Relapse: A Reappraisal of Assessment of Outcome in Schizophrenia

by Ian R.H. Falloon

Abstract

Although measurement of the course of schizophrenic disorder has relied heavily on the concept of relapse, a review of the literature reveals a paucity of clear definitions of relapse. In most research studies, the assessment of relapse has been made on the basis of clinical judgment, with little attempt to apply more rigorous psychometric standards. The limitations of this approach are discussed and several possible improvements are suggested. These include: operational definitions that specify the qualitative, quantitative, and temporal characteristics of symptomatic exacerbation; avoidance of potentially confounding social variables; and the use of standardized rating scales and target symptoms.

The increasingly rigorous attention paid to the diagnosis of schizophrenia has not been extended to the development of reliable and valid criteria for assessing the course of the illness. This situation continues despite the fact that the concept of relapse has become the predominant measure of the success of community treatment programs of schizophrenia over the past two or three decades. Kraepelin has been faulted for his lack of clarity in discussing his hypothesized association between the diagnosis of dementia praecox and a poor clinical outcome (World Health Organization 1975). Although his later work addressed the issue of diagnostic criteria, his lack of definition of the concept of relapse persisted. Stressing that “the general course of dementia praecox is very variable” (Kraepelin 1919), he outlined several possible courses of the illness, all of which showed an eventual state of terminal dementia.

Although Kraepelin remained skeptical that full recovery without any residual defect was possible, Adolf Meyer (1922) contended that functional recovery was possible and proposed that in many cases the illness could be regarded as episodic, with relapses representing fresh attacks of the disease. Kraepelin (1919, p. 188) acknowledged that “more than half exhibit marked improvement,” but noted that these recoveries “give way sooner or later to a relapse.” In support of his thesis of incomplete remission, he observed that subsequent relapse almost always consisted of symptoms similar to those presented in the original episode. This consistency of symptom patterns was also reported by Eugen Bleuler (1911), who supported the notion that complete restoration of premorbid mental health was a rarity. Bleuler cautioned against attributing much significance to published reports regarding “cure” rates, not only because of the subjective nature of such determinations, but also because of “the varying conditions of admission and release for each institution” (Bleuler 1911, p. 258) which often play a greater role in defining discharge status than objective changes in psychopathology.

Concern about the natural course of schizophrenia led these pioneers to focus discussion more upon the definition of remission than its counterpart relapse. With the advent of more powerful pharmacological and psychotherapeutic interventions, emphasis has increasingly shifted to the factors surrounding the reemergence of florid schizophrenia in remitted patients. Under current practice, patients are discharged from the hospital in a state of complete, or...
(more often) partial, clinical remission. The effectiveness of community aftercare programs is measured by their ability to sustain these remissions, and more often than not, by readmission of the patient to the hospital. The value of predictive factors for the course of schizophrenic disorder is often judged using this same criterion. Hospital readmission is arguably a social intervention which, although usually associated with symptom exacerbation, is often more closely related to behavioral disturbance—specifically, suicidal or homicidal behavior, or an inability to function in some sort of rudimentary, socially desirable manner (Wing 1968).

Although there is often an association between symptom severity and behavioral disturbance, the relationship cannot be assumed to be unswerving. Violent behavior, suicide attempts, and noisy, disruptive behavior are less well tolerated socially than withdrawn, stuporous behavior. Persons exhibiting the former kinds of disturbance are more likely to be actively removed from their community habitats than those exhibiting the latter, even though the underlying psychopathology may be of similar severity.

With the increasing emphasis on community management of schizophrenia, patients demonstrating severe, persistent florid symptoms are commonly being cared for at home. Assessing relapse in these patients constitutes a formidable methodological challenge. Owing to the lack of sufficiently sensitive measures, these patients may often be excluded from research studies (Leff 1973). Yet, these patients may well be among those most in need of investigation with new, potentially efficacious, treatment methods.

The present article seeks to examine critically the use of relapse as a major outcome variable in treatment studies of schizophrenia. It will attempt to address the following issues:

- Is there general agreement about what constitutes a relapse of schizophrenic disorder?
- Can the concept of relapse effectively chart all the courses of schizophrenic disorder?
- Can relapse be operationally defined in such a manner that it constitutes a sufficiently robust measure of outcome for comparing treatment approaches and for evaluating the role of various vulnerability and stress factors in predicting the course of schizophrenic disorders?

### The Definition of Relapse

Relapse has been defined in many different ways in recent outcome studies of schizophrenia (see table 1). Everyday usage in clinical settings would suggest a clear consensus on the criteria employed in its definition. However, a close perusal of published reports reveals considerable variation in researchers' notions of what constitutes a relapse. The usual definition uses hospital admission as the central criterion for relapse. Some investigators have used hospitalization as the sole determinant of relapse, regardless of symptom presentation or severity (Johnson 1975; Linn et al. 1979; Matthews et al. 1979). Others have incorporated the notion of impending hospitalization when they defined relapse as "clinical deterioration of such magnitude that hospitalization seemed imminent" (Hogarty et al. 1973, 1979).

### Table 1. Definitions of relapse in schizophrenia

<table>
<thead>
<tr>
<th>Components</th>
<th>Restricted</th>
<th>Broad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of psychopathology</td>
<td>Florid symptoms of schizophrenia</td>
<td>Exacerbation of any psychiatric symptoms, e.g., depression, anxiety</td>
</tr>
<tr>
<td>Major management change indicated</td>
<td>Increased neuroleptic medication at onset of florid exacerbation</td>
<td>Hospital admission, drug reactions, increased medication at onset of prodromal signs of exacerbation</td>
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<tr>
<td>Social impairment</td>
<td>—</td>
<td>Reduced social role function</td>
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<td>Behavioral disturbance</td>
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<td>Social crisis</td>
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Another common method of defining relapse has been to speak generally of significant "clinical deterioration in mental state" without mention of the specific symptoms being evaluated in tracing the course of deterioration. The inclusion of many different types of clinical deterioration has often resulted. For example, occurrences of suicide attempts (Hogarty et al. 1979) and exacerbations of depressive symptomatology (Quitkin, Rifkin, and Kane 1977) have been included as relapses in studies of schizophrenia.

Relatively few studies have restricted the definition of relapse to patients exhibiting an increase in psychotic symptoms (Leff and Wing 1971; Hirsch et al. 1973; Quitkin, Rifkin, and Kane 1977; Falloon, Watt, and Shepherd 1978; Kane et al. 1979). Further restriction of relapse to patients showing an increase in florid symptoms specific to schizophrenia has been even less common (Leff and Wing 1971; Hirsch et al. 1973; Falloon, Watt, and Shepherd 1978).

A further definition of relapse involves major changes in therapeutic management that may be undertaken when an exacerbation appears imminent. In double-blind, placebo-controlled studies, this may include instances in which a patient's condition has deteriorated to the point that double-blind research procedures had to be terminated to ensure the administration of active medication (Leff and Wing 1971; Hirsch et al. 1973; Johnson 1979). Goldstein et al. (1978, p. 1171) defined relapse as a "clinical deterioration such that [the patients] had to be hospitalized or their medication had to be altered substantially." This definition is representative of studies that included a change in medication management in the definition of relapse (Crawford and Forrest 1974; Schooler et al. 1980).

Thus, there is a lack of clear consensus about what constitutes a relapse in the course of schizophrenic illness (see table 1). No single variable has been common to all outcome studies. Admission to a psychiatric hospital unit, increase of medication, worsening of florid symptoms of schizophrenia, worsening of any psychiatric symptoms, and threatened clinical exacerbations have all been variables considered under the rubric of relapse.

Use of the Relapse Concept in Studies of Schizophrenic Populations

Scientific study is limited by the availability of measurement procedures to assess the phenomenon under scrutiny. Relapse appears to be a suitable concept for assessing change in the course of a condition that is characterized by remissions and exacerbations—a relatively common course for schizophrenia. However, it is by no means the only course followed by this illness in the community-based population of persons affected by the disorder. Perhaps 50 percent of schizophrenics do not attain a stable clinical remission, despite improved treatment (Bleuler 1974; Ciompi 1980). A major limitation of the concept of relapse is its lack of utility in describing the course of nonepisodic presentations of schizophrenia.

The problem of persisting psychotic symptoms has not been adequately addressed in most outcome studies of schizophrenia. Where relapse has been used as the major measure of the outcome, it has been generally assumed that a full remission of florid symptoms was present at the time of entry into the study. Few studies have assessed the state of remission before the study (Kane et al. 1979). In most studies, patients were clinically stable before beginning the community study. This usually entailed a state of "social remission," but included patients who were totally free of florid schizophrenic symptoms as well as those with persisting psychotic symptoms that were not contributing to gross behavioral disturbance. Strictly speaking, the latter group of patients cannot be considered to have "relapsed" when their preexisting symptoms worsen. The presence of schizophrenic symptoms at entry to an outcome study increases the risk of subsequent exacerbation (Falloon, Watt, and Shepherd 1978). Such a differential outcome for patients with persisting symptoms necessitates that they be assessed separately from those who begin a study in a stable clinical remission: for the latter patients, the concept of relapse might usefully apply to the reappearance of specific symptoms of schizophrenia.

If the effective use of relapse is restricted to the population of schizophrenics who attain clinical remission (i.e., absence of all psychotic symptoms), a large proportion of persons suffering from this disorder will be excluded. This has occurred in several drug maintenance studies (Hirsch et al. 1973; Johnson 1976; Quitkin, Rifkin, and Kane 1977; Schooler et al. 1980). Thus, these studies, which legitimately employed the relapse concept, are limited in their generalizability to the entire population of patients with schizophrenia.

Criteria for Relapse in Outcome Research

It is evident that the validity of the relapse concept in outcome research
is reduced by a lack of a consensual definition across research groups and that the applicability of this concept is limited to fully remitted populations. These criticisms notwithstanding, however, other evidence for the reliability and validity of relapse might commend its use as an outcome measure in schizophrenia research. It is sad that such data are notably absent from published reports. The majority of outcome studies have relied on the clinical judgment of a blind, but seldom independent, assessor to determine when relapse has occurred. Often, standardized rating scales have been applied simultaneously, but seldom has the contribution of these rating scales been specified. One exception was the study of Hirsch et al. (1973). In this study, the clinical team responsible for each patient’s community care made the decision to withdraw the patient from the placebo-control trial, but they avoided doing so unless there was evidence of worsening of the specific symptoms of schizophrenia, even if hospital admission had occurred. The standardized Present State Examination (PSE) (Wing, Cooper, and Sartorius 1974) was administered by the research team at the time of hospital admission or other exacerbation. Deterioration of schizophrenic symptoms on the PSE accompanied clinical relapse in 74 percent of relapsed patients. It may be concluded that in this study, in which detailed operational criteria were used, the application of clinical relapse as a measure of a significant exacerbation of schizophrenia appeared to meet minimal psychometric standards. Additional independent validation was provided by interviews of relatives who reported evidence of increased florid symptoms of schizophrenia in 85 percent of relapses.

In a series of studies of family factors (in particular, “expressed emotion”) associated with the course of schizophrenia, two types of relapse were defined (Brown, Birley, and Wing 1972; Vaughn and Leff 1976). A type I relapse involved any reappearance of florid psychotic symptoms (hallucinations, delusions, or thought interference) in patients in full clinical remission. A type II relapse, on the other hand, involved a significant exacerbation of florid psychotic symptoms that, although stabilized, had never fully remitted. The PSE was used to assist in these determinations, but it is not clear precisely how a “significant exacerbation” was operationalized. In the latest completed study of the “expressed emotion” series, researchers at the Mental Health Clinical Research Center in Los Angeles developed operational criteria for PSE changes that, when coupled with quantitative rating scale data, enabled two blind raters to attain 92 percent agreement on the presence of relapse (Vaughn et al. 1982).

In studies such as these in which social factors are examined for their ability to predict clinical outcome, it is crucial to develop criteria for relapse that are free from contamination by social variables. Strauss and Carpenter (1974, 1977) found that the best predictors of clinical course were clinical features, whereas social factors were the best predictors of social outcome. Thus, it is clear that to determine the independent contributions of each of these predictors, reliable and valid measures of clinical and social outcomes must be developed.

Recommendations
In view of the inadequacies of relapse as a rigorous measure of outcome in schizophrenia, the question arises, what alternatives exist? Before abandoning the concept, it might be expedient to examine ways in which the determination of relapse could be more effectively standardized. At a minimum, it is essential that investigators devote more attention to providing an operational definition of relapse. Such a definition should specify the qualitative and quantitative characteristics of symptom exacerbations that qualify as relapses. Qualitatively, it is desirable to specify the severity of symptom presentation that is required to meet criteria for a relapse. For example, if a patient reports hearing a soft mumbling voice occasionally at night, the precise words of which he cannot make out, this would probably not be considered to have met the quantitative (or severity) requirements for relapse. Quantitative criteria should also specify the length of time symptoms must persist to be considered significant. On all of these dimensions, the criteria must be sufficiently specific to permit a high level of agreement between independent assessors.

If relapse is to be used as a measure of illness severity, it should remain free from potentially confounding social variables, such as deterioration in social adjustment, hospital admission, and behavioral abnormalities not directly and unequivocally related to the illness (i.e., exclusive of incoherent speech, inappropriate affect, or catatonic behaviors) or psychiatric symptoms not specific to schizophrenia (e.g., depressed mood, anxiety attacks, and
somatic complaints). Measures of social functioning, community tenure, and nonschizophrenic symptoms are important aspects pertaining to the morbidity of the illness but should be assessed independently. In one study of schizophrenia, the most common cause of hospital admission was episodes of depression in the absence of schizophrenic exacerbation (Falloon, Watt, and Shepherd 1978). In the same study, two drugs demonstrated equal efficacy in preventing schizophrenic relapses but one was superior in reducing social impairment.

Reliable rating scales that assess social functioning are available (Katz and Lyerly 1963; Weissman and Paykel 1974; Strauss and Carpenter 1977; Platt et al. 1980). Nonschizophrenic symptoms contribute to the outcome of schizophrenia, and reliable methods of determining the qualitative and quantitative features of these episodes are also crucial. Temporal aspects of relapse have seldom been addressed. It is not clear whether a brief recurrence of florid symptoms lasting a matter of minutes or hours would be sufficient to constitute evidence of relapse. It would seem that a brief episode of florid symptoms should be treated differently from an episode of similar symptomatology extending over a period of several weeks. Since brief periods of symptomatic exacerbations are quite common in schizophrenia, it would be desirable to develop a simple rule about how to treat them. One could require symptoms to be present for at least 1 week to be considered a relapse. Although this rule is arbitrary, it is clearly specified and would permit assessment to be conducted in a reliable, replicable fashion.

An alternative approach to dealing with the “all or none” notion of relapse, with its inherent limitations, would be to abandon it and to substitute a “target symptom” approach similar to that which has been effectively employed with neurotic disorders (Gelder, Marks, and Wolff 1967; Sloane et al. 1975). This approach entails defining, on a case by case basis, the specific schizophrenic symptoms that each patient is known to have presented during past exacerbations, and rating each of them for severity at regular intervals (and especially during suspected exacerbations) during the study. Thus, one patient might have target symptoms of incoherent speech and catatonic posturing while a second might be targeted for auditory hallucinations and delusions of external control. Severity of each symptom can be rated on a scale similar to other psychopathology measures (Falloon et al. 1982).

The target symptom approach has several potential advantages. First, each patient’s idiosyncratic pattern of presenting symptoms can be specified, both qualitatively and quantitatively. Second, there are psychometric advantages to using quantitative rating scales such as these. Serial assessments can be conducted and analyzed using parametric statistics. Third, mild and moderate exacerbations can be included as well as major relapses. Fourth, patients who have persistent symptoms can nevertheless be included in a study cohort. Disadvantages of the target symptom approach include difficulty in choosing appropriate target symptoms, lack of comparability across subjects, difficulties in applying linear rating scales of severity to many of the phenomena of schizophrenia, and reliance on patients’ self-report of subjective experience. Another concern is the lack of clear data to support the longitudinal stability of specific symptoms. In the short term, schizophrenia tends to show similar symptom profiles (Kraepelin 1911; Leff and Wing 1971), but over longer periods of time there might well be changes in the relative prominence of certain target symptoms (Vaillant 1964).

Another alternative, being tried at the Mental Health Clinical Research Center for the Study of Schizophrenia in Los Angeles is the use of existing rating scales such as the Psychiatric Assessment Scale (Krawiecka, Goldberg, and Vaughan 1977). Brief Psychiatric Rating Scale (Overall and Gorham 1962), Inpatient Multidimensional Psychiatric Scale (Lorr et al. 1962), or the scoring system recently developed by Chapman and Chapman (1980). These scales provide severity ratings and, with cutoff points, can be adapted to provide operational definitions of relapse (Vaughn et al. 1982). With the exception of the Chapman’s rating system, these scales are not confined to exclusively schizophrenic symptoms, and it is important to note that only those items or factors relevant to florid schizophrenic symptoms should be used in operationalizing schizophrenic relapse.

Successful attempts to devise sophisticated quantitative measures of the course of schizophrenia are eagerly awaited and will undoubtedly portend further advances in this field. At this point, however, clinical ratings of relapse or exacerbation continue to dominate research on course and outcome. It is crucial that these rather crude measures be refined so that high standards of scientific endeavor can be maintained in this important area of psychiatry.
References


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Schizophrenia Bulletin
Index 1969/79

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