent in the control group during a 2-year study comparing fluphenazine with placebo supplementation for treatment of prodromal signs (Marder et al. 1994).

The results of these studies have led some investigators to conclude that prodromal symptoms are probably of limited value in predicting relapse. But one might ask whether prodromal symptoms should always predict relapse. Should it be expected that once prodromal symptoms are noted, the process of relapse is irreversible? Many personal, environmental, and therapeutic factors can influence the course of relapse after prodromal symptoms appear. Recognizing the role of these factors is central to understanding the relationship between prodromal symptoms and the process of relapse.

**Prodromal Symptoms and the Vulnerability-Stress Model of Schizophrenia.** The influence of personal and environmental factors on the process of relapse may be understood in the context of the vulnerability-stress model of schizophrenia. This model, which was originally conceptualized in an effort to establish a common denominator among several divergent approaches to the etiology of schizophrenia and relapse (Zubin and Spring 1977), is based on two well-established observations. First, most patients with schizophrenia have periods of active psychosis alternating with periods of partial or complete remission of symptoms. Second, stress plays a role in the exacerbation of symptoms. It should be noted that stress can originate from sources either internal or external to the individual, and that conditions that are stressful to one individual may not be stressful to another.

The vulnerability-stress model proposes that each patient with schizophrenia is endowed with a degree of vulnerability that, under certain conditions, will express itself as an episode of psychosis. The model makes a clear distinction between vulnerability, which is an enduring trait, and episodes of psychosis, which are intermittent. Many patients with schizophrenia are noted to have an ongoing inability to regulate strong affects (Carr 1983; Hogarty et al. 1995). This inability may be viewed as an enduring trait or vulnerability that can result in relapse under certain conditions. According to figure 1, which illustrates the relationship between challenging life events and vulnerability as originally proposed by Zubin and Spring (1977), acute symptoms of illness will result when the level of stress induced...
by challenging events exceeds a patient's threshold of vulnerability.

In discussing the threshold of vulnerability, Zubin and Spring emphasize the Selyean (Selye 1973) notion that strain on any organism will naturally set in motion that organism's adaptive capacities. The crucial role of personal coping and environmental supports in protecting vulnerable individuals from the effects of stress was subsequently elaborated on by Nuechterlein (1987). The ability of these factors to reduce prodromal symptoms has received little attention, however, and such recovery is often regarded as a "spontaneous remission" of symptoms. As noted by Beitman (1993), "The term spontaneous implies a kind of action out of the blue that cannot be explained. Spontaneous change in pharmacotherapy and psychotherapy is not so mysterious.... Patients are often scientists in their own right, attempting to understand their reality and trying to do something about it" (pp. 526-527). The fact that prodromal symptoms do not automatically progress to relapse is entirely consistent with the notion that patients themselves, in addition to family members and mental health professionals, are actively trying to prevent this progression from occurring.

Methodological Limitations of Studies of Prodromal Symptoms. It is well known that dysphoric and mild psychotic symptoms that have been described as prodromal in schizophrenia often do not progress to relapse. Sporadic occurrences of dysphoric symptoms are commonly experienced by most people, including those with a diagnosis of schizophrenia, in response to stressful life conditions or events. The fundamental issue is how to distinguish such usual fluctuations from those that signal the onset of the relapse process, which we shall henceforth refer to as the prodromal phase of relapse. Whether dysphoric and/or mild psychotic symptoms actually repre-
sent an early or prodromal phase of the relapse process may depend on their severity, duration, and progression. Because of the potential overlap between sporadically occurring symptoms and the prodromal phase of relapse, it is essential to recognize the distinction and to define the prodromal phase operationally to assess its predictive power.

Very few studies have operationally defined the prodromal phase of relapse (Herz et al. 1991; Marder et al. 1994). Although such a definition may lack precision, given our present state of knowledge, how can predictive power be evaluated unless such a definition exists? An example of how a prodromal phase or episode was operationally defined is seen in a recent double-blind, placebo-controlled study of intermittent medications. In this study, both nonpsychotic dysphoric symptoms and mild exacerbations of schizophrenic symptoms appearing before relapse were rated using the Problem Appraisal Scale (Spitzer and Endicott 1971) (Herz et al. 1991). Symptoms were considered prodromal if there was an increase in impairment on any Problem Appraisal Scale role-functioning item; if nonpsychotic symptoms increased from a baseline of none, slight, or mild to moderate or marked, or from a baseline of moderate to marked; or if psychotic symptoms increased from none at baseline to slight or mild or were present at baseline and increased mildly in severity. The duration of the symptom increase was required to be greater than 1 day. This operational definition was important to the study psychiatrists since the declaration of a prodromal episode resulted in stopping the patient’s double-blind medication and replacing it with active antipsychotic medication. After psychiatrists became more familiar with patients in the study, they had the option of temporarily using small doses of benzodiazepines in addition to the double-blind medication when patients had transient mild increases in dysphoric symptoms. These mild increases in dysphoric symptoms, or even in sporadic mild psychotic symptoms, were recognized as something that patients may have periodically and that this should not be considered part of a prodromal episode unless they continue to worsen.

Most studies assessing the course of schizophrenia have also failed to establish an operational definition of relapse (Falloon 1984). With few exceptions (Subotnik and Nuechterlein 1988; Herz et al.)
1991), studies of prodromal symptoms in schizophrenia share this shortcoming. Those that have defined relapse (Tarrier et al. 1991; Gaebel et al. 1993) have relied only on change scores rather than on absolute criteria. Such definitions have serious limitations since baseline symptoms vary considerably in severity among patients with schizophrenia. In the study by Herz et al. (1991), relapse was defined as an increase in any Problem Appraisal Scale psychotic symptom to moderate or severe, and a GAS score of 30 or less, with a duration of more than 2 days.

Other important issues that are relevant to comparing and evaluating studies of prodromal symptoms include choice of assessment instruments, involvement of key informants, and frequency of monitoring. No two studies of prodromal symptoms have used the same assessment instruments and procedures. While it has been reported that family members are more likely than patients to notice changes before relapse (Herz and Melville 1980; Birchwood et al. 1989), most studies did not use relatives or other key informants regularly to monitor for prodromal symptoms. In addition, the literature suggests that the time between onset of prodromal symptoms and relapse is less than 2 weeks for many patients, but only three of the studies (Carpenter et al. 1990; Herz et al. 1991; Marder et al. 1994) monitored patients at least weekly, and many evaluated patients only monthly. It is likely that this infrequent monitoring to detect emerging prodromal symptoms contributed to the low sensitivity of these symptoms reported in some studies.

Is Monitoring for Prodromal Symptoms and Intervening Early When They Occur Effective in Preventing Relapse?

Perhaps the most crucial question about prodromal symptoms concerns their clinical utility. Can monitoring for them and intervening early when they arise prevent relapse in schizophrenia? Four controlled studies provide answers to this question. Pietzcker and colleagues (Pietzcker 1985; Pietzcker et al. 1986) conducted a prospective, randomized, nonblinded multicenter study of intermittent medications in a group of 99 patients with chronic schizophrenia. Patients were randomized to one of three groups: a maintenance group that received continuous antipsychotic medication, an early intervention group that was treated with antipsychotic medication only when prodromal symptoms of relapse occurred, and a crisis intervention group that received antipsychotic medications only when a relapse occurred. Prodromal symptoms were monitored every 2 to 4 weeks using a documentation list based on Herz and Melville (1980). Relapse was defined as an increase of $\geq 10$ on the psychosis factor of the BPRS, a decrease of $\geq 20$ on the GAS, and deterioration of $\geq 7$ on the Clinical Global Impressions (Guy 1976). Although patients on continuous medication had the lowest relapse rates, patients in the early intervention group showed prodromal symptoms (given only when the patient showed prodromal symptoms) with moderate doses of maintenance medication. Both groups of patients received psychoeducation regarding the importance of prodromal symptoms and were actively monitored for such symptoms during weekly group therapy sessions and contact with families. In addition, both groups received prompt psychosocial and pharmacological intervention when prodromal symptoms were observed. Prodromal episodes and relapse were operationally defined as previously discussed.

Primary analysis of the data revealed that intermittent patients had a higher relapse rate than maintenance patients. However, the low 2-year relapse rates achieved by both groups (16% for the intermittent group and 30% for the maintenance group, a nonsignificant difference) suggest that monitoring for prodromal symptoms with early intervention could significantly reduce relapse rates among many outpatients with schizophrenia. In fact, further analysis shows there were no significant differences in relapse rates between female patients in the intermittent group and male or female patients in the maintenance group; only male patients in the intermittent group were found to
have higher relapse rates than the maintenance group patients (Herz 1994).

Interestingly, patients who complied with medications when the beginning of a prodromal episode was recognized were much less likely to relapse than were those who did not comply. Although insight at baseline failed to predict compliance at episode, past compliance behavior during previous episodes strongly predicted compliance during the study. Furthermore, patients on maintenance medication were significantly more likely than those in the intermittent group to have short prodromal episodes lasting 2 days or less. It was noted that some patients in the maintenance group became noncompliant with medication only a few days before relapse. It is likely that medications masked the presence of prodromal symptoms, leading patients to decompensate rapidly when they abruptly stopped medications during the unrecognized prodromal phase.

In a double-blind study of low-dose neuroleptic maintenance treatment in schizophrenia, Marder et al. (1994) examined the clinical utility of intervention when prodromal symptoms appear. Thirty-six male patients maintained on 5 mg fluphenazine decanoate every 2 weeks who developed prodromal symptoms were later randomly assigned to a double-blind comparison of either 5 mg fluphenazine HCl twice a day or placebo. Prodromal symptoms were monitored weekly in each group using an individually tailored Idiosyncratic Prodromal Scale (Marder et al. 1984). Based on baseline interviews with each patient and a key informant, this scale consisted of the three symptoms that were reported to occur most reliably before previous relapses. While relapse was not defined as an outcome, psychotic exacerbation was defined as an increase of at least 4 points on the sum of the BPRS cluster scores for thought disturbance and paranoia or of at least 3 points on either cluster. Survival analysis beginning at the start of the second year indicated a significant reduction in exacerbation risk for patients receiving active drug supplementation. Such patients were also found to spend less time in an exacerbated state in the second year of the study. Patients and their clinicians improved over time in their ability to detect true prodromal symptoms, and this improvement was believed to contribute to the decreasing risk of exacerbations found in the fluphenazine supplementation group.

The efficacy of monitoring for prodromal symptoms in patients on maintenance medications and of providing early intervention when such symptoms emerge has recently been examined in a randomized, controlled study (Herz et al. 1995). Eighty-two medicated outpatients with schizophrenia or schizoaffective disorder and at high risk for relapse were randomly assigned to receive either control treatment (n = 41), which consisted of biweekly individual supportive therapy and family intervention as needed, or early intervention treatment (n = 41), which consisted of a combination of weekly group therapy emphasizing coping skills, twice-monthly multifamily group meetings involving psychoeducation and shared problem solving, and active monitoring for prodromal symptoms. Crisis intervention occurred whenever prodromal symptoms were observed in patients in this group. Early results have shown trends toward fewer patients hospitalized (p = 0.07, χ² = 3.28, 1 df, one-tailed), fewer total hospital admissions (p = 0.08, Mann-Whitney U, one-tailed), and fewer total hospital days (p = 0.08, Mann-Whitney U, one-tailed) in the early intervention group compared with the control group. It should be noted that two noncompliant substance-abusing patients were responsible for 51 percent of all hospital days in the early intervention group.

Taken together, these studies suggest that monitoring for prodromal symptoms and intervening early when the patient is considered to be in the prodromal phase can reduce relapse rates among many patients with schizophrenia. Despite the evidence from these studies, however, it is not current practice in the United States to monitor patients closely for prodromal symptoms and to intervene clinically if symptoms appear.

**Early Intervention in Schizophrenia.** In figure 3, the process of relapse in schizophrenia is illustrated as a gradual one during which intervention may occur at different points. This process should not be viewed as mechanistic, invariably progressing to full relapse. The relapse process is certainly not irreversible when intervention occurs during the prodromal or early psychotic exacerbation phase. Although there is probably a point in the relapse process at which progression to full relapse is inevitable, such a point is likely to occur relatively late.
Figure 3. Phases of relapse and intervention in schizophrenia

Given the considerable personal and economic costs associated with relapse, the period between onset of the prodromal phase and major exacerbation of psychotic symptoms should be viewed as a window of opportunity for early intervention. Unfortunately, psychiatric intervention often does not occur until psychotic symptoms become seriously exacerbated, at which time emergency treatment is required and emergency room management or hospitalization may result.

Conclusions

On the basis of the current literature, we have come to the following conclusions about the questions raised earlier in this article about prodromal symptoms and the relapse process. First, relapse is usually preceded by prodromal symptoms that may last from a few days to several weeks or more. The prodromal phase of relapse usually consists of moderate to severe dysphoric symptoms but may also include mild psychotic symptoms and/or idiosyncratic behaviors.

Second, studies have recently reported that the sensitivity, specificity, and PPV of prodromal symptoms for predicting relapse appear limited. Conceptually, one might ask whether prodromal symptoms should invariably predict relapse. In fact, the process of relapse is not irreversible following the onset of the prodromal phase. The probability of progression to relapse depends on the complex interaction of many personal and environmental factors, including the availability of prompt and effective psychiatric intervention. In addition, studies of the ability of prodromal symptoms to predict relapse have suffered from a number of methodological problems, including failure to establish an operational definition of the prodromal phase of relapse and of relapse itself.

Last, four recent studies have suggested that clinical monitoring for prodromal symptoms and early intervention when they occur can reduce relapse rates among many patients with schizophrenia. Studies have also suggested that the effectiveness of monitoring for prodromal symptoms is enhanced by...
the frequency of such action as well as by the involvement of family members and other key informants.

Research is needed to clarify the distinction between the appearance of sporadic prodromal-type symptoms and onset of the prodromal phase of relapse in schizophrenia. In this regard, biochemical, psychophysiological, or other markers of the prodromal phase of relapse need to be established. A major challenge for psychiatry continues to be finding methods to decrease the vulnerability of patients and to improve interventions to reduce the likelihood of relapse in schizophrenia.

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The Authors

Marvin I. Herz, M.D., is Professor, and J. Steven Lamberti, M.D., is Assistant Professor, Department of Psychiatry, University of Rochester Medical Center, Rochester, NY.