The Varied Outcomes of Schizophrenia

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Objective: *To review variations in outcomes in schizophrenia across individual, historical, and cross-cultural boundaries, as well as within specific domains of functioning.*

Method: *Research literature on the outcomes of schizophrenia appearing within the last 8 years was reviewed.*

Results: *First, a review of follow-up studies published in the developed world suggests that heterogeneity in outcome across individuals with schizophrenia remains the rule, with affective symptoms, later and acute onset, and responsiveness to biological treatments predictive of good outcome. Negative symptoms are associated with poor outcome, cognitive impairments, and incapacity in social and work domains. Deterioration appears to occur within the first few months of onset if not already in the prodrome, with recent early-course studies finding longer duration of untreated psychosis associated with insidious onset, negative symptoms, social and work incapacity, and poor outcome. Second, a review of recent cross-cultural and historical studies provides evidence that outcome varies across time and place, schizophrenia having a more favourable outcome in the developing world and becoming a more benign disorder over the course of this century. Third, a review of studies of the domains of functioning within individuals identifies 4 relatively independent dimensions of depression and negative, psychotic, and disorganized symptoms. Cognitive deficits, which are associated with negative symptoms, also constitute a relatively stable dimension over time, showing neither marked deterioration nor improvement once established early in the course of disorder.*

Conclusions: *The early appearance and stability over time of negative symptoms and cognitive impairments call for assertive intervention efforts early in the course of disorder to prevent chronicity and prolonged disability.*

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Key Words: *follow-up studies, prodrome, onset, heterogeneity, outcome, duration of untreated psychosis, negative symptoms*

This paper will review the varied outcomes of schizophrenia in 3 senses. First, there is the variation in outcomes seen *across individuals* with the disorder, what has come to be called the "heterogeneity of the long-term course of schizophrenia" (1). Second, there appears to be a variation in outcomes *between groups* of individuals when one considers both sociocultural and historical context, with outcome varying in part as a result of time and place (2,3). Third, there is a variation in outcomes *within any given individual* when one considers in finer detail the relatively independent domains of functioning that constitute global measures of outcome (4–6). These domains include positive, disorganized, and negative symptomatology and neurocognitive functioning, among others. In this review, we summarize the recent literature in each of these 3 areas, beginning with 1) overall course and outcome, moving through 2) cross-cultural and historical influences on outcome, and closing with 3) outcome in specific domains of functioning. Following this review, we conclude with a brief consideration of future directions for research.

Variations in Course and Outcome as of 1988

We take as our point of departure for this section the reviews of international long-term follow-up studies of schizophrenia collected into a 1988 special issue of the *Schizophrenia Bulletin* (7). This issue provides a comprehensive picture of the accumulated knowledge of the course and outcome of schizophrenia as of the late 1980s and offers a convenient benchmark for the identification of recent advances made in understanding the longitudinal aspects of the disorder.

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Several conclusions were drawn from these reviews of long-term follow-up studies in Europe, North America, and non-Western developing countries, the most consistent of which is that there was a *heterogeneity* in long-term outcome for individuals with schizophrenia within each study sample, regardless of setting (3,8,9). Each study found a range in long-term outcome from fully recovered to severe and continuous incapacity, with substantial numbers of patients in each of the various categories. Differences in the percentages of patients achieving favourable outcomes across studies were attributed at least in part to differing sample characteristics and diagnostic systems (7,8), with the one exception of mounting evidence for a more favourable outcome for individuals in the developing world (3).

With Kraepelinian negative prognosis and progressive, deteriorating course refuted, the remainder of this issue focused on ways to reduce heterogeneity by identifying dimensions of chronicity, prognostic factors, and course patterns. McGlashan (9) suggested 4 dimensions of chronicity: length of mental illness, institutionalization, resistance to biological treatments, and age of onset. In addition, he considered gender, the paranoid–nonparanoid distinction, and a range of other nondiagnostic predictors such as family history of schizophrenia and level of premorbid functioning as useful determinants of outcome. Building upon the earlier work of Ciompi (10), Harding (11) described 8 course patterns based on combinations of acute versus chronic onset, simple versus undulating course, and end states ranging from recovery to severe incapacity. As a first step toward reducing the heterogeneity of course and outcome, Carpenter and Kirkpatrick (1) suggested the delineation of 3 epochs in the course of schizophrenia for use in future long-term studies: the onset epoch, the middle-course epoch, and the late-course epoch. In looking toward the next generation of research, several investigators suggested that a focus on the onset epoch or the early course might be particularly useful in future prospective studies, as existing studies may have underestimated recovery rates because of the failure to include, or early attrition of, healthier subjects who would have met initial diagnostic criteria for schizophrenia.

Studies of Variations in Course and Outcome Appearing since 1988

The most concentrated research efforts examining outcome since the late 1980s have had just such a focus on the onset epoch and early course of disorder through prospective studies of first-episode patients. In addition to this focus, new findings from several follow-up studies have appeared within the last 8 years, largely confirming the findings of earlier studies, particularly in relation to cross-cultural differences. Two prognostic factors have been the focus of considerable attention. With few exceptions (12,13), the most recent studies and reviews continue to provide evidence that substance abuse, most often alcohol and cannabis and most frequently in young men, has a detrimental effect on course and outcome (14–24). Literature on gender differences has been more mixed, with a comprehensive review of 102 studies pointing out that only half of the studies provided evidence for superior outcome in women, the remaining half showing no differences (25). Consistent with this mixed picture, some recent studies continue to provide support for later onset, greater responsiveness to treatment, and better outcomes for women (26–29), while other studies show either no differences (30) or superior outcome in men (31).

In the remainder of this section, we first review the recent long-term follow-up studies completed in developed countries before turning to consider new studies focusing on the onset epoch and early course of disorder. In the next section, we review the cross-cultural findings produced from studies in the developing world, in addition to considering evidence of historical changes in the severity of schizophrenia over the course of this century.

Long-Term Follow-up Studies

We were able to locate 9 follow-up studies that have been completed within the last 8 years in the developed world (32–44). While primarily confirming the findings of earlier long-term studies regarding the heterogeneity of course and outcome in schizophrenia, several of these studies provide important indications about course and outcome that we describe below.

In the most recent report to come out of their landmark study of the International Pilot Study of Schizophrenia (IPSS) Washington cohort, Carpenter and Strauss (32) provided 11-year follow-up data on 40 of the original 131 patients evaluated between 1968 and 1969 who met DSM-II criteria for schizophrenia. These data were consistent with the findings at both 2- and 5-year follow-up that suggested that symptom severity, duration of hospitalization, and work and social functioning constituted "loosely linked" domains of functioning, with level of functioning in each domain at or prior to index admission being most predictive of outcome in that domain. In addition, a global measure of outcome at 11 years remained consistent with outcome assessed at 2 and 5 years, providing evidence of neither marked deterioration nor improvement over the 6- to 9-year period. The investigators suggested that these findings of a lack of deterioration and consistency in outcome indicate that psychopathology tends to plateau early in the course of illness following an initial deterioration, with later-course improvement more likely than progressive deterioration.

Two additional studies provide evidence for this pattern of initial deterioration followed by a plateau in functioning early in the course of disorder and followed by later-course improvements. Mason and others (33) reported on the 13-year outcome of an epidemiologically defined cohort of 67 patients with an ICD-9 diagnosis of schizophrenia having their first contact with psychiatric services in Nottingham,

England, between 1978 to 1980. Of the 58 patients available for follow-up after 13 years, 52% were without psychotic symptoms, 52% were without negative symptoms, and 55% demonstrated good to fair social functioning. While only 22% of the sample had been employed during the last 2 years of follow-up, 97% were living independently in the community, and 44% achieved a mild to recovered global outcome. Carone and others (35) followed a group of 79 young patients with DSM-III schizophrenia 2.5 and 5 years after hospitalization and found an improvement between first and second follow-up, with 10% achieving a good outcome after 2.5 years to 17% after 5 years. There was more consistency among the 58% of the sample achieving a poor outcome, most of whom already had demonstrated the worst outcome at 2 years. This study also found a decrease in rates of hospitalization over the follow-up period, despite persisting symptoms and dysfunction in a majority of the sample.

Breier and others (36) examined the outcome of 58 patients with Research Diagnostic Criteria (RDC) schizophrenia hospitalized between 1976 and 1984 at the National Institutes of Health in Bethesda, Maryland. Patients tended to be relatively young and referred from community-based settings, but also had been only partially responsive to conventional treatments and had continued to experience residual positive and negative symptoms an average of 7 years into their illness. On a composite overall outcome measure an average of 6 years later, 42% of the sample had a poor outcome, 38% had a moderate outcome, and 21% had a good outcome. Seventy-four percent of the sample had moderate to high levels of positive symptoms, 84% had moderate to high levels of negative symptoms, and 50% had either no or only superficial social contacts. Patients with a longer duration of illness had significantly more negative symptoms. Of note is that 24% of the sample experienced at least one episode of major depression during the follow-up period, and that these patients spent less time in the hospital during this period than those who did not experience depression. Levels of both positive and negative symptoms were related to functional incapacity in social, work, and independent living domains. Frontal lobe dysfunction was associated both with negative symptoms and with social functioning but not with positive symptoms. Lastly, while index symptom levels measured drug-free were not related to outcome, both positive and negative symptom levels during optimal medication predicted both outcome symptoms and functioning, suggesting that responsiveness to biological treatments and post-medication symptom severity may be strongly predictive of outcome.

Another study to emphasize the role of treatment as a factor influencing outcome was conducted by DeSisto and others (37,38) in Maine. Using a retrospective, group-matching design, the investigators compared the long-term outcome of 269 patients with DSM-III schizophrenia admitted to Maine hospitals between 1956 and 1961 with that of the cohort of 269 patients reevaluated 32 years after discharge from the Vermont State Hospital in the earlier Vermont Longitudinal Study (45,46). Comparisons between the 119 Maine subjects who were available for follow-up interviews 36 years after their index admission with the 180 subjects interviewed for the Vermont study showed that Vermont subjects were more productive and had fewer symptoms and better community adjustment and global functioning than Maine subjects. The investigators suggest that the more favourable outcome in Vermont may be attributable to the model rehabilitation program and focus on a return to community living developed there in the 1950s, when no similar programs or assistance were available in Maine, suggesting that assertive rehabilitation can exert a beneficial effect on the outcome of the disorder.

Two studies have looked at outcome for patients with schizophrenia as compared with other psychotic disorders. Johnstone and others (39) followed up 326 patients with psychotic disorders over a 2.5-year period and compared those with schizophrenia (DSM-III and Present State Examination [PSE]) with those with affective disorders. They found outcome to be worse for those with schizophrenia on all dimensions, and those with schizoaffective disorders to be in the midrange between schizophrenia and affective disorders. The presence of cognitive impairments, however, was found to be equal across all diagnoses and to be strongly associated with the presence of negative symptoms, regardless of diagnosis. As part of the Cologne long-term study, Marneros and others (40–42) followed up, over a mean duration of 25 years, 148 patients with narrowly defined DSM-III schizophrenia, categorizing 101 patients with affective symptomatology as schizoaffective. Patients with schizophrenia had consistently poorer outcome as compared with patients with either schizoaffective or affective disorders, with only 19% achieving no to slight disturbances and 70% having severe to very severe disturbances. Good to excellent adjustment was achieved by only 36% of those with schizophrenia, as compared with 90% of those with schizoaffective disorders. Given the relatively favourable outcome of schizoaffective and affective disorder patients, the investigators suggest that the more narrow the diagnostic criteria for schizophrenia, the less favourable the outcome will be.

Lastly, 2 studies provide information regarding patients who avoid admission to inpatient care, thereby constituting a subpopulation who may not have been included in prior outcome studies conducted in clinical sites. Helgason (43) reported on a 20-year follow-up of 107 patients with ICD-9 schizophrenia first presenting for treatment in Iceland between 1966 and 1967. By the end of the 20-year period, 20% had yet to be admitted to the hospital. Overall outcome was good for 33% of the total sample, and extremely poor for 21%, with the remainder in the moderate range. There was a mean delay between symptom onset and first psychiatric contact of 6 to 7 years, with those patients who sought treatment earlier

in the course of illness having a more favourable outcome. In addition, a comparison of the number of patients presenting for treatment with the number expected to manifest the disorder suggests that only 60% of people with schizophrenia in Iceland seek psychiatric care at all, possibly comprising a biased sample of those with more severe forms of the disorder.

Geddes and Kendell (44) identified 66 people diagnosed with schizophrenia in the United Kingdom between 1978 and 1989 who had no history of hospitalization prior to 1991. This sample constituted 6.7% of the estimated annual rate of first diagnosis. When compared with a control group of patients admitted to the hospital within 3 months of diagnosis, these patients were generally less disturbed, had lower levels of violent behaviour, less evidence of neglect or hallucinations, a longer duration of illness prior to diagnosis, and were more often unemployed. Outcome for 43 patients who could be traced and who met RDC criteria was heterogenous, however, with the majority demonstrating residual impairments and subsequent exacerbations. The investigators found no significant differences in outcome between this group and the control group of hospitalized patients, suggesting that the exclusion of patients who are not hospitalized should have little influence on future outcome studies. It should be noted, however, that this study compared outcome only among individuals receiving outpatient care, as opposed to those hospitalized, and did not include those individuals who remained outside of the treatment system altogether.

In summary, recent follow-up studies continue to find a broad heterogeneity in long-term outcome in schizophrenia, with 21% to 57% of subjects achieving a good outcome ranging from mild impairment to recovery. These studies provide further evidence that deterioration occurs within the first few months of onset, followed by a plateau in functioning which then may or may not be followed by gradual improvements later in the course of disorder. Affective symptoms and depressive episodes appear to be predictive of a more favourable outcome, with the result that the more narrow the diagnostic criteria for schizophrenia, the less favourable the outcome. Negative symptoms appear to be associated with poor outcome, cognitive impairments, and functional incapacity in social and work domains. Assertive rehabilitation efforts appear to improve long-term outcome, while responsiveness to biological treatments early in the course of illness may be strongly predictive of long-term outcome. Lastly, early results are inconclusive in relation to the importance for outcome studies of identifying and following individuals who do not seek care. While a longer duration of untreated illness may be predictive of poor outcome, those who do not seek care may also constitute a less, or at least more quietly, disabled population. With increasing attention shifting to the examination of negative symptoms (47), a more adequate characterization of this population may become an important area for future research.

Early-Course Studies

Following a workshop on first-episode psychosis organized by the National Institute of Mental Health in 1991 (48), 3 special issues of the *Schizophrenia Bulletin* have been devoted to early-course, first-episode, and early-detection and -intervention studies (48–50), breaking what may be considered to be new ground in schizophrenia research. A comprehensive review of the existing studies of first-episode patients in North America and Europe as of 1992 (51) found that approximately one-third of first-admission patients were relapse-free for the 2 years following discharge, with a larger proportion of first-episode patients achieving a good outcome when compared with previous follow-up samples of consecutive admissions. Better premorbid social and work functioning, acute onset, shorter duration of untreated illness, rapid treatment response, and shorter duration of first hospitalization were all predictive of good outcome. These findings have since been replicated and expanded in more recent early-course studies, which we review below.

In a series of reports examining hospitalization rates, Eaton and others (52,53) used case registers to track 20 years of hospitalizations for individuals discharged from their first-ever hospitalization in Victoria, Australia; Maryland, United States; Salford, England; and Denmark. The percentage of patients eventually rehospitalized following their first admission varied from 50% to 80% in the 4 areas, but consistently showed a significant decrease in hospitalizations 2 to 3 years following discharge. Early age of onset predicted higher risk for rehospitalization. The clustering of most hospitalizations within the first 2 years after first admission, as well as the decrease in hospitalizations over time, suggested a course of progressive amelioration of the disorder rather than progressive deterioration.

Drawing from an ongoing, prospective study of first-episode patients, Lieberman and others (54) reported on the first 70 subjects to complete at least 8 weeks of the study, including both biological and clinical measures and a standardized treatment protocol. Median time to recovery was 11 weeks, 74% of the sample achieved a full remission of symptoms, and outcome assessed 6 months after remission revealed 38% of the sample to be in the excellent to good range, with 45% fair, and 17% poor. Treatment response and remission of symptoms were associated with the presence of akathisia and dystonia. Longer time to remission and poor outcome were associated with elevated GH levels, abnormal brain morphology, longer duration of untreated psychosis, higher levels of negative symptoms, and the presence of the "deficit syndrome." In addition, significant abnormalities were found in eye movement function as well as a psychotogenic response to dopamine agonists. Thus, although the treatment response of these first-episode patients was encouraging, the preliminary study results suggest that significant psychobiological dysfunction may already be present at the time of the first episode of psychosis and that the presence of

such abnormalities may be predictive of treatment response and outcome.

In a related study, Bilder and others (55) compared evidence of the premorbid intellectual and social functioning and cognitive deterioration of 51 first-episode patients with those of 50 chronic patients with schizophrenia and 22 healthy controls. Evidence of early developmental social and cognitive impairments was found in both first-episode and chronic groups. These groups did not differ on estimates of premorbid intellectual ability. First-episode patients were found to have substantial deficits in current intellectual functioning when compared with the controls, but these deficits were less severe than those found in the chronic sample, suggesting that cognitive deterioration occurs both prior to and following the onset of psychosis. These findings were supported by evidence of enduring neurocognitive deficits in first-episode patients in a study of psychobiological vulnerability indicators in schizophrenia by Nuechterlein and others (56).

A number of studies have found a heterogeneity among first-episode patients in terms of premorbid functioning, clinical presentation, and treatment response that parallels the longer-term follow-up studies reviewed previously. Shtasel and others (57), for example, compared the symptom profiles of 37 first-episode patients with those of 70 more chronically affected patients and found no significant differences in symptom profile or severity. Negative symptoms, in particular, were no less severe in first-episode patients. Consistent with long-term findings, they also were associated with poor premorbid and current functioning. In a related study (58), this group also found no differences in response to neuroleptic treatment between first-episode patients and chronic patients experiencing an acute exacerbation, suggesting that maximum symptomatic improvement occurs within the first 6 months of treatment regardless of the timing of the episode in the course of the disorder.

Looking back retrospectively from onset, Haas and Sweeney (59) characterized the premorbid adjustment and clinical history of 71 first-episode patients meeting DSM-III-R criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder. They found that 39.4% of the sample had a history of good premorbid adjustment, another 39.4% had a history of chronically poor functioning from childhood through onset of symptoms, and the remaining 21.2% had a pattern of progressive decline from childhood through onset, with a higher percentage of males in this last category. The good premorbid group had a later age of onset and first treatment, while the group showing an insidious decline in functioning had a longer history of psychotic symptoms before hospitalization and more negative symptoms on admission.

In a pair of articles also examining the link between premorbid adjustment and onset, Larsen and others (60,61) characterized the premorbid and early-course parameters of a sample of 43 first-episode patients with nonaffective psychoses in Norway. They found that longer duration of untreated psychosis was associated with poor work, social, and global functioning in the year before admission, a more insidious onset, and more negative symptoms at admission. Males were found to be more likely to be single, have a lower educational status, an earlier age of onset, and lower global functioning in the year before admission, show a rapid deterioration in functioning prior to onset of psychosis, and have a duration of untreated psychosis almost 4 times that of women. Strong support for the prognostic significance of duration of untreated psychosis was also found in a study by Loebel and others (62), which involved 70 first-episode patients meeting RDC criteria for schizophrenia or schizoaffective disorder. They found that a longer duration of untreated psychosis was associated both with longer time to remission of symptoms and with lower level of remission and that later age of onset and higher premorbid functioning were associated with better levels of remission.

Mounting evidence for the presence of an active disease and deterioration process early in the course of illness, if not predating onset, and for the deleterious impact of untreated psychosis on outcome have most recently moved investigators to focus on early detection and intervention during or prior to the first episode (63–67). Although quite preliminary and exploratory, early results from these studies suggest that it is feasible to identify a group of young people who are at high risk for developing psychosis and at least to reduce the duration of untreated psychosis and delay onset, if not prevent psychosis altogether (63–66). Studies of early intervention with first-episode patients (67) have been more complicated to interpret thus far, but they have generated considerable interest and optimism that chronicity may be prevented in some patients through targeted and intensive efforts to ameliorate symptoms and restore functioning prior to the development of secondary deficits and disability. We anticipate that these 2 areas will attract increasing attention in the near future, as research continues to explore and attempt to address the active disease and deterioration processes that are now evident in the earliest phases of illness.

Cross-Cultural and Historical Influences on Course and Outcome

Cross-Cultural Studies

One of the most striking and unexpected findings of the World Health Organization (WHO) IPSS conducted in the 1960s and 1970s was the more favourable outcome for patients in the developing world. This finding, while controversial, has received additional confirmation over the last 8 years with the completion of 5 longer-term studies that were outgrowths of the IPSS (31,68–71). We review these studies here.

The first study is actually the report of the 5-year outcome of the original IPSS cross-cultural cohort of 1202 patients with a PSE diagnosis of schizophrenia drawn from Colombia,

Czechoslovakia, Denmark, India, Nigeria, China, the United Kingdom, the United States, and the Union of Soviet Socialist Republics (68). At 5-year follow-up, information was obtained on 807 patients, representing 76% of the original cohort. Results largely confirm the 2-year findings of broad heterogeneity and a more favourable outcome for developing countries, specifically finding better clinical and social outcomes for patients in India and Nigeria (up to 67% were asymptomatic) and better social outcome in Colombia. Being female, having an acute or recent onset, and having negative life experiences before onset predicted better outcome, while having a premorbid personality disorder predicted poor outcome.

In one of the studies to build on the IPSS, Leon (69) reported on the 10-year follow-up of the cohort of 101 patients first identified in Cali, Colombia, as part of that study who were later rediagnosed as having schizophrenia by ICD-8 and ICD-9 criteria. This rediagnosis eliminated 8 cases (of the 84 located) as not fitting the more rigid criteria, leaving 76 patients for 10-year follow-up. Complete recovery was found in 43.4% of the sample, with an additional 8% achieving partial recovery. A number of these patients married, completed secondary education, and experienced upward vocational mobility during the follow-up period. Only one patient had committed suicide. Positive prognostic indicators included being female, having less education, and having a "normal" childhood. Outcome at 10 years was consistent with that at 2 and 5 years, suggesting a more favourable outcome for people in Colombia than for those in Europe and North America.

A series of studies have been completed in India that also continued the work of the IPSS. First, a multicentre study (70) in Lucknow, Vellore, and Madras of 323 early-course patients meeting modified Feighner's criteria for schizophrenia found a 66% remission rate at 2-year follow-up. As in Colombia, there was only a 2% suicide rate, and 40% of patients were employed at 2 years. Positive prognostic factors included short duration of illness, compliance with medications, rural background, and being agitated at intake. Poor prognosis was associated with economic difficulties, decrease in religious activity, perceived dangerousness, and premorbid schizoid personality. In a second study, Thara and others (71) then followed up the Madras cohort after 10 years and located 76 of the original 90 cases meeting ICD-9 criteria. Both positive and negative symptoms showed a significant decline at the end of 10 years, with 67% of the sample showing a good pattern of course leading to partial or complete recovery. Sixty percent of the subjects were employed at 10 years, while only 4 people had committed suicide. Being female and having an earlier age of onset predicted good outcome, while insidious onset and longer duration of illness predicted poor outcome.

In the last study to be stimulated by the IPSS, Ohaeri (31) conducted a retrospective follow-up of 142 patients meeting RDC criteria for schizophrenia that spanned a range of 7 to 26 years. Outcome was consistent over the 7 years of follow-up, with a good outcome achieved by 50.7% and a moderate outcome achieved by 23.9%. The most typical course was acute onset followed by an episodic course with rapid remission in response to treatment. Negative symptoms were rarely noted. Women had an older age of onset and, in a rare finding, a poorer outcome than men. The author noted that many men, even those in moderate- to poor-outcome categories, were able to complete education and/or work in order to become self-sustaining.

As they continue to demonstrate a better outcome for patients in the developing world, with a range from 52% to 67% achieving a good outcome, these studies raise intriguing and important questions about the possible role of sociocultural factors in shaping the course and outcome of schizophrenia. The poorer prognosis of women in Nigeria and the prognostic significance of decreased religious activity in India draw attention to specific examples of ways in which cultural norms and practices may influence outcome and provide valuable directions for future research.

Schizophrenia in Historical Perspective

In addition to considering variations in outcome for schizophrenia across cultures, people continue to speculate about the possibility of schizophrenia disappearing, or at least becoming a more benign disorder, over the course of this century (72–74). Whether due to the natural evolution of the illness itself, changes in diagnostic criteria, improved treatments, or the shift to community care, clinical accounts are suggestive of less severe forms of the disorder, with catatonia, for example, apparently disappearing from the developed world (75–78). One important study conducted recently provides some empirical support for this contention and has stimulated interest in this possibility.

Hegarty and others (78) conducted a metaanalysis of outcome studies for the years 1895 to 1991, limiting the comparative analysis to 320 studies (of 51 800 subjects) that assessed outcome under 10 years to detect trends by decade. The analysis revealed an increase in the proportion of patients showing improvement over an average of 6 years of follow-up after midcentury, with 35.4% showing improvement between 1895 and 1955 versus 49.5% between 1956 and 1985. This rate has declined again over the last decade to 36.4%, however, possibly reflecting a narrower conception of the disorder. The study clearly demonstrated that outcome is influenced by choice of diagnostic criteria, with broader criteria producing a better outcome (46.5% improvement with broad criteria versus 27.3% with narrow criteria). What remains to be determined is whether the improvement in outcome seen at midcentury is due entirely to diagnostic criteria or if other as yet unknown factors brought about changes in disease severity.

Outcome in Specific Domains of Functioning

As noted at the beginning of this paper, earlier studies have established a heterogeneity of levels of symptoms and functioning *within* individuals with schizophrenia as well as across individuals (46). This section reviews recent advances made in differentiating these domains, exploring their relationships over time, and investigating their links to neurocognitive functioning and outcome.

Building on the earlier work of Strauss and Carpenter pointing out the "loosely linked" nature of the relationships between symptoms and functioning (5,6) and resurrecting the positive and negative symptom dichotomy (79), many researchers have been devoted in recent years to identifying these relatively independent domains both cross-sectionally and over time, with a particular emphasis on negative symptoms and the "deficit syndrome" (47,80,81). These latter components, while considered essential to schizophrenia since Kraepelin and Bleuler, were deemphasized in DSM-III because of concerns that they could not be rated as reliably as positive symptoms and that their inclusion as diagnostic criteria would generate an overly broad conception of schizophrenia (82–85). Research conducted over the last 8 years has demonstrated, however, that negative symptoms can be identified, distinguished from affective symptoms, and rated in an objective and reliable fashion (85–87). Field trials for DSM-IV also showed that including negative symptoms did not lead to a significant inflation in the rate of diagnosis (82). While there do not appear to be 2 distinct types of schizophrenia, a "purely positive" and a "purely negative" type, these categories do seem to represent independent symptom clusters both cross-sectionally and longitudinally (88,89). The negative symptom cluster, once established, is more stable over time and is more likely to be associated with neurocognitive impairments (36,39,90), brain abnormalities (36,54,84), genetic inheritance (84), and work and social incapacity (36,87,91). In conjunction with these findings, the concept of the "deficit syndrome," first introduced by Carpenter and colleagues (80,81), constitutes a relatively stable dimension that is associated with poor premorbid social functioning; lower intelligence, educational level, and work capacity; insidious onset; a continuous course which appears unresponsive to life events; and a high risk of poor outcome with long-term disability (92).

Within the positive symptom cluster, a finer distinction has been drawn between the 2 relatively independent dimensions of "psychotic" symptoms (hallucination and delusions) and the "disorganized" symptoms of disorganized speech, disorganized behaviour, and inappropriate affect (93). This 3-factor model first proposed by Liddle (94) (including negative symptoms as the third factor) has since been confirmed through several factor analytic studies (89,90,93,95–97) but has also been potentially broadened to include depression as a fourth dimension (98,99). Because these symptom dimensions are found consistently to show independent patterns of evolution over the course of the disorder (89,93), evidence accumulates for a dimensional as opposed to categorical approach to symptomatology in schizophrenia. Future research will need to determine if such an approach can replace the conventional subtypes of paranoid, undifferentiated, and hebephrenic or if the coexistence of these symptom clusters within a given individual presents a more complicated picture.

The last domain of functioning to attract increasing attention in recent literature has been the area of neurocognitive functioning. While there continues to be a wide heterogeneity in cognitive functioning in individuals with schizophrenia, a number of recent studies (100–102) have suggested that cognitive deficits, once established, are relatively stable over time. As mentioned previously, first-episode studies have shown that cognitive impairments can be established early in the course of the disorder, if not already present in the premorbid phase. Studies of cognitive functioning have suggested that these impairments remain consistent over the course of the disorder, showing neither marked improvement nor deterioration (100–102). In addition to being linked to negative symptoms (36,39,90), cognitive deficits have been associated with work incapacity (103,104). Attempts to remediate these deficits (105–112), although still in the early stages of development, show some promise of being able to help patients regain abilities or compensate for more enduring deficits. More work will be required, however, to assist patients in generalizing the gains they are able to make in controlled laboratory conditions to their day-to-day lives in the community.

Conclusion

Several discussions of methodological issues for long-term follow-up, early-course, first-episode, and early-detection and -intervention studies (113–116) have identified a range of shortcomings in existing studies, including those reviewed in this paper. These issues include, most predominantly: concerns about the lack of clear and broadly accepted criteria for diagnosis and definitions for such key concepts as the prodrome, onset, and recovery; the sample bias introduced through the underidentification and exclusion of healthier subjects for follow-up studies; the lack of control and comparison groups because of ethical considerations and resource constraints; the complicated interplay of disease processes, treatment effects, and social and cultural contexts; and the practical and logistic complexities of gaining access to and closely tracking large-scale populations for epidemiologic and prevention studies.

Despite these considerable challenges to improving the rigour and validity of future studies, we have gained a few important insights about the course and outcome of schizophrenia over the last few years. First, it appears that the broad prognostic heterogeneity that was initially discovered through long-term follow-up studies may already be present

at the time of the first episode. It also appears that the most significant amount of deterioration in functioning that will occur for many individuals with schizophrenia has already occurred by the time of the first episode, if not by the prodromal phase. Negative symptoms and the deficit syndrome continue to represent an important component of the phenomenology and outcome of the disorder, being relatively stable over time and associated with cognitive impairments and incapacity in social and work domains. In addition to there being variations within individuals with respect to symptom dimensions and levels of functioning, as well as variations across individuals with respect to global outcome, there also appear to be variations in clinical presentation and outcome across sociocultural and historical boundaries. Challenges for future research and clinical practice include developing a better understanding of the sources of cross-cultural, historical, and individual differences in outcome and applying these findings to the improvement of current clinical and rehabilitative efforts (117,118). A new but related and equally important challenge will be to focus intensively on the prodromal and early phases of the course of disorder in a concerted effort to prevent disability and chronicity. Progressing from recognition of heterogeneity in outcome to efforts to prevent the worst outcomes from occurring represents a logical next step in the evolution of schizophrenia research and treatment. This is a new conceptualization of a disorder once assumed to have a progressive course leading inevitably to premature dementia. It remains for future research to determine how successful this new approach will be.

Clinical Implications

- With considerable evidence suggesting that the active disease and deterioration process is established by onset of psychosis, efforts need to be directed at early detection and intervention to prevent secondary deficits and disability for those individuals experiencing the more severe forms of the disorder.

Limitations

- Limitations identified in the studies reviewed include the lack of clear and broadly accepted criteria for diagnosis and definitions of such key concepts as the prodrome, onset, and recovery; the sample bias introduced through exclusion of healthier subjects for follow-up studies; and the lack of control and comparison groups.

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Résumé

Objectif : *Passer en revue des variations de dénouements dans la schizophrénie sur des plans individuels, historiques et interculturels ainsi que dans des domaines précis de fonctionnement.*

Méthode : *Faire une analyse de la littérature décrivant des dénouements de la schizophrénie et publiée au cours des huit dernières années.*

Résultats : *Premièrement, une révision d'études de contrôle ultérieur publiées dans les pays industrialisés fait penser que l'hétérogénéité de dénouements parmi des schizophrènes demeure la règle alors que des symptômes affectifs, une apparition plus tardive et aiguë ainsi qu'une sensibilité à des traitements biologiques sont prévisionnels d'un bon dénouement. La détérioration semble se produire au cours des quelques premiers mois de l'apparition si elle n'existe pas déjà dans la phase prémonitoire, alors que des études récentes de début d'évolution trouvent une durée plus longue de psychose non traitée était associée à une apparition insidieuse, à des symptômes négatifs, à une incapacité sociale ou professionnelle et à un mauvais dénouement. En deuxième lieu, une révision d'études interculturelles et historiques récentes démontre que le dénouement varie dans le temps et l'espace, le dénouement de la schizophrénie étant plus favorable dans les pays en voie de développement alors qu'elle est devenue un trouble plus bénin au fil du vingtième siècle. Troisièmement, une analyse d'études des domines du fonctionnement chez les particuliers identifie quatre dimensions relativement indépendantes de dépression et des symptômes négatifs, psychotiques et désorganisés. Les déficits intellectuels (qui sont associés à des symptômes négatifs) forment aussi une dimension relativement stable au fil du temps, sans révéler de détérioration ou d'amélioration marquées, une fois qu'ils sont établis vers le début de l'évolution du trouble.*

Conclusions : *Afin d'empêcher une chronicité et une invalidité prolongée, l'apparition précoce et une stabilité au fil du temps de symptômes négatifs et déficits cognitifs exigent des efforts d'intervention énergique vers le début de l'évolution du trouble.*