Long-Term Diagnostic Stability and Outcome in Recent First-Episode Cohort Studies of Schizophrenia

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Knowing the long-term outcomes of schizophrenia and stability of a schizophrenia diagnosis are important from a clinical standpoint as well as essential to future research on diagnostic classifications and outcome. As in prior research on schizophrenia, prospectively designed long-term studies over the past 30 years find that the predominant course of illness includes chronically poor functioning, with little evidence of long-term improvement. Mortality due to suicide is significant at about 10% over 10-year periods of follow-up. Within studies, outcome domains are interrelated, and the relatively consistent predictors of poorer outcome include family history of schizophrenia, insidious onset, poor premorbid functioning, severity of negative symptoms, and severity and duration of untreated psychosis. Residing in a developed rather than a developing country is also associated with a poorer long-term course. The diagnostic stability of schizophrenia is less well studied. The positive predictive value exceeds 90%, and preliminary findings from the 10-year follow-up of the Suffolk County Mental Health Project cohort have found that the agreement across time increased from $k = .52$ (baseline to 10 years) to $k = .76$ (6 or 24 months to 10 years). After discussing several limitations of the existing body of research, we suggest that future studies incorporate more "modifiable" risk factors into the assessment battery that could potentially be used as building blocks in experimental intervention designs.

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Introduction

This review focuses on the diagnostic stability and outcome of schizophrenia as determined from long-term follow-up studies initiated within the past 30 years. Consistent with an earlier review by McGlashan,[1] *long-term* is defined as duration of follow-up of at least 10 years. For this review, we selected prospective studies that meet the following methodologic criteria: first-admission or first-contact patients (i.e., incident samples) admitted after 1975; systematic and reliable diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder; sample not restricted to children or young adolescents; explicit methods for case ascertainment and for follow-up; minimum initial sample size of 50 to assure adequate power and reliability; and clearly defined, reliable outcome measures. Thus, we excluded studies of consecutive admissions (i.e., prevalent samples), studies with follow-ups less than 10 years, and studies of small, highly selected samples.

This review of diagnostic stability and outcome, which is intended to complement and update the many thoughtful reports that precede it,[1–4] is divided into 3 sections. First, we give an overview of the findings from prospective studies initiated in the past 30 years. Second, since few of the studies evaluated diagnostic stability, we include a set of supplementary analyses on this from our ongoing 10-year follow-up of the Suffolk County Mental Health Project cohort. Finally, we weigh the strengths and weaknesses of the research and reconsider the optimistic conclusion from the pooled analysis of the World Health Organization incident cohorts that "a significant proportion of treated incident cases of schizophrenia achieve favorable long-term outcome."[5] (p506)

Review of Prospective Long-Term Follow-up Studies

McGlashan reviewed 10 long-term follow-up studies of schizophrenia that had been conducted in North America and concludes that schizophrenia is a disabling and chronic illness although patients did not necessarily show progressive decline over time.[1] Subsequent reviews of cohorts assembled before the era of modern pharmacologic treatments, including the European long-term follow-back studies, also failed to support the notion that schizophrenia is a disease with a steady downhill

course. On the contrary, the studies suggest that the course is quite variable, and in the long-term, only a minority of patients (~25%) were deemed "recovered."[4] The problems with interpreting many of the long-term studies are that the attrition rates were unacceptably high and the reliability and validity of the study diagnoses, constructed retrospectively from clinical records, were uncertain.

At the time of our 1992 review,[4] a series of prospective studies had recently been initiated. These served as the starting point for our search for long-term follow-up studies of first-episode or first-admission patients with schizophrenia initiated after 1975. To expand our literature search, we collected studies published after 1985 by performing keyword searches using www.pubmed.gov and citation searches using Web of Science. Keyword searches employed terms such as *schizophrenia long-term follow-up*, *schizophrenia long-term outcome*, and *psychosis diagnostic stability*. For each "hit," we then reviewed the references to find other studies that fulfill the criteria described above. Citation searches were conducted using several seminal long-term follow-up publications. The net result of our search is summarized in Table 1. Included are the Groningen,[6] Nottingham,[7–10] and Sofia[11–12] first-contact cohorts ascertained as part of the World Health Organization–Determinants of Outcome of Severe Mental Disorders project along with 6 separately initiated studies.[13–28] Table 1 also includes key findings from pooled analyses of the incident cohorts included in the International Study of Schizophrenia (ISoS).[5, 29–30] Compared to the follow-back studies, the prospective long-term studies had substantially lower attrition, better articulated diagnostic methods, and modern psychopharmacologic and psychosocial treatment options. Unfortunately, details about the actual treatment exposures in the various research centers are rarely discussed, although it is safe to argue that the specific interventions, and adherence to them, would have varied from setting to setting as well as over time.

Overview of Findings

In spite of variations in diagnostic criteria, age distributions of the cohorts, ascertainment (inpatient only versus any form of mental health contact), follow-up measures, type of rater (psychiatrist, medical student, professionally trained social worker), treatment, and the cultural settings in which the studies were conducted, some patterns emerge. First, when compared with patients with other psychoses, patients with schizophrenia did more poorly in multiple domains (e.g., symptomatology, social disability, work functioning).[17–19] Second, with some exceptions, the predominant pattern of outcome is best summarized as "marginal." In most studies, only a minority appear to have good outcomes. Specifically, only 27% of the Groningen cohort is categorized as having com-

plete remission at 15-year follow-up,[6] and 15% of the Madras cohort is classified as "recovered."[25–26] In Sofia, 59% was rated as having continuous or episodic psychotic symptoms.[11–12] The median Global Assessment Functioning (GAF) in the Manchester follow-up was 51.5,[24] and the mean Global Assessment Scale in the Cologne sample with schizophrenia was 42.1,[17–18] indicating significant impairment. In the Chicago cohort, which is not a pure first-admission sample but, rather, is described as including only "recent-onset" patients, 71.7% had "severe or moderately severe" outcomes.[23] A somewhat better pattern emerged from the Nottingham cohort,[7–10] in which 50% had GAF scores >60, and from Singapore,[27–28] in which 43.5% were rated as having good or superior functioning. The first pooled analysis of the ISoS incident cohorts found that ~50% had reasonably good GAF symptom and functioning ratings (e.g., above 60) and that in the 2 years before follow-up, 43% had not been psychotic.[5] However, the range of site-specific percentages with GAF >60 is extremely wide (Table 1; the medians and interquartile ranges were not given), and the number of respondents in each site contributing to the analysis is varied. A subsequent analysis comparing the incident cohorts from developed and developing countries on the same outcomes[30] has found that the percent with good functioning was considerably smaller in the developed ($n = 319$) than in the developing ($n = 183$) countries. Fewer than half of patients in the developed countries (versus 73% in developing countries) had worked for most of the 2 years before follow-up, only 37% (versus 53%) had not had psychotic symptoms in the past 2 years, and only 24% (versus 53%) had global disability scores in the "excellent or good" range. Thus, at best, the take-home message from the recent studies is that outcome overall is marginal and highly variable from study to study. A small minority of individuals in each of the studies appear to be functioning reasonably well in the long run, but the rate of actual "recovery," when reported, is very small.

Third, the domains of outcome were intercorrelated. Although Strauss and Carpenter argue that domains of functioning operate independently and are best predicted by earlier measures of the same domain,[31] the recent long-term studies indicate that outcome domains are significantly and strongly related to one another. In addition, several studies have found a strong relationship between severity of negative symptoms and work performance,[21] as well as other aspects of outcome.[16] Thus, severity of negative symptoms might be considered as an underlying dimension that at least in part explains the interrelationships among the outcome variables in schizophrenia.

Fourth, the severity as well as the duration of untreated (or inadequately treated) psychosis (DUP) prior to or during the first few years after initial hospitalization are a significant predictor of poorer outcome in several

studies.[29] Based on this finding, aggressive intervention very early in the course of schizophrenia has been proposed as a way to decrease the potential for a chronic or deteriorating course. Other predictors of poorer outcome are positive family history of schizophrenia, insidious onset, and poor premorbid functioning. The latter variables are correlated with DUP since onset is usually dated by the first reported occurrence of psychosis (positive or negative symptoms) and/or start of decline in functioning. Thus, in effect, the findings suggest that the degree of chronicity observed prior to hospitalization predicts post-hospitalization chronicity.

Finally, the suicide rate continues to hover around 10% in the prospectively followed cohorts. In the ISoS, young males were at highest risk, and overall survival rates ranged from 91 to 99% at 5 years and 86 to 97% at 10 years.[5] In the Suffolk County cohort described below, the overall survival rates were similar, namely, 97% at 5 years and 95% at 10 years.[32] Furthermore, the latter study has found no significant differences by diagnosis (schizophrenia versus affective psychosis).

Surprisingly little attention has been given to diagnostic stability (last column of Table 1), perhaps in part because the diagnostic systems shifted from ICD-9 to ICD-10 during the periods of observation. In the Nottingham follow-up,[7] all 31 patients initially diagnosed with DSM-III-R schizophrenia retained the diagnosis 13 years later, and 17 of the 20 who shifted into this category were originally diagnosed with schizophreniform disorder. Ninety percent of the Cologne cohort with schizophrenia at first episode retained the diagnosis 25 years later.[17–18] In spite of the dearth of empirical evidence, there seems to have been a consensus that the predictive value positive of the diagnosis of schizophrenia is 90% or higher. Because only 2 studies report on the temporal stability of the diagnosis of schizophrenia, the next section describes preliminary findings from the ongoing 10-year follow-up of the Suffolk County Mental Health Project.

10-Year Diagnostic Stability of Schizophrenia in the Suffolk County Mental Health Project Design

From late 1989 to 1995, we assembled a cohort of patients experiencing their first psychiatric admission to the facilities in Suffolk County, New York (population 1.3 million), in order to examine diagnostic stability and prognosis of severe mental disorders.[33] Patients were recruited by the head nurse or social worker (or project staff at 2 facilities) using the following criteria: (i) first admission or current admission within 6 months of index admission; (ii) age 15–60 years; (iii) resident of Suffolk County; (vi) presenting clinical evidence of psychosis, prescription of antipsychotic medication, or a clinical diagnosis indicating psychosis; (v) absence of moderate to severe mental retardation; (vi) ability to speak English; and (vii) capacity to provide written informed consent. For those aged 15–17, written informed consent was also obtained from a parent. Overall, 675 patients were recruited from 12 hospitals at baseline (72% response rate).

Phase I of the study entailed face-to-face interviews at baseline, 6-month, and 24-month follow-ups using the "Structured Clinical Interview" for DSM-III-R (SCID)[34] administered by master's level mental health research clinicians who received rigorous training and testing for inter-rater reliability during the course of the study. Shorter in-person 4-year follow-up assessments were also conducted, as well as interval telephone contacts every 3 months from baseline to 24 months, every 6 months from 24 to 48 months, and annually thereafter. Best-estimate research diagnoses were reached by consensus of 2 project psychiatrists after the baseline interview (DSM-III-R) and by consensus of at least 4 psychiatrists following the 6- and 24-month follow-ups (DSM-IV). The follow-up diagnoses were longitudinal best-estimate diagnoses based on all sources of information, including the SCID, standard rating scales, medical records (or discharge summaries), interviews with relatives, information on treatment experiences and psychosocial functioning, and detailed narratives written by the interviewers after each encounter.[35–36]

Phase II of the study involves a 10-year follow-up that is ongoing. The 10-year assessment includes the psychosis and mood disorders modules of the SCID and a reevaluation of the principle study diagnosis using the procedure outlined above. As in phase I, the interviewers receive extensive training, and inter-rater reliability is maintained over time by having the project director (B. Naz) randomly observe and rate 5–10% of the interviews. The kappas for psychotic symptoms range from .81 to 1.0, while the kappas for negative symptoms range from .57 to 1.0. As of December 31, 2004, 263 respondents had been rediagnosed.

Results

Figure 1 shows the change in the diagnosis of schizophrenia (including schizophrenia and schizoaffective and schizophreniform disorders) and other psychoses (primarily affective disorders) between the baseline, interim (6- and/or 24-month diagnosis), and 10-year points for the 263 respondents. At baseline, 122 respondents (46%) were diagnosed with schizophrenia by either the research team or the clinician. At 10-year follow-up, 145 respondents (55.1%) were diagnosed with schizophrenia by the research team. Although there was considerable temporal consistency in the diagnosis of schizophrenia, a number of shifts were also seen across time. Table 2 presents the concordance statistics for the shifts in diagnosis across the 3 time points. The lowest concordance is between baseline and the 10-year follow-up, while the best

Table 1. Long-Term Follow-up Studies of First-Admissions With Schizophrenia: Studies Initiated After 1975

Reference(s)	Location	Follow-up	N/Study Group	Sample Characteristics	Outcome	Comments	Diagnostic Stability
Bottlender, Sato, Jäger, et al., 2003; Bottlender, Strauss, & Möller, 2004; Jäger, Bottlender, Strauss, & Möller, 2004; Möller, Bottlender, Wegner, Wittmann, & Strauss, 2000	Munich, Germany	12 and 15 years	241 inpatients at baseline; 222 at 15 years	ICD-10: 105 SZ—44% male, mean age 29; 41 SA—15% male, mean age 30; 95 AFFEC—23% male, mean age 42	average GAF: SZ—46; SA—61; AFFEC—68	33 died; negative sx and longer DUP were associated with poorer outcome	not reported
Harrison, Mason, Glazebrook, Medley, Croudace, & Docherty, 1994; Mason, Harrison, Croudace, Glazebrook, & Medley, 1997; Mason, Harrison, Glazebrook, Medley, & Croudace, 1996; Mason, Harrison, Glazebrook, Medley, Dalkin, & Croudace, 1995	Nottingham, U.K.	13 years	99 incident cohort at baseline; 95 traced; 69 full assessment; 15 partial assessment	67/99 ICD-9 SZ—67% male; age 15–54 (mean = 29)	median time to first relapse = 1.4 years; median time to first readmission = 1.75 years; course stable after 5 years; 49% GAF sx score = ≥61; 50% GAF disability score = ≥61; 76% in tx at follow-up; 51% depot neuroleptics; 18% did not relapse	9 died (4 suicides); no evidence of progressive improvement or deterioration over 13 years; vast majority lived independently or with family at follow-up	86 were rediagnosed at 13-year follow-up; baseline DSM-III-R SZ = 100% stable; 20 non-SZ dx at baseline became SZ at follow-up (17/20 dx with SF at baseline); 88.6% baseline ICD-10 SZ retained dx at follow-up
Weirsma, Nienhuis, Slooff, & Giel, 1998	Groningen, the Netherlands	15 and 17 years	82 incident cohort at baseline; 63 at 15 years; 50 at 17 years	ICD-9 non-AFFEC functional psychosis; 61% onset <25 years; 62% male	at 15 years: 27% complete remission; 50% partial/ negative remission; 11% chronic psychosis; 12% unknown	8 suicides, 1 unknown; acute onset and prompt tx associated with time to remission	not reported
Ganev, 2000; Ganev, Onchev, & Ivanov, 1998	Sofia, Bulgaria	16 years	60 incident cohort at baseline; some information on 55 at 16 years	onset of illness <2 years before first assessment; ICD-9 SZ or other psychosis; age 15–54 (mean = 43); 35% male	55% on disability; 24% lived alone; 46% continually psy sx; 13% episodic sx; 53% had GAF in severe range; 65% continued tx	2 suicides during first 2 years of follow-up; social disability and psychosis strongly related; improvement related to acute onset and negative family history	not reported

Table 1. Continued

Reference(s)	Location	Follow-up	N/Study Group	Sample Characteristics	Outcome	Comments	Diagnostic Stability
Marneros, Deister, & Rohde, 1991, 1992	Cologne, Germany	25 years	402 inpatients at baseline; 355 at follow-up	"modified" DSM-III: 148 SZ—58% male, age 28; 101 SA—37% male, age 30; 106 AFFEC—25% male, age 36	mean GAS: SZ—42.1; SA—76.2; AFFEC—87.4	retrospective cohort design	90% of SZ at first episode retained the dx at 25 years
Harrow, Grossman, Herbener, & Davies, 2000; Herbener & Harrow, 2001; Herbener, Harrow, & Hill, 2005; Marengo, Harrow, Sands, & Galloway, 1991; Racenstein, Harrow, Reed, Martin, Herbener, & Penn, 2002	Chicago	10 and 20 years	~260 inpatients at baseline (not all first admission); 210 at 10 years; substudy of 61 with SZ at 20 years	Research Diagnostic Criteria dx; age 17–30 at baseline; 52 SZ; 20 SA; 36 other psychosis; 42 nonpsychotic AFFEC	56% of SZ and 50% of SA on neuroleptics; 13% of SZ with signs of psychosis were working; SZ patients had poorer work functioning than other groups	75% had ≤ 1 prior hospitalization at baseline; rank ordering of poor outcome: SZ > SA > psy AFFEC > nonpsychotic; significant relationship between psychosis and work impairment; SZ/SA patients had more negative sx than other dx; anhedonia, work, and social impairment were fairly stable across 20 years	not reported
Stirling, White, Lewis, et al., 2003	Manchester, U.K.	~10.5 years	112 inpatients at baseline; 49 with neuropsych at follow-up	DSM-IV psychosis (84% SZ); onset age 16–50 (mean = 26); no substance abuse; 57% male	median GAF 51.5; 82% lived independently >5 years; 49% on disability; 98% on medication	neurocognitive impairment at follow-up but not at baseline correlated with clinical outcome	not reported
Eaton, Thara, Federman, & Tien, 1998; Thara, Henrietta, Joseph, Rajkumar, & Eaton, 1994	Madras, India	10 years	90 inpatients at baseline; 76 at 10 years	first-onset ICD-9 SZ: mean onset age = 23; 50% male	15% recovered; 3% residual sx; 49% multiple episodes with full remission; 28% incomplete remission; 4% continually psy	4 suicides, 5 deaths from other causes; 18 did not meet DSM-III-R criteria for SZ (most had duration <6 months); AFFEC sx and younger onset age predicted early remission	not reported

Table 1. Continued

Reference(s)	Location	Follow-up	N/Study Group	Sample Characteristics	Outcome	Comments	Diagnostic Stability
Kua, Wong, Kua, & Tsoi, 2003; Tsoi & Wang, 1991	Singapore	10, 15, and 20 years	402 inpatients at baseline; 290 at 10 years; 300 at 15 years; 216 at 20 years	first-admission ICD-9 SZ: age 13–39 (mean = 23); 61% male; 82% Chinese	10 years: 45% unemployed; 44% not in tx; 35% poor functioning 15 years: 52% unemployed; 47% not in tx; 38% poor functioning 20 years: 53% unemployed; 48% not in tx; 35% poor functioning	at 20 years, 39 suicides (mostly in the first 10 years), 20 deaths by natural causes; 125 (31%) lost to follow-up; shorter illness duration before admission predicted better outcome	not reported
Wiersma, Wanderling, Dragomireck, et al., 2000	6 ISoS sites: Dublin, Groningen, Mannheim, Nottingham, Prague, Sofia	15 years (13–16 years)	500 at baseline; 349 at follow-up	ICD nonaffective functional psychosis: % male ranged from 33% (Sofia) to 65% in (Nottingham); mean age at follow-up ranged from 40 (Groningen, Mannheim) to 45 (Dublin)	early complete remission achieved by 25% (Sofia) to 61% (Nottingham); rating of social disability: none—14%; some—26%; obvious—34%; severe—25%	more patients were "socially deteriorating" than improving; DUP and insidious onset predicted level of disability at 15-year follow-up	not applicable
Harrison, Hopper, Craig, et al., 2001	14 ISoS sites with incident cases	15–25 years	1,171 incident cases; 776 at follow-up	502 SZ; 274 other psychoses	SZ incident cohorts: 50.2% continually or episodically psy; GAF functioning mean = 50.7 (range 16.7–77.8); GAF sx mean = 54.0 (8.3–78.4)	SMRs ranged from 0 (Rochester) to 8.9 (Groningen); unnatural causes (mostly suicide) were higher than natural causes in industrialized countries; % of time psy in first 2 years was strongest predictor of outcome	not applicable
Hopper & Wanderling, 2000	13 ISoS sites with incident cases	13–17 years	410 incident cases from developing centers; 265 at follow-up 813 from developed centers; 544 follow-up	ICD-10 SZ: 319 from developed countries; 183 from developing countries	among ICD-10 SZ: 38% in developed versus 27% in developing countries were continually psy; 46% in developed versus 73% in developing countries worked in past 2 years	patients in developing centers did better; finding could not be explained by confounding variables	not applicable

Note: DUP = duration of untreated psychosis, GAF = Global Assessment Functioning, GAS = Global Assessment Scale, SZ = schizophrenia, SA = schizoaffective disorder, SF = schizophreniform disorder, AFFEC = affective disorder, ISoS = International Study of Schizophrenia (coordinated by the World Health Organization), psy = psychotic, sx = symptoms, tx = treatment, dx = diagnosis.

is between the interval and the 10-year longitudinal diagnoses.

As expected, the temporal stability of the specific categories varied. Schizophrenia was the most stable. Thus, among the 62 respondents initially diagnosed with schizophrenia, 58 (93.5%) retained the diagnosis at 10 years. Two (3.2%) were rediagnosed with schizoaffective disorder; 1, with a substance-induced psychosis; and 1, with psychosis not otherwise specified. Eleven (78.6%) of the 14 respondents diagnosed with schizophreniform disorder initially were rediagnosed with schizophrenia at 10-year follow-up (6 received the diagnosis by the 24-month follow-up), only 1 (7.1%) retained the diagnosis of schizophreniform disorder, and 1 each was rediagnosed with bipolar psychosis and drug-induced psychosis. Last, of the 14 respondents with a baseline diagnosis of schizoaffective disorder, 4 (28.6%) retained the diagnosis, 4 (28.6%) were rediagnosed with schizophrenia, 5 (35.7%) were rediagnosed with a mood disorder, and 1 (7.1%) could not be classified.

We next examined the structural validity of the diagnosis of schizophrenia using the combined symptom/functioning GAF rating as our confirmatory measure. Respondents were stratified into 4 groups according to whether they were diagnosed with a schizophrenia-type disorder initially (at baseline, 6-month, or 24-month follow-up) and/or at 10-year follow-up or never diagnosed with schizophrenia. Of the 263 respondents, 130 (49.4%) received a schizophrenia diagnosis initially and at 10-year follow-up, 21 (8.0%) received this diagnosis only initially, 15 (5.7%) received it only at 10 years, and 97 (36.9%) never received this diagnosis. Figure 2 shows each group's mean GAF ratings of best functioning in the past year (past 6 months at 6-month follow-up) at baseline, 6 months, 24 months, 48 months, and 10 years. Respondents diagnosed with schizophrenia both initially and at 10-year follow-up had the poorest functioning from baseline to the 48-month follow-up. In contrast, those receiving this diagnosis for the first time at 10-year follow-up started out with better functioning, showed a decline at 48 months, and at 10-years had GAF scores that were similar to the consistently diagnosed group. Respondents who only received a diagnosis of schizophrenia initially started out with a small advantage over the consistently diagnosed group and improved across time. Those who never received a schizophrenia spectrum diagnosis had reasonably good baseline GAFs for the year before baseline and maintained their level of functioning across time. At 10-year follow-up, the 2 groups without a current schizophrenia diagnosis (initially only and never) had similar GAF scores. Results of a repeated-measures analysis of variance found that the Fs for diagnostic group and for the interaction of diagnosis and time were highly significant ($p < .001$), while the effect for time per se was nonsignificant.

Last, we tested the concurrent validity of the diagnosis by examining differences in premorbid and baseline clinical features among the 4 diagnostic groups and among the 3 groups ever diagnosed with schizophrenia. As shown in Table 3, respondents never diagnosed with schizophrenia had significantly better premorbid adjustment and were less likely to have a long DUP, Schneiderian symptoms, or severe negative or positive symptoms compared to those ever diagnosed with schizophrenia. When the 3 schizophrenia groups were compared, however, there were fewer significant differences, and those that emerged were consistent with the diagnostic decisions at the time they were made. Thus, compared to the 10-year-only group, respondents diagnosed with schizophrenia initially had a younger age of onset and were more likely to have severe negative symptoms at baseline.

Because the sample included respondents with significant substance abuse histories, we also considered whether substance abuse affected the temporal reliability of the diagnosis (Table 3). Substance abuse was not significant in either the 4-group or the 3-group analysis, suggesting that including individuals with significant substance abuse enriches the representativeness of the sample without affecting the reliability of the diagnostic formulations.

Discussion and Conclusions

In comparison with findings from cohorts hospitalized prior to the introduction of antipsychotic medications, we expected that a more hopeful picture would emerge from more recent prospective studies. One reason for our optimism was our assumption that unlike many patients in the follow-back cohorts, the prospective cohorts all received modern treatments rather than custodial care, which clinical follow-up studies have shown to be the most important predictor of favorable outcome. However, we did not find detailed information on the actual treatments that participants in these cohorts received initially or across time, and it may be, as 1 study has reported,[27–28] that a sizable percentage dropped out of treatment, at least from time to time, diminishing its potential effectiveness. Another reason for our optimism stemmed from the positive perspective about course and outcome expressed in an ISoS report.[5] However, when we inspected virtually the same sources of information (Table 1), we were struck by the paucity of truly favorable outcomes. To some extent, our less positive impression from the same information base may stem from our own follow-up experience (Figure 2). In short, whether one views the overall findings optimistically or pessimistically, that is, whether the glass is half full or half empty, is influenced by one's own empirical and clinical experiences.
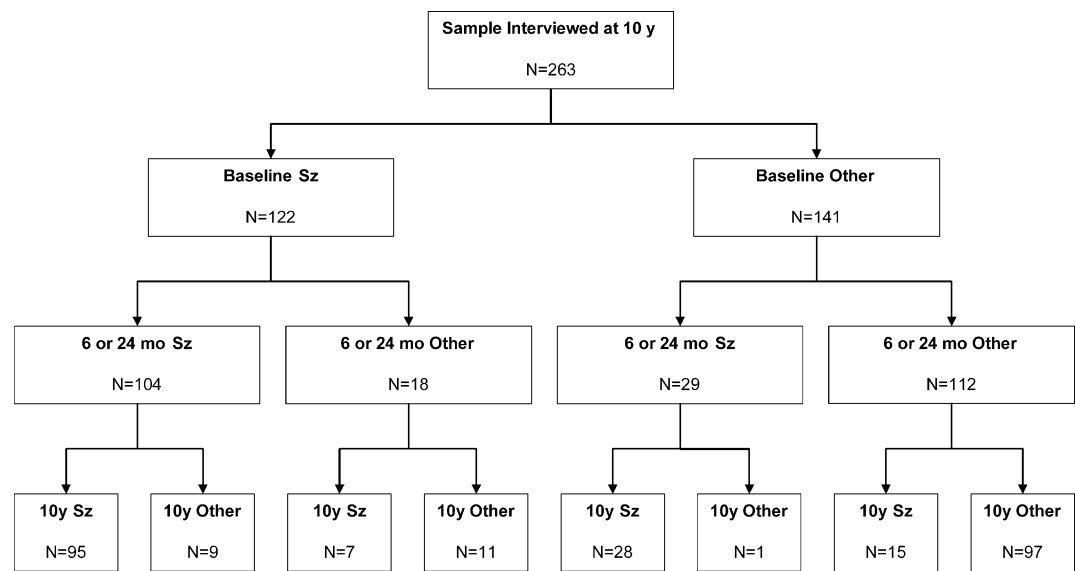
Fig. 1. Stability of the Diagnosis of Schizophrenia/Schizoaffective/Schizophreniform Disorder (SZ) Across a 10-Year Interval.

Given that we do not find great improvement in outcome in the recent studies, 1 factor that could have contributed is the nosological change that occurred in the interim. In particular, under previous classification systems, schizophrenia was a much broader concept, whereas current nosologic systems define it as a chronic illness of at least 6-months duration. This will select for individuals with poorer outcomes, canceling out any benefits that might be seen from pharmacotherapy. Indeed, many respondents classified with affective psychosis or psychosis not otherwise specified in our study would have been diagnosed with schizophrenia in DSM-II, and the overall outcome would have been more favorable.

In fact, there is considerable variability in outcomes across the studies that defies easy explanation,[30] and the variability is so striking that it is perhaps not correct to draw a specific conclusion about the overall pattern. No doubt there was considerable variability in ascertainment, response and attrition, implementation of the ratings, sources of practical and emotional support, and most important, type of and adherence to psychiatric treatment, including psychosocial, pharmacologic, and vocational therapies. Disparities in access to and quality of health care are major issues that will affect the findings from U.S. cohorts to a greater extent than cohorts from countries with national health insurance. Access to care also influences duration of illness or degree of functional impairment before initial treatment contact, which in turn will influence the outcomes across the cohorts. Indeed, in our cohort, not only were most patients with schizophrenia ill with psychosis for a considerable period of time before their first hospitalization, but most also had marginal functioning since childhood. To this end, the current studies of high-risk adolescents ascertained during the prodromal stage of the disorder, that is, before chronicity has set in, will help determine whether very early intervention alters the long-term course.

Limitations

Several limitations of this body of research should be noted. Many authors use the terms *first admission* and *first episode* interchangeably. In either case, the patients

Table 2. Agreement Among Baseline, 6- to 24-Month Interval, and 10-Year Diagnoses of Schizophrenia in 263 Suffolk County Mental Health Project Respondents

Period	Kappa	Predictive Value Positive	Predictive Value Negative	Sensitivity	Specificity
Baseline to Interval	.64	85.2	79.4	78.2	86.2
Baseline to 10 Years	.52	83.6	69.5	70.3	83.1
Interval to 10 Years	.76	92.5	83.1	84.8	91.5

Note: Table combines schizophrenia, schizoaffective disorder, and schizophreniform disorder. "Baseline" comprises DSM-III-R research or clinical diagnoses, "interval" comprises 6- and/or 24-month diagnoses. Strating at 6 months, all are DSM-IV.
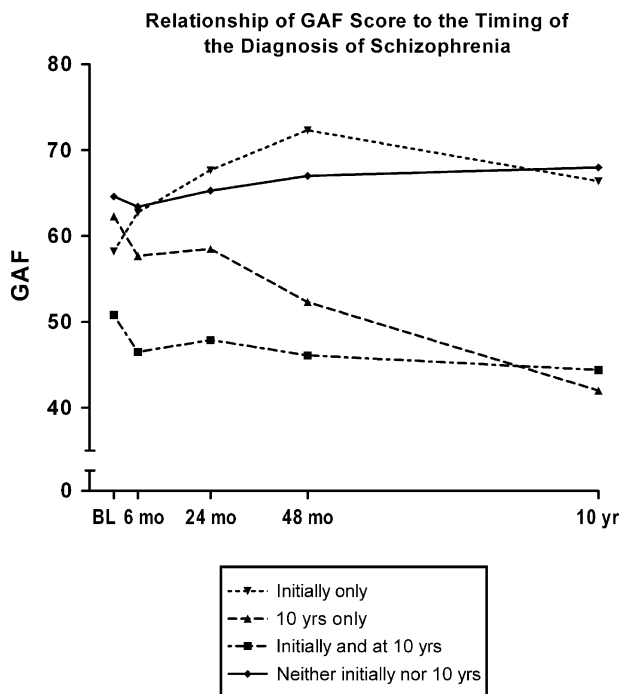
Relationship of GAF Score to the Timing of the Diagnosis of Schizophrenia

Fig. 2. Relationship of Global Assessment Functioning Score to the Timing of the Diagnosis of Schizophrenia: Initially (Baseline—24 Months) and at 10 Years.

making up the various cohorts were not necessarily ascertained at the start of their psychosis. If early diagnosis (shorter "lead time") is linked to better long-term course, then what would appear to be differences in outcome across studies might be attributable to variation in DUP before hospitalization. Since current chronicity is best predicted by past chronicity, comparisons across samples that do not take DUP into account are potentially misleading.

Although some studies describe the overall illness course using well-known scales and categories developed in previous outcome research,[23, 37] the definitions of remission, improvement, and recovery are not always consistent or clear.[38] Moreover, very few data are presented on specific changes in functioning over time. Thus, many of the studies describe the level of functioning at or within the 2 years preceding the long-term follow-up contact but not when that level of outcome was reached during the follow-up interval, how long it endured, or at what point it stabilized. In all of the long-term studies, it is also difficult to evaluate the progression of the illness with any degree of specificity because the outcome points are far apart. For those remaining in treatment, retrospective accounts can be supplemented by medical record information, but that introduces bias into the study because the quality of the retrospective data for the treated and untreated groups is unequal. Thus, the actual trajectories of positive and negative symptoms and of social and occupational functioning can only be charted broadly

from the studies as currently designed. This is a special limitation for evaluating diagnostic stability and determining the point at which individuals who start out with a nonschizophrenia diagnosis "convert" to schizophrenia.

While the predictive value positive of an initial diagnosis of schizophrenia is very high, there is a dearth of information on specificity. The diagnoses in the Suffolk study have reasonable psychometric properties, but the design is not blind to previous diagnoses. To the extent that baseline samples are restricted to individuals diagnosed with schizophrenia per se, they will be biased by having omitted false negatives whose symptoms and course will evolve in such a way that they meet the criteria for schizophrenia later. Our data also suggest that including respondents with significant substance abuse does not diminish the reliability of the diagnosis or contribute to misclassification. It does improve on the representativeness of the sample and hence the generalizability of the results. Thus, it will be important for future studies to evaluate the specificity and negative predictive value of nonschizophrenia diagnoses using raters and diagnosticians who are blind to prior clinical information.

Similarly, details about treatment experiences, as noted above, were either not provided or not evaluated in relation to outcome. A few of the studies describe initial treatment, or cross-sectional descriptions of the medications patients received,[19] but the long-term interventions experienced by the cohort and the relationships of time-varying treatment exposures to different aspects of long-term outcomes were not examined.

With the exception of the 2 German studies[13–18] and 1 from the United States,[19–23] most of the studies contained small sample sizes and did not include sufficiently large comparison groups of patients with other psychotic disorders. Thus the power to detect differences across time was diminished, as was the ability to draw conclusions about the specificity of the findings for schizophrenia. In our sample, individuals with schizophrenia had poorer GAF scores than patients with nonschizophrenia psychoses (mostly mood disorders), although the patients with nonschizophrenia disorders were also struggling in many areas of their lives.

In conclusion, in most of the long-term follow-up studies initiated within the past 30 years, more than half of the patients with schizophrenia had either not recovered or had suffered a relapse. Very few could be described as fitting within the World Health Organization category of "single psychotic episode with full remission." At least half were unemployed or living on disability compensation at follow-up. Nevertheless, we believe that although these findings are consistent with those of earlier long-term follow-up studies, the recent studies do add to our understanding of the natural history of schizophrenia. Compared to research on the follow-back cohorts,[4] the recent studies have lower attrition (and hence more generalizable results); use more standardized, reliable,

Table 3. Predictors of Diagnostic Stability of Schizophrenia in Suffolk County Mental Health Project Respondents Diagnosed With Schizophrenia (SZ) During the Initial 24-Month Follow-up Period and at 10-Year Follow-up

Predictor	Initial and 10-Year SZ (n = 130)	Initial-Only SZ (n = 21)	10-Year-Only SZ (n = 15)	Never SZ (n = 97)	4 Group p	3 SZ Group p
Age of Onset (mean ± SD)	28.4 ± 8.5	24.8 ± 7.9	31.9 ± 8.0	30.3 ± 10.5	<0.05	<0.05
Childhood Premorbid Adjustment (mean ± SD)[39]	.35 ± 0.17	.33 ± 0.14	.33 ± 0.19	.26 ± 0.15	<0.01	ns
% Male	63.8	52.4	60.0	47.4	ns	ns
% With >6-Month Duration of Psychosis Before First Hospitalization	51.2	47.6	28.6	14.3	<0.001	ns
% Substance Abuse at Baseline	25.4	33.3	26.7	24.7	ns	ns
% With Schneiderian Symptoms at Baseline	45.4	47.6	33.3	18.6	<0.001	ns
% With Scale for the Assessment of Negative Symptoms >2 at Baseline[40]	34.9	14.3	6.7	8.2	<0.001	<0.05
% With Scale for the Assessment of Positive Symptoms >2 at Baseline[41]	38.8	23.8	33.3	18.6	<0.001	ns
% With First-Degree Relative With Schizophrenia[42]	14.0	5.0	7.1	8.9	ns	ns

Note: Table includes DSM-IV schizophrenia, schizoaffective disorder, and schizophreniform disorder; ns = not specified.

and multidimensional approaches to examining course and outcome; and provide a window into of the role of negative symptoms that affect many aspects of functioning.

Although there is growing interest in research on the course and outcome of individuals identified during the prodromal stages of schizophrenia, most individuals who develop schizophrenia will be identified only after their illness has progressed to the point that they require treatment. Based on Berkson's bias, the vast majority will present with other comorbidities, such as anxiety disorders, depression, and substance abuse. Those meeting DSM-IV criteria for schizophrenia at their first contact will start out with an unfavorable prognostic profile in many areas, as Figure 2 and Table 3 demonstrate. Unfortunately, DUP, premorbid social competence, and family history are not "modifiable" risk factors for these patients. Moreover, at least in the United States, most patients with schizophrenia will not be living with their families in the long run. Thus, the challenge is to identify significant individual risk or protective factors that can be modified. Psychologists have begun to develop measures that may prove relevant in this regard, such as hardiness, positive states of mind, positive coping strategies, and inner strengths. New psychoeducational and vocational treatment programs also provide promise, particularly when conceptualized as long-term, sustained interventions. In short, we would advocate that future outcome studies be designed more programmatically by including and testing potentially "modifiable" risk factors that can subsequently be evaluated in experimental clinical research.

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