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Current Directions in Psychological Science 2010 19: 220
DOI: 10.1177/0963721410378034

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Schizophrenia Course, Long-Term Outcome, Recovery, and Prognosis

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Abstract
Our 26-year longitudinal study and other longitudinal studies confirm older views that outcome for schizophrenia, while showing some variation for different schizophrenia patients, is still significantly poorer than that for other psychiatric disorders, with the exception of the dementias. Our research leads us to propose that risk factors, either stress related or those related to vulnerability to psychosis, account for the episodic course of periods of recovery followed by periods of recurrence that is experienced by most schizophrenia patients. These risk factors interact with personality, temperament, and cognitive traits that, while not causing psychosis, influence its course. It is these interactions that account for the heterogeneous outcome trajectories of different subgroups of people with this condition. Our research and that of others has focused on the contributions of these risk factors, such as vulnerability to trait anxiety, poor developmental achievements before the illness, personality traits such as locus of control, cognitive styles, neurocognitive impairments, length of untreated psychosis, and several others. Despite the proven efficacy of antipsychotic medications over the short term, there is a subgroup of schizophrenia patients who, a few years after the acute phase, function adequately or experience periods of recovery for a number of years, without treatment.

Keywords
schizophrenia, prognosis, longitudinal research, outcome, recovery

Long-term outcome in schizophrenia and whether recovery is possible have long been central issues in theoretical views of the nature of the disorder (Liberman & Kopelowicz, 2002; Harrow, Grossman, Jobe, & Herbener, 2005; Jobe & Harrow, 2005; McGlashan, 1988, Silverstein & Bellack, 2008). Central to ideas about the nature of schizophrenia and about its definitional boundaries is its very poor long-term course. Emil Kraepelin originally viewed this disorder as involving a progressive downhill course like forms of dementia (e.g., Alzheimer’s) but beginning in late adolescence or young adulthood; he thus called it dementia praecox (“premature dementia”). Eugen Bleuler was slightly more optimistic. Although he recognized that some of the symptoms in the disorder are chronic, he did not believe that patients always show a downward course; he noted that chronic symptoms are often less severe after the initial acute phase. Bleuler renamed the disorder schizophrenia to reflect his observations that connections between ideas are often “split” (i.e., loose associations). A series of modern follow-up studies, including our own longitudinal research and that of others, has suggested that despite the advent of the modern era of psychopharmacological treatment and psychosocial rehabilitation, schizophrenia is still a diagnosis with a relatively poor outcome (Harrow, Sands, Silverstein, & Goldberg, 1997; Harrow, Jobe, & Astrachan-Fletcher, 2008; Harrow, McDonald, Sands, & Silverstein, 1995; McGlashan, 1988, Tsuang, Woolson, & Fleming, 1979); however, some recent studies show that modern treatment methods may produce some limited improvement in disease course, as well as periods of complete recovery for a number of patients with schizophrenia (Jobe & Harrow, 2005; Harrow et al., 2005; Liberman & Kopelowicz, 2002; Silverstein & Bellack, 2008).

Thus, when we look at the recent literature, we find both promising and disappointing features associated with outcome and recovery in schizophrenia. On the negative side, our longitudinal research from the Chicago Followup Study (Harrow et al., 2005; Jobe & Harrow, 2005) and the research of Tsuang et al. (1979), McGlashan (1988), and the World Health Organization Study (Harrison et al., 2001), as well as others who also use control groups of other severely disturbed patients, provide very strong evidence that, despite modern treatment, the course and outcome for schizophrenia patients are poorer than those for other psychotic and nonpsychotic patients. A consistent feature during early phases (the first 10 to 15 years) is more recurrent psychopathology for many patients. Even after the first 10 years,

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outcome and the potential for periods of complete recovery are poorer for schizophrenia than they are for other psychotic and nonpsychotic disorders. The majority of patients with schizophrenia are vulnerable to recurring positive symptoms, such as psychosis and/or disorganized thinking/thought disorder and also to negative symptoms (i.e., reduced or flattened affect, reduced or impoverished speech, and reduced or retarded motor movements), with more persistent symptomatic and functional impairment over time than is found in other types of psychotic patients (Harrow et al., 2004; Harrow et al., 2008; Herbener & Harrow, 2004). The functional impairment—particularly work disability (in regard to obtaining or maintaining employment)—is considerable (Harrow et al., 2004; Harrow et al., 2005; Herbener & Harrow, 2004).

On the positive side, with modern-day treatment during the acute phase, over 40% of patients with schizophrenia will later show one or more periods of global recovery (defining recovery as a period of 1 or more years with no positive symptoms or negative symptoms, no psychiatric hospitalizations, adequate socialization, and at least half-time instrumental work functioning). Rather than viewing recovery as a static state, one should view it in terms of periods of recovery; partly depending on the extent of a particular patient’s underlying biological vulnerability to psychosis, these periods may last for a relatively short period, or they may last over 10 years or even for a lifetime.

Figure 1 shows results on periods of recovery in patients hospitalized with schizophrenia and mood disorders whom we have followed up seven times over 26 years. For many of the more resilient and less vulnerable schizophrenia patients, the disorder is not chronic and continuous but, rather, is episodic, although episodes are still generally more frequent, more severe, and last longer than those of other major disorders.

We have looked at our longitudinal data in terms of a stress-diathesis model in which the internal biological diathesis component plays a dominant role in vulnerability to future potential psychopathology. In this model, stress is viewed as external or environmental factors that can create anxiety in the particular person; a diathesis is a constitutional or biological predisposition to certain types of psychopathology, and vulnerability is viewed in terms of areas of greater internal and/or external susceptibility to various types of psychopathology. Using this model, patients with schizophrenia (a) have an underlying biological vulnerability to psychosis, negative symptoms, and poor outcome; and (b) this vulnerability is accentuated by a large group of internal and external risk factors (e.g., vulnerability to anxiety, external locus of control, low self-esteem). The combination of these risk factors with other unfavorable cognitive biases and deficits (e.g., jumping to conclusions, externalizing attributional biases, poor understanding of the intentions of other people) emphasized by Garety and Freeman (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001), and by Bentall and others can dramatically increase these patients’ chances of expressing overtly their underlying biological/genetic vulnerability to psychosis. A combination of some of the above factors, in a patient with greater vulnerability to psychosis, can sometimes result in new acute episodes.

Other aspects of a model of course and outcome in schizophrenia involve a neurodevelopmental view in which poor premorbid developmental achievements, poor prognostic features, and neurocognitive impairment strongly increase the recurrence and persistence of later positive and negative symptoms and produce poorer global course, poorer outcome, and lower chance of periods of recovery years later (Harrow et al., 2005; Zigler & Glick, 2001).

**Model of Outcome in Schizophrenia**

On the basis of our data and other data reported previously, one could propose a model in which, with modern-day antipsychotic medications to shorten periods of extreme psychosis, virtually all patients with schizophrenia improve some after the original acute phase of hospitalization. After the acute phase, a small- to moderate-sized subsample of schizophrenia patients (25%–35%) show chronic or continuous psychotic symptoms and/or show other chronic symptoms that last for many years (Harrow et al., 1997, Harrow et al., 2008). However, for a moderate to large percentage of schizophrenia patients (over 50%), the disorder is not chronic but, rather, is characterized by episodic periods of symptoms, often with continual or chronic malfunctioning, adjustment difficulties, and some impairment in functioning between episodes (Harrow & Jobe, 2010).

**Antipsychotic Medications: A Subgroup of Patients With Schizophrenia Who Leave Treatment**

At this point, another important subgroup of schizophrenia patients that is often ignored in treatment studies should be mentioned. Our longitudinal studies have found evidence of a subgroup of 20% to 35% of patients with schizophrenia who, after showing signs of better functioning and partial or global recovery for a period of time, have gone off or been taken off...
antipsychotics or have left treatment (Harrow & Jobe, 2007). Many schizophrenia patients from this subgroup continue to function well for a number of years without treatment. This would suggest that not all schizophrenia patients need to be on antipsychotic medications throughout their lives (Harrow et al., 2005; Harrow & Jobe, 2007; Bleuler, 1978). Since many patients from this subgroup of patients are not in treatment, this subgroup, many of whom are experiencing periods of recovery, are almost never included in double-blind drug-placebo studies. Findings by our group, by M. Bleuler (1978), and by Fenton and McGlashan (1987) agree that some unmedicated schizophrenia patients are doing well. Also, data from the longitudinal studies of the World Health Organization (WHO; Harrison et al., 2001) and of R. Bland would support the conclusion that not all schizophrenia patients need to be treated with antipsychotics throughout their lives. This in no way detracts from the strong evidence of some improvements with both psychopharmacological, psychological, and psychosocial treatment of schizophrenia over the short term of months to a few years.

Other Aspects of Outcome in Schizophrenia

Many long-term follow-up studies in both the United States and Europe suggest that after about 5 years, the symptom picture in schizophrenia becomes stable and does not worsen. Other data suggest that the overall picture for some schizophrenia patients could improve as they get older, although this latter possibility still awaits solid research on those patients’ longitudinal course. Despite the fact that a plateau or stabilization process appears to occur, this does not imply a single trajectory for the later course of the illness. Rather, as with many other disorders, there can be a high degree of divergence or heterogeneity among individuals. Also, this stabilization process does not protect against a relatively high mortality rate for schizophrenia (Jobe & Harrow, 2005).

Overall, the lifespan for schizophrenia patients is shortened by 9 years or more. Some, but not all, of this is accounted for by a high suicide rate during the first 10 years of the disorder for middle-socioeconomic-class male schizophrenia patients (Harrison et al., 2001). People with other major mental disorders and with substance abuse also have a shorter life expectancy.

Cultural variables also affect long-term follow-up. The WHO study followed a large sample of culturally diverse subjects for up to 15 and 25 years (Harrison et al., 2001). Surprisingly, outcome for the patients with schizophrenia was better in developing countries than it was in developed countries. This finding could be influenced, in part, by greater acceptance of schizophrenia by patients’ families in developing countries; the mechanism could be less anxiety and stress, although many other as-yet-unknown factors are probably involved.

Risk and Protective Factors for Course and Outcome in Schizophrenia

In addition to genetic/biological factors that contribute to a poor outcome, there are many other patient-centered factors that contribute substantially. These include poorer cognitive skills, longer duration of untreated psychosis, less continuity of treatment, substance abuse, family overinvolvement with high expressed emotion, higher vulnerability to trait anxiety (Harrow et al., 2008; Walker, McMillan, & Mittal, 2009), poorer developmental achievements prior to becoming ill (Zigler & Glick, 2001; Harrow & Jobe, 2007), and other important developmental variables, as well as unexpected, unpredictable life events.

In addition, older research by Vaillant (1978) and by J. Stephens, our own group, and others produced empirical evidence that an important series of variables predict subsequent poor prognosis in schizophrenia. These variables include indicators such as lack of acute onset, no precipitating stress at index hospitalization (index refers to early hospitalization, when patients first begin to be studied), poor work and social adjustment before index, absence of depressive symptoms, no preoccupation with death, no guilt, no confusion, being unmarried, and having blunted affect. Modern, narrow definitions of schizophrenia (e.g., DSM-III-R and DSM-IV) have already incorporated in the diagnostic criteria for schizophrenia some of these prognostic variables that predict unfavorable outcome. However, despite this, some of these classical prognostic variables that have not been incorporated into modern narrow criteria for schizophrenia still have negative prognostic significance.

The Role of Anxiety

We view the issue of risk and protective factors in terms of the stress-diathesis vulnerability model. One example is a combination of high internal vulnerability to psychosis and vulnerability to anxiety (as part of the diathesis) coupled with the experience of external stress. Stress-related anxiety as a factor presents some complexity since the difficulty is a function of both external stress and a person’s biological vulnerability to anxiety. Thus some people get “anxious” much more quickly than others, because of a higher vulnerability to anxiety, and also the biological system (the hypothalamic-pituitary-adrenal [HPA] axis) of some patients with schizophrenia may produce more negative effects on other functions when those patients get anxious. The research and reviews of a number of major investigators have emphasized the importance of anxiety and stress as potential factors involved in the genesis and maintenance of psychosis in vulnerable people (Corcoran et al., 2003; Harrow et al., 2008; Docherty et al., 2009; Walker et al., 2009).

Our multiple follow-up research design has allowed us to begin to explore this issue on a longitudinal basis. Our research using standardized anxiety scales suggests that some, but not all, patients with schizophrenia are vulnerable to high anxiety. Our longitudinal data suggest high anxiety is one prominent risk factor increasing the chances for more sustained and chronic pathology in patients who are biologically vulnerable to psychosis and schizophrenia (Harrow et al., 2008).
While our anxiety data suggest that not all patients with schizophrenia are vulnerable to anxiety, our research has indicated that those schizophrenia patients with greater vulnerability to anxiety are more likely to have a poorer or more chronic course. Looked at from this perspective, anxiety is not a specific diathesis for schizophrenia, but it is a nonspecific risk factor that increases vulnerability to psychosis in already-vulnerable patients and that can influence overall course and outcome in schizophrenia in a negative direction.

It has been proposed that the biological response to stress, which is linked to the level of the hormone cortisol and is regulated by the HPA axis, can trigger a downstream cascade of neurochemical events—events that could exacerbate psychosis through several neural circuits as well as lead to hypersensitivity of the D2 dopamine receptor, as noted by P. Seeman and other major investigators (Corcoran et al., 2003; Walker et al., 2009). A high vulnerability to anxiety combined with external stress, high cognitive arousal, and other genetic risk factors can trigger excess HPA axis and neurochemical activity, leading to psychosis in biologically vulnerable patients. The longitudinal data on anxiety also could be consistent with the view, advanced by some, that the release of dopamine (a neurotransmitter that is one factor playing an important role in the emergence of psychosis) is differentially increased by exposure to stress and anxiety in schizophrenia. Our findings are also consistent with other proposed mechanisms that may increase vulnerability to anxiety in schizophrenia patients, such as increased presynaptic striatal dopamine release during stress and increases in aberrant salience, which refers to the attribution of undue importance to insignificant stimuli and/or emotions (Howes & Kapur, 2009). British social psychiatrists have found evidence, replicated many times, that schizophrenia patients tend to have poorer outcomes when living in family environments with high expressed emotion (EE), in which key relatives are critical of or hostile to the patient or are emotionally overinvolved with him or her. Our group and several other groups link the poor outcome to the patients living in a high-anxiety environment in which they sense their family’s unhappiness about them and, as a result, continuously feel under pressure and anxious (Docherty et al., 2009; Harrow et al., 2008). Other factors are probably also involved.

### Other Risk and Protective Factors

In our studies of the role of various personality dimensions, we have looked at a number of personality factors, including locus of control (LOC). The concept of LOC, originally proposed as part of Rotter’s social learning theory, is assessed by asking people whether they believe that events in their lives result from their own efforts, skills, and internal dispositions (internal control). The alternative to this belief is that events result from external forces such as luck, chance, fate, or powerful others (external control). Our data indicate that external LOC is not specific to schizophrenia (Harrow, Hansford, & Astrachan-Fletcher, 2009). However, patients with psychosis (including schizophrenia patients) and also those with depression tend to be more external. We also have looked at our longitudinal data to see if being internal predicts recovery (Harrow et al., 2009). Our results indicate that internality is significantly associated with recovery in schizophrenia.

The data could be interpreted as suggesting a possible reciprocal effect between recovery and increased internality on LOC (internal attitudes increase the chances of recovery, and successful recovery encourages a view of positive events such as recovery as due to one’s own efforts and skills). This finding would fit within the results of Strauss and Carpenter’s concept of an open-linked system (Strauss & Carpenter, 1972). This refers to the linkages between predictor variables and outcome variables in which some predictor variables are more highly correlated with themselves at outcome than with other predictor variables at outcome when outcome is assessed over multiple years. It is an open-linked system in the sense that outcome variables are moderately intercorrelated, and no one variable comes to dominate the others.

Longitudinal research on outcome has challenged some seemingly promising formulations on the background basis of recovery and of psychosis in schizophrenia. Thus, research indicates that a multitude of different complex factors, rather than only one factor, influence the behaviors associated with psychosis, outcome, and recovery.

### Overview

Overall, longitudinal research on outcome has substantially increased our knowledge of schizophrenia and provided new leads concerning issues that need further study. As far as our current knowledge of course and outcome in schizophrenia, the research has provided data showing both negative and positive aspects concerning their 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 modern-day treatment, patients with schizophrenia 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, there is overwhelming evidence that very few patients with schizophrenia show a progressive downhill course and that a moderate-sized subgroup of more resilient schizophrenia patients show intervals or periods of recovery. However, still open to question are the percentage of patients with schizophrenia who have the potential for long-term recovery, the factors involved in facilitating recovery, and how (and whether) those factors fit together (Harrow et al., 2005).

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 in schizophrenia. We have also been alerted to potential problems in the management and treatment of schizophrenia, as well as to the possibility of intervals or periods of recovery. The heterogeneity that has been found in schizophrenia should alert us to explore in greater detail the internal characteristics that lead to different individuals having different outcomes and to the factors involved in the multiple different variables that can lead to the
poorer outcome of patients with schizophrenia. This level of complexity in outcome of schizophrenia supports the view that therapies need to be varied and evidence based (Silverstein, Spaulding, & Menditto, 2006). Finally, whether antipsychotic medication should be used continuously beyond 2 years from the initial acute episode is also a question that needs to be answered based on the evidence, given the potential of failure of antipsychotic drugs, breakthrough hypersensitivity psychosis (where D2 dopamine receptors become hypersensitive to compensate for their persistent blockade by antipsychotic medications taken by the patient), and rebound psychosis—factors that may contribute to the poorer outcome of schizophrenia patients on antipsychotic medication than of those not on medication over the longer term (Chouinard & Chouinard, 2008).

Have modern-day treatments changed the course or prognosis of schizophrenia in the last 60 years? The data on long-term course and treatment clearly indicate that, largely as a result of antipsychotic medications, the flagrant psychosis that is often present at the acute phase has been shortened for many patients. Partly as a result of antipsychotics and other modern treatments, and partly as a result of changes in social attitudes and outlooks, long-term hospitalization has been discouraged. Outcome during the first 2 years after the acute phase is also probably somewhat better than before. The improvement in outcome provides a more favorable therapeutic framework for starting rehabilitation. Numerous rehabilitative efforts have been attempted (including supported employment), with a number showing some limited promise. However, beyond shortening the acute phase, reducing long-term hospitalization, and reducing the chances of remission during the first few post-hospital years (all important gains), researchers still disagree on the extent to which the long-term outcome of schizophrenia has been improved.

### Recommended Reading


Harrow, M., Grossman, L., Jobe, T., & Herbener, E. (2005). (See References). A longitudinal (15 years) study providing data on periods of recovery in schizophrenic patients, comparing those patients to other psychotic and nonpsychotic patients, and also providing data on the issue of recovery in unmedicated patients and on whether schizophrenia is a chronic or continuous disorder.

Jobe, T., & Harrow, M. (2005). (See References). An article reviewing longitudinal studies of outcome in schizophrenia and discussing the methodological strengths and weaknesses of each study design.


Walker, E., McMillan, A., & Mittal, V. (2009). (See References). A compelling overview of one of the most robust models of stress-induced vulnerability to psychosis in schizophrenia research, with an important discussion of how antipsychotic medication may affect this model, which involves the HPA axis and its effect upon the hippocampus.

### Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

### Funding

Supported, in part, by United States Public Health Service Grants MH-26341 and MH-068688 from the U.S. National Institute of Mental Health, to Martin Harrow.

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