# Long-Term Outcome of Patients With Schizophrenia: A Review

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**Objective:** To review empirical studies that assess outcome of patients with schizophrenia and evaluate the degree to which reported outcome is affected by research methodology, treatment variables, prognostic factors, epidemiologic factors, and patient resilience.

**Method:** We reviewed studies that used control subjects and lasted for a decade or more, comparing them with respect to research methodology and choice of outcome variables.

Results: Like other mental illnesses and medical illness in general, the natural course of schizophrenia showed itself to have a threefold division of mild, moderate, and severe. Although a great deal of variance in outcome occurred across the studies reviewed, schizophrenia is nevertheless a disorder with relatively poor outcome. Patients with schizophrenia consistently showed poorer courses and outcomes than patients with other psychotic and nonpsychotic psychiatric disorders. On the positive side, subgroups of schizophrenia patients had extended periods of recovery—some without the benefit of extensive mental health aftercare treatment—and patients with schizophrenia did not show a progressive downhill course.

**Conclusion:** While documenting the heterogeneity in outcome and the generally poorer outcomes of patients with schizophrenia, the studies reviewed also alert us to the danger of suicide and early death in schizophrenia. In addition, they expose problems in clinical management and treatment and also help us anticipate the possibility of intervals or periods of recovery, some of which appear spontaneously and may be tied to individual patient factors such as resilience.

(Can J Psychiatry 2005;50:892–900)

Information on funding and support and author affiliations appears at the end of the article.

#### **Clinical Implications**

- While schizophrenia is generally a poor-outcome disorder, a moderate-to-large subgroup of
  patients potentially experience periods of recovery (including both the absence of major
  symptoms and adequate psychosocial functioning) lasting several years or longer.
- Mental health professionals should be alerted to the high risk of completed suicide among schizophrenia patients, especially in the first 10 to 12 years of this disorder.
- Long-term outcome is influenced by current treatments, but the personal strengths, the
  developmental achievements, and the resiliency of individual patients are equal or more
  important influences.

#### Limitations

- This review focuses primarily on long-term North American studies of schizophrenia and also on the WHO study. There is less focus on European studies.
- This review only focuses somewhat on prognostic factors that may be involved in outcome and recovery.
- The lack of uniform methods among long-term outcome studies limits generalizations regarding the difference between current outcomes in schizophrenia and outcomes prior to the advent of current treatments.

**Key Words: s**chizophrenia, longitudinal, recovery, outcome, follow-up studies, resilience, prognostic factors, psychotic disorders

A mong the major psychiatric disorders, schizophrenia's longitudinal course and outcome has been studied the most extensively (1). In part, this is because fundamental concepts about the nature of schizophrenia were formerly based on views about its longitudinal course. The disorder was originally viewed as having a progressive downhill course (2). Considerable longitudinal research has changed this outlook to one that is less negative. These long-term follow-up studies have provided more detailed information on course and outcome in schizophrenia; on diagnostic issues, specific symptoms, and problems in functioning; on treatment; and on important prognostic factors.

In addition, these long-term follow-up studies—a few of which cover periods before the introduction of psychotropic medication—have helped to gradually strengthen the operational definitions of both the diagnosis of schizophrenia and the definition of recovery. The outcomes of most psychiatric disorders, as well as of most medical illnesses, show heterogeneous results that are usually divisible into the categories of mild, moderate, and severe. Schizophrenia, however, has traditionally been associated with concepts of progression, relapse, and chronicity. It is now possible to say with a high degree of certainty that schizophrenia can also be grouped with other major disorders that have a heterogeneous outcome. Some of the heterogeneity is influenced by patient-related factors, such as age of onset, acuteness of onset, and other prognostic factors that can influence later outcome and may be linked to the disorder's severity (3-5). Antipsychotic medications and responses to them have contributed to reduced morbidity and relapse rates. They have contributed more dramatically during the acute phase of psychosis by drastically reducing the duration and intensity of florid psychotic symptoms.

# Overview of Major North American Follow-Up Studies of Schizophrenia Lasting 10 or More Years

In this review, we have focused on 10 long-term studies: 9 from North America and the WHO-coordinated ISoS (6). Most of these also have been reviewed by McGlashan (7).

# Abbreviations used in this article

CFU Chicago Follow-Up Study
ECT electroconvulsive therapy

GAF Global Assessment of Function Scale

GAF-D GAF Disability Scale

ISoS International Study of Schizophrenia

#### The Iowa 500 Follow-Up Study

The Iowa 500 study is one of the landmark follow-up studies (8). It addressed important methodological issues, such as use of control groups (both medical and psychiatric), rigorous diagnostic criteria, and a sample of patients exhibiting a natural course without modern medication, ECT, or specific psychosocial treatments, at least during the initial course of their disorder. As a result, this study more completely documented the negative course of schizophrenia than did any other long-term study (9-11). This retrospective study of 500 psychiatric patients admitted to Iowa State Psychiatric Hospital between 1934 and 1944 used the restrictive Feighner criteria to diagnose both schizophrenia and affective disorders (12). Over 60% of the original patients with a chart diagnosis of schizophrenia were rejected as not meeting the Feighner criteria. Follow-up data were acquired between 1972 and 1976, averaging roughly 35 years after the index hospitalization; 95% of the original schizophrenia cohort were characterized. Each of the 4 outcome dimensions (symptom severity, work history, marital status, and residential status) were scored on a 3-point scale indicating poor, fair, and good outcome. The 200 patients with schizophrenia had a substantially poorer outcome on all outcome dimensions, compared with other psychiatric patients and nonpsychiatric surgical patients. Despite the overall poor outcome, 30% of the schizophrenia cohort were married, and 20% emerged from the study symptom-free.

# Vermont State Hospital Follow-Up Study

Almost at the opposite end of the recovery spectrum, the Vermont study exhibited far different results. Harding and others conducted a retrospective study of 268 psychiatric patients diagnosed according to DSM-I criteria, 168 of whom received a diagnosis of schizophrenia. Patients were recruited from the hospital if they met criteria to enter a new rehabilitation program between 1955 and 1960 (13,14). The average age at follow-up in 1982 was 61 years for the 82 patients who further qualified by meeting the DSM-II and DSM-III criteria for schizophrenia. The criteria for referral to the outpatient rehabilitation program provided a selection bias for higherfunctioning patients. Also, the DSM-I diagnosis did not require 6 months of active symptoms or dysfunction. Even so, there was no difference in outcome among the groups diagnosed according to the DSM-I, the DSM-II, and the DSM-III. After 20 years, 60% of the schizophrenia cohort scored over 61 on the GAF. In contrast to the Iowa study, there was no difference in outcome between schizophrenia patients and other psychiatric patients. This was a most unusual result that has not been replicated in any of the many other comparable follow-up studies. Equally surprising, the schizophrenia cohort scored very well on the Strauss and Carpenter outcome dimensions (15), with 68% showing minimal or no symptoms and 61% employed in the last year of the study, although the criteria for employment status were not reported (15). This study of patients with schizophrenia in their 60s opens up the possibility of some gradual improvement as patients with schizophrenia get older. The differences in outcome between this study and the Iowa 500 are attributable not only to diagnostic criteria and a positive selection bias but also to the fact that the Vermont cohort of schizophrenia patients benefited both from medication and from intensive outpatient rehabilitation (16,17).

#### Chestnut Lodge Follow-Up Study

A closer parallel to the Iowa 500 study was conducted by McGlashan and others on a cohort of chronically ill, medication-resistant patients. This study followed 532 patients discharged from Chestnut Lodge, a 90-bed private tertiary care hospital in Rockville, Maryland, between 1950 and 1975 (18,19). (This hospital has recently closed, in part because of the recent de-emphasis on long-term inpatient care.) The sample predominantly comprised patients from an upper socioeconomic background. All patients were rediagnosed according to DSM-III criteria, and 8 different diagnostic groups were followed, including patients with schizophrenia, schizophreniform psychosis, and schizoaffective psychosis. Outcome was assessed between 1977 and 1983, with an average of 15 years' follow-up by personal interviews. On a 5-point global outcome scale, the 163 patients with schizophrenia were distributed as follows: recovered, 6%; good, 8%; moderate, 22%; marginal, 23%; and continuously incapacitated, 41%. The average score for the schizophrenia cohort on a scale similar to the GAF (Luborsky's Health-Sickness Rating Scale, 20) was 37.

### Columbia Psychiatric Institute Follow-Up Study

This retrospective study shared some similarities with the Chestnut Lodge Study: chronic patients were selected and treated with inpatient, psychoanalytically oriented psychotherapy. Stone and others retrospectively examined 552 patients with a DSM-III diagnosis who had at least a 3-month hospitalization at New York State Psychiatric Institute (21). Of the total number of patients, 99 met criteria for schizophrenia. Interestingly, this was the only study to control for IQ (it used a cut-off score of 90). Patients were followed up for between 10 and 23 years, and 92% of the total sample completed the follow-up. The results again showed that other psychiatric patients did substantially better than the schizophrenia patients, who, on average, had a GAF score of 39 (range 6 to 81). The cut-off for "good" or "recovered" was a GAF score of 61, achieved by only 8% of the schizophrenia patients.

#### Vaillant's Follow-Up Studies

George E Vaillant conducted 2 follow-up studies using patients admitted to the Massachusetts Mental Health Center, one of the university teaching hospitals in Boston, Massachusetts. The first, a retrospective study, provided important data on prognostic factors associated with outcome in schizophrenia (22).

Vaillant's second study attempted to identify a group of patients who could sustain remission and to determine which of 7 prognostic variables best predicted this positive outcome result. He selected 51 of 56 patients from the first study who had achieved complete remission between 1959 and 1962. This cohort of good-prognosis patients was followed prospectively for 4 to 16 years. Sustained remission was defined by 5 conditions: freedom from psychotic symptoms for at least 1 year, freedom from Bleuler's primary symptoms for at least 1 year, reattainment of premorbid level of adjustment, no use of antipsychotic medication, and finally, having at least one friend (23). Results showed that 61% of patients sustained remissions, whereas 39% could not and developed a chronic course. Most important, Vaillant's hypothesis that prognostic criteria could not discriminate outcome completely was partly confirmed, although the successful prediction for 61% of the schizophrenia patients does suggest some degree of accuracy. The results also confirm that patients with schizophrenia can sustain remissions for long periods of time (5,22). Vaillant's important study of prognostic variables may provide clues concerning some of the person-related factors that contribute to the heterogeneity often found in outcome for schizophrenia.

#### Phipps Clinic Follow-Up Study

Another attempt to find predictors of outcome, or prognostic factors, was the follow-up study conducted by Stephens and others (3). Stephens used the Phipps Clinic in Baltimore, Maryland, to test the predictive power of the process-reactive distinction. This large retrospective study included 472 patients discharged with a diagnosis of schizophrenia after their first hospital admission of at least 3 weeks' duration. Their charts were classified as process or nonprocess and were scored for presence or absence of 43 prognostic variables. Follow-up averaged 10 years, and 3 outcome categories were defined. Patients considered recovered (24%) had complete recovery without evidence of further relapses and remissions. The second category, improved (46%), included patients who showed repeated relapses and remissions as well as those who showed continuous residual symptoms. The third category, unimproved (30%), included patients who remained hospitalized or who had continuous psychotic symptoms. Stephens proved that those who were lost to follow-up did not bias the outcome. With conclusions differing slightly from Vaillant's, Stephens, who also contributed to the prognostic literature, was more optimistic about the value of the process–reactive groups and the prognostic variables as predictors of outcome (4,24,25).

#### Alberta Follow-Up Study

Among the North American long-term studies, only one Canadian study effectively controlled for geographic distribution and incidence of schizophrenia. This was the Alberta Hospital Follow-Up Study conducted by Bland and others (26). The Alberta study drew patients equally from all parts of the province of Alberta, Canada. Like the Vermont study, the Alberta study also showed a more positive overall outcome than was seen in the other studies, which relied disproportionately on city populations with potential downward social mobility. In 1976, the first part of the Alberta study followed up 92 patients who met DSM-II criteria and who had a first admission to the Alberta Hospital in 1963. Deceased patients were included, and 88 patients were successfully examined for 6 levels of outcome graded from full recovery to chronic, unremitting institutionalization. Surprisingly, 58% of the patients fell into the full recovery category, and only 8% fell into the chronic category. These results were of further interest because 45% of the patients had discontinued their psychotropic medication 10 months after discharge from the hospital. This finding was one of the first indications that some patients not on psychotropic medications may have good outcomes.

Bland's group then did a second follow-up of the same cohort (27). Stricter criteria for diagnosis, including Feighner criteria for "probable" schizophrenia, narrowed the sample to 45 subjects. Roughly the same period (1963 to 1977) was chosen, and the same outcome criteria were used. The percentage in the first category (fully recovered) dropped from 41% to 21%, but the extent of time on medication remained roughly the same at 51%. This research clearly showed how strong a role the diagnostic criteria used to select the sample played in determining the outcome.

#### Chicago Follow-Up Study

One of the few prospectively designed multifollow-ups of some length is the CFU, directed by our own research group. In this study, which is ongoing, a large sample of patients with schizophrenia and other types of psychotic, as well as nonpsychotic, disorders were originally studied at the acute phase. The same cohort was then followed up 2 years later (28), 4.5 years later (29), 7.5 years later (30,31), 10 years later (32,33), 15 years later (34), and 20 years later (35).

This prospectively designed study of an initially young and relatively early-onset sample of patients (mean age at index hospitalization, 23 years) from 2 Chicago hospitals included, at the 15-year follow-up, 73 patients with schizophrenia, 40 patients with schizoaffective disorder, 40 patients with

bipolar disorder, and 134 patients with other types of psychotic and nonpsychotic disorders. Information was available for another 37 patients who had died, many by suicide (36,37).

This research has used the longitudinal data to focus on course, outcome, potential suicide, and potential recovery in schizophrenia and bipolar disorders. It also has studied the course of key symptoms, including psychosis, thought disorders, negative symptoms, depression, and anhedonia, as well as major factors involved in thought disorder, psychosis, and work disability in schizophrenia (38–42).

In terms of course and outcome for schizophrenia, on the negative side, the longitudinal data over 20 years indicated that, at each follow-up, patients with schizophrenia showed poorer outcomes than patients with other types of psychotic disorders. Most of these modern-day schizophrenia patients fluctuated over time between moderate disability and severe disability, with several experiencing some intervals of complete recovery.

On the positive side, while functioning more poorly than patients with other types of psychotic disorders, over 40% showed periods or intervals of recovery (including both adequate psychosocial functioning and the absence of major symptoms) that could last for several years (34). Several schizophrenia patients from this subgroup were able to function effectively for a period of years without antipsychotic medications. Most of this smaller subgroup were schizophrenia patients with better premorbid developmental achievements and more internal resources, which played a large role in their relatively favourable course while they were untreated. A methodological caution for other studies is that these untreated patients who left the mental health caretaking system are not included in some of the other follow-up studies, nor are they included in many of the classical medication-versus-placebo studies, since they are less likely to come to the attention of clinicians and researchers who work with and study patients in treatment clinics.

The longitudinal design comparing control groups with other types of psychotic disorders and also patients with bipolar mania has produced findings indicating that 1) thought disorder is not continuous over time in all or most patients with schizophrenia, as Bleuler had originally proposed; and 2) thought disorder is not unique to schizophrenia and is a factor in acute mania in patients with bipolar disorder (43,44). Similarly, other data have indicated that negative symptoms are not unique to schizophrenia and are not continuous in all patients with schizophrenia (45,46).

The CFU also has shown that schizophrenia patients have greater vulnerability to subsequent depressive syndromes than was once thought (65% by the 20-year follow-up),

although some, and perhaps much, of this relatively high rate is linked to the use of first-generation antipsychotics (47).

The CFU was one of the early studies to show that, when followed longitudinally, patients with bipolar mania taking lithium do not have the 70% to 80% success rate indicated by earlier data (48,49).

# Washington International Pilot Study of Schizophrenia Follow-Up

The other prospective study among the North American group is the 11-year follow-up of the Washington, DC, cohort of the International Pilot Study of Schizophrenia carried out by Carpenter, Strauss, and others (50-53). The sample comprised 131 patients admitted to psychiatric units of general hospitals in Prince George's County, Maryland, in 1968-1969. Only acute and subacute patients diagnosed according to DSM-III and ICD-9 criteria were included, and the study followed 55 patients assessed at 5 and 11 years. Outcome was multidimensional and showed no significant difference in outcome status between the 5-year and 11-year periods (53). On all outcome dimensions, which included work status, hospital use, symptom severity, social functioning, and global outcome measure, schizophrenia patients showed poorer outcome than patients with such other psychiatric disorders as bipolar disorder. An important contribution, emphasized in the Carpenter-Strauss research, is that different outcome dimensions often only show modest to moderately strong relations to each other, rather than very strong relations. Carpenter-Strauss emphasize that these outcome dimensions represent loosely linked dimensions or, as they put it, an open-linked system of outcome (51,53).

#### WHO Study

In addition to the North American long-term studies discussed above, there are other important studies from North America, Europe, and Asia (54-65). The WHO Study, known as the ISoS, included an American component and is important enough that we briefly summarize a few of its results. In the ISoS, a total of 1633 subjects were followed up at 15 and 25 years; this sample comprised 14 culturally diverse treated incidence cohorts and 4 prevalence cohorts (6). The ICD-10 was used to subcategorize diagnostically the surviving participants in the study. Important findings that emerged from the ISoS study were data indicating that outcome in schizophrenia in developed industrialized countries is poorer than in developing countries. Possibly, greater tolerance and a more benevolent attitude exists in developing countries toward some of the symptomatic and poorer-functioning patients; this may contribute to the view that these patients are functioning moderately well, with some of their problematic features being downplayed. However, more recent epidemiologic analysis suggests that this cannot account for all the difference in outcome between developed and developing countries (66).

Assessed only according to the Bleuler Scale for outcome, the living ISoS subjects did well, with 56% of the incidence cohort and 60% of the prevalence cohort scoring a 4 (recovered). However, assessed with both a Bleuler Scale score of 4 and a GAF-D score of greater than 60, only 37.8% of subjects with schizophrenia and 54.8% of subjects with other psychoses within the incidence cohort would be rated as recovered. Again, if treatment received within the past 2 years was controlled for, only 16.3% of subjects with schizophrenia and 35.8% of subjects with other psychoses in the incidence groups qualified as recovered. Even using the strictest criteria for recovery, there remained some level of symptoms and disability among some recovered patients.

# Other Factors to Consider Concerning the Longitudinal Course of Schizophrenia

Several factors in relation to course and outcome should be considered. The relatively recent addition of neuropsychological measures of neurocognitive impairment in outcome studies and the emerging connection between neurocognitive deficits and poorer outcome in schizophrenia has strengthened the hypothesis that there is a substantial neurodevelopmental component in the etiology of schizophrenia (67,68). The role of second-generation or atypical antipsychotics in preserving cognitive function in patients with neurocognitive deficits and in limiting the progression of negative symptoms is only now being scrutinized in follow-up studies (69). Our own data (from the CFU Study) suggest that first-generation antipsychotics increase the rate of depressive syndromes in schizophrenia patients and that second-generation antipsychotics do not induce such syndrome (35,47).

Of central importance, there is now evidence that a moderate number of schizophrenia patients do have complete symptomatic remissions without further relapses, at least for a good period of time, and that some of these patients do not require maintenance medication (35,70). In addition, both the prognostic studies and the long-term follow-up studies indicate that patient-specific factors can strongly affect an individual's resilience in overcoming psychotic episodes. As mental health professionals, we sometimes overemphasize our treatments and forget the importance of patient efforts and the importance of the patient's internal resources in his or her improvement and possible recovery (71). This also speaks to the current criticism of "one size fits all" therapies or simple treatment algorithms that ignore individual differences (72).

There are, however, serious challenges that need to be addressed in the future. It would be desirable to standardize methodology across follow-up studies, as was first attempted in the WHO study (6). To some degree, integrating the outcome field within the vast body of schizophrenia research has been compromised by the following factors: 1) low comparability of long-term follow-up studies, arising from differing criteria for both diagnosis and outcome variables; 2) different statistical analyses; 3) the fundamental division between the European phenomenological and the North American criterion-based approaches; 4) selection biases between inpatient and outpatient indexing; and 5) prospective and retrospective designs.

McGlashan's 1988 and 1991 reviews of North American longitudinal outcome studies provide a point of origin to appraise both the strengths and the weaknesses of the outcomeresearch field (7,73). Historically, the Iowa 500 study was the first study to compare outcome in schizophrenia patients with a comparison group of medical patients and other psychiatric patients while using rigorous, modern diagnostic criteria. This study established the expected result that schizophrenia patients fared worse than patients with other psychiatric conditions and other medical disorders. However, the Feighner criteria (which are extremely narrow diagnostic criteria) were used to diagnose schizophrenia, which created a selection bias toward severity in course. Nevertheless, these findings were replicated by the Chestnut Lodge Follow-Up Study, which used the more inclusive DSM-III criteria. This study also showed that schizophrenia patients have poorer outcomes than patients with schizoaffective disorder, schizotypal personality, and borderline personality disorder (74). Finally, our own prospectively designed follow-up study has also consistently found large significant differences in course and outcome when schizophrenia patients are compared with patients having other psychotic and nonpsychotic conditions (31, 32,34,35). Of the studies McGlashan examined, only the Vermont study contradicted these results, finding no difference in outcome between schizophrenia patients and other psychiatric patients. A subsequent analysis of this study, however, revealed several factors that may have influenced its results. First, the average age of onset was substantially older (this is a favourable prognostic factor). Second, some patients were later rediagnosed as having a nonschizophrenic psychiatric disorder; there was a strong selection bias toward including them in the program and then studying high-functioning patients because the "best workers in the hospital" were thought to be the most appropriate patients for the study (7). McGlashan's review also supports a long-held clinical observation of European follow-up studies that schizophrenia plateaus several years after onset. In a New York City outpatient clinic follow-up study that used outpatients for the index episode (75), 63% of patients who were rehospitalized were admitted during the first 2 years of the follow-up. Even the Vermont follow-up showed a definite stabilization and

gradual improvement after 5 years. Despite the fact that a plateau or stabilization process appears to occur, this does not imply homogeneity in the outcome of the later course of the illness. Rather, there is partial independence of outcome variables in the broad mid-range of the spectrum, and there can be a high degree of divergence among individuals (76). Also, this stabilization process does not protect against a relatively high mortality rate, which remains higher than that of most other psychiatric patient groups. Overall, the lifespan for schizophrenia patients is shortened by approximately 10 years for men and 9 years for women (77). The suicide rate was 8% in the Chestnut Lodge Follow-Up Study and as high as 10% for the Columbia Psychiatric Institute and Iowa 500 studies. In our own longitudinal study, the rate of completed suicides was about 10% by the 10-year follow-up (29,36) and over 12% by the 20-year follow-up. Medical conditions, especially infections and circulatory diseases, also contribute to the increased mortality of schizophrenia patients (78).

The fundamental question raised by McGlashan's review is still with us today: how much of the heterogeneity in outcome found in schizophrenia is due to the methodological differences in the studies, and how much is due to actual etiologic subtypes or separate pathophysiological trajectories within the disorder itself that interact with environmental factors? McGlashan's answer to this question was to divide chronicity into 4 variables that could be measured within 3 of the 10 studies he reviewed, given their overlapping methodologies. The results may have been independent of treatment, and McGlashan concluded that "long-term follow-up studies have yet to demonstrate clearly the effects of treatment on the natural history of schizophrenia" (7, p 531). One of the critical problems here is the difficulty in following up patients who leave the mental health care system so that they can be compared with a treatment group. Fenton and McGlashan concluded, and our data agree, that some of the schizophrenia patients who leave the mental health care system, and thus are usually not included in treatment studies, are patients who have recovered (35,70). Further, some outcome studies that followed patients retrospectively all the way back to before the medication era found little difference in outcome, compared with later studies (25); however, others believe that, because of modern hospital care, short-term hospital stays, and widespread use of antipsychotic medication as well as psychosocial treatments, fewer schizophrenia patients are dying from multiple medical diseases and fewer are becoming long-term, chronically institutionalized patients.

These follow-up studies again show heterogeneity in long-term outcome, with between 21% and 57% showing good outcome, depending on the strictness of the criteria used to diagnose schizophrenia. The strictness of diagnosis appears to be related to the degree to which affective symptoms are

excluded, since they are associated with better outcome when present during the acute phase. Also, some of these studies measured negative symptoms, which seem to be associated with cognitive impairments, poor outcome, and work and social impairment. Some of the studies from the Carpenter–Kirkpatrick research group (79,80) have led to a reframing of the concept of negative symptoms, with a focus on an important subgroup of schizophrenia patients who have a more enduring type of negative symptoms, labelled "deficit syndrome," and who have poorer outcomes, as well as other important differences.

#### **Overall Outlook**

When one surveys the research on long-term course and outcome in schizophrenia, one can find several flaws in the studies outlined above. These include, among others, a lack of uniform criteria used to diagnose schizophrenia, a lack of uniform assessment methods, different statistical approaches, a lack of clarity regarding the stages of the disorder at which patients were being studied, and the study of patients under different treatment regimes. At the same time, while each of the studies is imperfect, each has produced some unique advances in the field. In addition, when considered as a group, they have substantially increased our knowledge of schizophrenia and provided many new leads concerning issues about schizophrenia that need further study. In regard to our current knowledge of course and outcome in schizophrenia, the studies have provided data showing both negative and positive aspects of outcome. On the negative side, the long-term studies that compare schizophrenia patients with other types of patients have produced data indicating that, even with current treatments, schizophrenia patients as a group show poorer outcome than patients with other types of psychiatric disorders; in this sense, schizophrenia is a poor-outcome disorder. On the positive side, these studies have provided important data on prognostic factors, as well as overwhelming evidence that very few patients with schizophrenia show a progressive downhill course and that a subgroup of schizophrenia patients shows intervals or periods of recovery. However, still open to question is the percentage of patients with schizophrenia who have this potential for recovery as well as all the factors involved in facilitating

Overall, we now have a much better understanding of how the course of schizophrenia differs from that of other disorders, and we have been alerted to the danger of suicide and early death among schizophrenia patients. We have also been alerted to potential problems in the management and treatment of schizophrenia as well as the possibility of intervals or periods of recovery. Even the heterogeneity that has been found should alert us to explore in greater detail the internal

characteristics of our schizophrenia patients that lead to this heterogeneity.

#### **Funding and Support**

This research was supported in part by US Public Health Service Grants MH-26341 and MH-068688 from the National Institute of Mental Health to Dr Harrow.

#### References

- Hegarty J, Baldessarini R, Tohen M, Waternaux C. One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am J Psychiatry 1994; 151:1409–16.
- McGlashan T, Carpenter WJ, Bartko J. Issues of design and methodology in long-term follow-up studies. Schizophr Bull 1988;14:569–74.
- Stephens J, Astrup C, Mangrum J. Prognostic factors in recovered and deteriorated schizophrenics. Am J Psychiatry 1966;122:1116–21.
- Stephens J, Astrup C, Mangrum J. Prognosis in schizophrenia: prognostic scales cross-validated in American and Norwegian patients. Arch Gen Psychiatry 1967;16:693

  –8.
- Vaillant G. The prediction of recovery in schizophrenia. J Nerv Ment Dis 1962:135:448–57.
- Harrison G, Hopper K, Craig T, Laska E, Siegal C, Wanderling J, and others. Recovery from psychotic illness: a 15- and 25-year international follow-up study. Br J Psychiatry 2001;178:506–17.
- McGlashan T. A selective review of recent North American long-term follow-up studies of schizophrenia. Schizophr Bull 1988;14:515

  – 40.
- Winokur G, Tsuang M. The natural history of mania, depression, and schizophrenia. Washington (DC): American Psychiatric Press; 1996.
- Morrison J, Clancy J, Crowe R, Winokur G. The Iowa 500: I. Diagnostic validity in mania, depression, schizophrenia. Arch Gen Psychiatry 1972;27:457–61.
- Clancy J, Tsuang M, Norton B, Winokur G. The Iowa 500: a comprehensive study of mania, depression, and schizophrenia. J Iowa Med Soc 1974;64:394–8.
- Tsuang M, Winokur G. The Iowa 500: field work in a 35-year follow-up of depression, mania, and schizophrenia. Can Psychiatr Assoc J 1975;20:359

  –65.
- 12. Feighner J, Robins E, Guze S, Woodruff R, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 1972;26:57–63.
- Harding C, Brooks G, Ashikiga T, Strauss J, Breier A. The Vermont longitudinal study of persons with severe mental illness, I. Methodology, study sample, and overall status 32 years later. Am J Psychiatry 1987;144:718–26.
- Harding C, Brooks G, Ashikiga T, Strauss J, Breier A. The Vermont longitudinal study of persons with severe mental illness: II. Long-term outcome of subjects who retrospectively met DSM-III criteria for schizophrenia. Am J Psychiatry 1987;144:727–35.
- Strauss J, Carpenter W. The prediction of outcome in schizophrenia. I. Characteristics of outcome. Arch Gen Psychiatry 1972;27:739

  –46.
- Brooks G, Deane W. The chronic mental patient in the community. Diseases of the Nervous System 1965;26:85–90.
- Brooks G, Deane W, Laqueur P. Fifteen years of work therapy: its impact on a mental hospital and its community. Diseases of the Nervous System 1970;31(Suppl):161–5.
- McGlashan T. The Chestnut Lodge Followup Study. I. Follow-up methodology and study sample. Arch Gen Psychiatry 1984;41:573–85.
- McGlashan T. The Chestnut Lodge Followup Study. II. Long-term outcome of schizophrenia and the affective disorders. Arch Gen Psychiatry 1984;41:586–601.
- Luborsky L. Clinicians' judgment of mental health: a proposed scale. Arch Gen Psychiatry 1962;7:141–4.
- Stone M. Exploratory psychotherapy in schizophrenia-spectrum patients: a reevaluation in the light of long-term follow-up of schizophrenia and borderline patients. Bull Menninger Clin 1986;50:287–306.
- Vaillant G. An historical review of the remitting schizophrenias. J Nerv Ment Dis 1964;138:48–56.
- Vaillant G. A 10-year followup of remitting schizophrenics. Schizophr Bull 1978:4:78–85.
- Stephens J, Astrup C. Prognosis in "process" and "non-process" schizophrenia. Am J Psychiatry 1963;119:945

  –54.
- Stephens J, Pascal R, McHugh P. Long-term follow-up of patients hospitalized for schizophrenia, 1913 to 1940. J Nerv Ment Dis 1997;185:715–21.
   Bland R, Parker J, Orn H. Prognosis in schizophrenia: a ten-year follow-up of
- first admissions. Arch Gen Psychiatry 1976;33:949–54.
  27. Bland R, Orn H. Fourteen-year outcome in early schizophrenia. Acta Psychiatr
- Scand 1978;58:327–38.

  28. Silverstein M, Harrow M. First rank symptoms in the post-acute schizophrenic: a
- followup study. Am J Psychiatry 1978;135:1481–6.
  29. Carone J, Harrow M, Westermeyer J. Posthospital course and outcome in
- Carone J, Harrow M, Westermeyer J. Posthospital course and outcome in schizophrenia. Arch Gen Psychiatry 1991;48:247–53.

- Sands J, Harrow M. Depression during the longitudinal course of schizophrenia. Schizophr Bull 1999;25:157–71.
- Harrow M, Sands J, Silverstein M, Goldberg J. Course and outcome for schizophrenia vs other psychotic patients: a longitudinal study. Schizophr Bull 1997;23:287–303.
- Harrow M, Grossman L, Herbener E, Davis E. Ten-year outcome: patients with schizoaffective disorders, schizophrenia, affective disorders, and mood-incongruent psychotic symptoms. Br J Psychiatry 2000;177:421–6.
- Herbener E, Harrow M. Are negative symptoms associated with functioning deficits in both schizophrenic and non-schizophrenic patients? A ten-year longitudinal analysis. Schizophr Bull 2004;30:813–25.
- Harrow M, Grossman L, Jobe T, Herbener E. Do patients with schizophrenia ever show periods of recovery? A 15-year multi-followup study. Schizophr Bull 2005;31:723–4.
- Harrow M, Jobe T, Grossman L, Martin E, Faull R. Do all patients with schizophrenia need antipsychotic medications continuously? A 20-year multi-followup study. Schizophr Bull 2005;31:486.
- Westermeyer J, Harrow M, Marengo J. Risk for suicide in schizophrenic and other psychotic and nonpsychotic disorders. J Nerv Ment Dis 1991;179:259–66.
- Kaplan K, Harrow M. Psychosis and functioning as risk factors for later suicidal activity among schizophrenia and schizoaffective patients: an interactive model. Suicide Life-Threat Behav 1999;29:10–24.
- Racenstein J, Harrow M, Reed R, Martin E, Herbener E, Penn D. The relationship between positive symptoms and instrumental functioning in schizophrenia: a 10-year followup study. Schizophr Res 2002;56:95–103.
- Harrow M, Lanin-Kettering I, Prosen M, Miller J. Disordered thinking in schizophrenia: intermingling and loss of set. Schizophr Bull 1983;9:354

  –67.
- Harrow M, Lanin-Kettering I, Miller J. Impaired perspective and thought pathology in schizophrenic and psychotic disorders. Schizophr Bull 1989;15:605–23.
- Harrow M, Jobe T, Herbener E, Goldberg J, Kaplan K. Thought disorder in schizophrenia: working memory and impaired context. J Nerv Ment Dis 2004;192:3–11.
- Jobe T, Harrow M. Delusions. In: Kadzin A, editor. Encyclopedia of Psychology. New York (NY): Oxford University Press; 2000:467–9.
- Harrow M, Quinlan D. Is disordered thinking unique to schizophrenia? Arch Gen Psychiatry 1977;34:15–21.
- Harrow M, Grossman L, Silverstein M. Thought pathology in manic and schizophrenic patients: its occurrence at hospital admissions and seven weeks later. Arch Gen Psychiatry 1982;39:665–71.
- Pogue-Guile F, Harrow M. Negative symptoms in schizophrenia: their longitudinal course and prognostic importance. Schizophr Bull 1985;11:427–39.
- Herbener E, Harrow M. Longitudinal assessment of negative symptoms in schizophrenia/schizoaffective patients, other psychotic patients and depressed patients. Schizophr Bull 2001;27:527–37.
- Harrow M, Yonan C, Sands J, Marengo J. Depression in schizophrenia: are neuroleptics akinesia or anhedonia involved? Schizophr Bull 1994;20:327–38.
- Harrow M, Goldberg J, Grossman L, Meltzer H. Outcome in manic disorders: a naturalistic followup study. Arch Gen Psychiatry 1990;47:665–71.
- Goldberg J, Harrow M, Grossman L. Course and outcome in bipolar affective disorders: a longitudinal followup study. Am J Psychiatry 1995;152:379

  –84.
- Carpenter W, Bartko J, Strauss J. Signs and symptoms as predictors of outcome: a report from the International Pilot Study of Schizophrenia. Am J Psychiatry 1978;135:940–5.
- Carpenter W, Strauss J. The prediction of outcome in schizophrenia IV. Eleven-year follow-up of the Washington IPSS cohort. J Nerv Ment Dis 1991;179:517–25.
- Strauss J, Carpenter W. The prognosis of schizophrenia: rationale for a multidimensional concept. Schizophr Bull 1978;4:56–67.
- Hawk A, Carpenter W, Strauss J. Diagnostic criteria and five-year outcome in schizophrenia: a report from the International Pilot Study of Schizophrenia. Arch Gen Psychiatry 1975;32:343–7.
- Angst J. European long-term follow-up studies of schizophrenia. Schizophr Bull 1988;14:501–13.
- Ciompi L. Catamnestic long-term study on the course of life and aging of schizophrenics. Schizophr Bull 1980;6:606–18.
- Breier A, Schreiber J, Dyer J, Pickar D. National Institute of Mental Health Longitudinal Study of Chronic Schizophrenia: prognosis and predictors of outcome. Arch Gen Psychiatry 1991;48: 236–46.
- Bleuler M. The schizophrenic disorders: long-term patient and family studies.
   New Haven (CT): Yale University Press; 1978.

- DeSisto M, Harding C, McCormick R, Ashikaga T, Brooks G. The Maine and Vermont three–decade studies of serious mental illness. II. Longitudinal course comparisons. Br J Psychiatry 1995;167:338–42.
- Hinterhuber H. Zur Katamnese der Schizophrenien. Fortshritte der Neurologie-Psychiatrie. 1973;41:527–88.
- Huber G, Gross G, Schuettler R, Linz M. Longitudinal studies of schizophrenic patients. Schizophr Bull 1980;6:592

  –605.
- Jeste D, Twamley E, Zorrilla L, Golshan S, Patterson T, Palmer B. Aging and outcome in schizophrenia. Acta Psychiatr Scand 2003;107:336–43.
- Kulhara P. Outcome of schizophrenia: some transcultural observations with particular reverence to developing countries. Eur Arch Psychiatry Clin Neurosci 1994;244:227–35.
- Lynge I, Jacobsen J. Schizophrenia in Greenland: a follow-up study. Acta Psychiatr Scand 1995;91:414

  –22.
- Marinow A. Prognosis and outcome in schizophrenia. Int J Ment Health 1988;17:63–80.
- Ogawa K, Miya M, Watarai A. A long-term follow-up study of schizophrenia in Japan—with special reference to the course of social adjustment. Br J Psychiatry 1987:151.
- McGrath J. Myths and plain truths about schizophrenia epidemiology—the NAPR lecture 2004. Acta Psychiatr Scand 2005;111:4–11.
- 67. Weinberger D. From neuropathology to neurodevelopment. Lancet 1995;346:552–7.
- Pantelis C, Yucel M, Wood S, McGorry P, Velakoulis D. Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences. Aust N Z J Psychiatry 2003;37:399–406.
- Bilder R, Goldman R, Volavka J. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002;159:1018–28.
- Fenton W, McGlashan T. Sustained remission in drug-free schizophrenic patients. Am J Psychiatry 1987;144:1306–9.
- Tooth B, Kalyanasundaram V, Glover H, Momenzadah S. Factors consumers identify as important to recovery from schizophrenia. Australasian Psychiatry 2003;11:70–7
- Weiden P, Daniel DG. The standard of care in treating psychiatric disorders.
   Johns Hopkins University School of Medicine Advanced Studies in Medicine. 2005;5:S216–S239.
- McGlashan T. Selective review of recent North American long-term follow-up studies of schizophrenia. In: Mirin S, Gossett J, editors. Psychiatric treatment: advances in outcome research. Washington (DC): American Psychiatric Association; 1991:61–105.
- Davidson L, McGlashan T. The varied outcomes of schizophrenia. Can J Psychiatry 1997;42:34–43.
- Engelhardt D, Rosen B, Feldman J, Engelhardt J, Cohen P. A 15-year follow-up of 646 schizophrenic outpatients. Schizophr Bull 1982;8:493–503.
- Carpenter W, Kirkpatrick B. The heterogeneity of the long-term course of schizophrenia. Schizophr Bull 1988;14:645–52.
- Tsuang M, Woolson R, Fleming J. Premature deaths in schixophrenia and affective disorders: an analysis of survival cures and variables affecting the shortened survival. Arch Gen Psychiatry 1980;37:979–83.
- Tsuang M, Woolson R, Fleming J. Causes of death in schizophrenia and manic-depression. Br J Psychiatry 1980;136:239

  –42.
- Carpenter WJ, Heinrichs D, Wagman A. Deficit and nondeficit forms of schizophrenia: the concept. Am J Psychiatry 1988;145:578–83.
- Kirkpatrick B, Buchanan R, Ross D, Carpenter WJ. A separate disease within the syndrome of schizophrenia. Arch Gen Psychiatry 2001;58:165–71.

Manuscript received and accepted June 2005.

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# Résumé : Le résultat à long terme de patients souffrant de schizophrénie : une analyse

**Objectif :** Examiner les études empiriques qui évaluent le résultat de patients souffrant de schizophrénie et qui estiment le degré auquel le résultat déclaré est influencé par la méthodologie de recherche, les variables du traitement, les facteurs pronostiques, les facteurs épidémiologiques et la résilience des patients.

**Méthode :** Nous avons examiné des études qui utilisaient des sujets témoins et duraient dix ans ou plus, et les avons comparées quant à la méthodologie de recherche et au choix des variables de résultat.

**Résultats :** Comme d'autres maladies mentales ou maladies somatiques en général, le cours naturel de la schizophrénie s'est avéré comporter trois divisions : doux, modéré et grave. Même s'il y avait beaucoup de variance dans les résultats des différentes études examinées, la schizophrénie est néanmoins un trouble dont le résultat est relativement mauvais. Les patients souffrant de schizophrénie montraient de façon constante des cours et résultats plus mauvais que ceux des patients souffrant d'autres troubles psychiatriques psychotiques et non psychotiques. Du côté positif, les sous-groupes de patients souffrant de schizophrénie avaient des périodes de rémission prolongées — certains sans les avantages d'un traitement de suivi prolongé en santé mentale — et les patients souffrant de schizophrénie ne montraient pas de cours descendant progressif.

Conclusion: Tout en documentant l'hétérogénéité des résultats et les résultats généralement mauvais des patients souffrant de schizophrénie, les études examinées nous avertissent aussi du danger de suicide et de décès précoce dans la schizophrénie. En outre, elles exposent les problèmes de prise en charge et de traitement cliniques, et nous aident à prévoir la possibilité d'intervalles ou de périodes de rémission, dont certains apparaissent spontanément et peuvent être liés aux facteurs individuels du patient, comme la résilience.