

Natural Course of Schizophrenic Disorders: A 15-Year Followup of a Dutch Incidence Cohort

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Abstract

Data are presented on the 15-year natural course of schizophrenia and other nonaffective functional psychoses in a cohort of 82 first-contact cases from a circumscribed area in the Netherlands. The subjects were suffering from functional psychosis with International Classification of Diseases–Ninth Revision (ICD–9) diagnoses 295, 297, or 298.3–9 (broad definition of schizophrenia) on entry. Standardized assessments of psychopathology, psychological impairments, negative symptomatology, social disability, and use of mental healthcare were used. The study reveals a pattern of chronicity and relapses with a high risk of suicide: Two-thirds of the subjects had at least one relapse and after each relapse 1 of 6 subjects did not remit from the episode; 1 of 10 committed suicide; and 1 of 7 had at least one episode with affective psychotic symptoms that started on average 6 years after the onset of the schizophrenic disorder. Diagnoses were reclassified in five patients, according to *DSM-III-R* criteria for a bipolar disorder. The predictive power—in terms of time in psychosis and in partial or full remission—of demographic, illness, and treatment variables at onset of the illness was very limited. Insidious onset and delays in mental health treatment are risk factors that predict a longer duration of first or subsequent episodes. The importance of mental health treatment in regard to outcome is probably subject to change because an early warning and intervention strategy could prevent further damage and deterioration. Our data support the need for an adequate relapse prevention program as a priority for our mental health services.

Key words: Course, prediction, relapse.

Schizophrenia Bulletin, 24(1):75–85, 1998.

The numerous longitudinal studies of schizophrenia have left us with a confusing picture of course, levels of out-

come, functional status, and associated predictors and risk factors. Ram et al. (1992), reviewing seven long-term follow-back studies of 5 to 30 years and 13 prospective studies with a followup of 1 to 5 years, did find an overall pattern of a “good” outcome of almost complete remission after one or more episodes in 28 percent of patients, a “moderate” outcome of partial remission in 50 percent, and a “poor” outcome of chronic psychosis or permanent hospitalization in the remaining 22 percent. In a meta-analysis of 100 years of outcome literature on schizophrenia, Hegarty et al. (1994) calculated an average of 40.2 percent of patients who could be considered improved after an average 5.6 years (range = 1–40 years), but that percentage has decreased during the last two decades.

This downward trend could reflect a change to narrower diagnostic concepts. Eaton (1991) reported a considerable variation in natural course and outcome in a number of selected followup studies of early onset cases: The range of chronic psychosis was from 10 to 40 percent, and the range of “good” outcomes was from 10 to 64 percent.

As Ram et al. (1992) noted, one of the most serious methodological deficiencies is the heterogeneity of the cohorts with respect to illness stage and representativeness. Illness-stage homogeneity is required to test hypotheses about predictors of course and outcome from first onset. Many followup studies focus on consecutive hospital admissions or discharges. In these studies, the more chronic cases are overrepresented. They do not include all new incident cases, because first contact with the general healthcare system (e.g., the general practitioner) or with psychiatric outpatient services does not necessarily occur during the very first episode of the patients’ lives. Some patients may not come to the attention of psychiatric services at all. In prevalent cases with a

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preceding history of the illness, the first assessment data (e.g., unemployment and marital status) should not be taken as independent but as dependent variables in the prediction of course, since they may be consequences of the illness. The first assessment in many studies is not corrected for the time of onset and its corresponding demographic, situational, and personal characteristics. For example, 14 percent of the patients from the World Health Organization (WHO) 10-country study, which focused on the identification of new cases, had been ill for more than 1 year before their inclusion in the study, and only about 35 percent had been ill less than 1 month (Jablensky et al. 1992). This has an influence on all kinds of ratings of patients' diagnostic and functional status and possible predictor variables at first assessment.

In this article we present data on the natural course of schizophrenia and other nonaffective functional psychosis over a 15-year period after first onset. The cohort consists of all new cases from a circumscribed area in the Netherlands with a first treatment contact with inpatient or outpatient services because of symptoms of functional nonaffective psychosis. In the short-term, over 3 years since onset, we recorded complete remission after one or more episodes in 35 percent of the patients, partial remission (neurotic syndrome or personality change) in 35 percent, chronic psychosis in 24 percent, and suicide in the remaining 6 percent (Slooff 1984; Wiersma et al. 1988). These are relatively favorable results compared with those in the review of Ram et al. (1992).

The 3-year course since onset (complete remission, partial remission with a neurotic syndrome or a personality change [negative symptoms], or chronic psychosis) appeared little related to the overall pattern of treatment (one instance of inpatient or outpatient care only, or a combination of inpatient and outpatient treatment, or two or more spells of inpatient or outpatient care). Some patients with a remitting course had been hospitalized nearly half of the time, whereas half of those with chronic psychosis (including the suicides) had remained less than 20 percent of the time in a mental healthcare setting (Wiersma et al. 1988). We concluded that the intensity of care did not follow the type of course (remission vs. chronicity), and that there was evidence of many unmet patient needs.

Our interest, therefore, is to determine whether a gradual process of amelioration evolves, as Eaton et al. (1992) suggested, on the basis of admission data collected in case registers. Some studies also suggest that schizophrenia tends to plateau at about 5 years and that functional deterioration may remit even after 10 years of manifest illness (Engelhardt et al. 1982; Carpenter and Kirkpatrick 1988; McGlashan 1988; Carpenter and

Strauss 1991). Furthermore, we want to investigate the predictive power of a number of demographic and non-symptom characteristics of patients with respect to time to remission, level of remission, and time in treatment during the whole followup period. We focus on the following questions: (1) What is the overall pattern of course in terms of number and duration of psychotic episodes and remissions? Did the illness worsen or ameliorate relative to the 3-year followup? (2) Which demographic, illness, and treatment factors at onset predict time in psychosis, remission and partial remission, and treatment? (3) Are similar results found in the incidence cohorts of other countries in these respects?

Method

The selection of cases took place in the context of the WHO Collaborative Study on the Assessment and Reduction of Psychiatric Disability. The study was initiated to explore the applicability, reliability, and validity of a set of instruments and procedures designed to evaluate impairments and disabilities in a population of patients with severe mental disorders (Jablensky et al. 1980). In 1978 and 1979 an incidence cohort of 82 patients was collected in a geographically circumscribed area of two provinces in the north of the Netherlands. These patients suffered from functional psychosis of a nonaffective type with International Classification of Diseases—Ninth Revision (ICD-9; World Health Organization 1978) diagnoses 295, 297, or 298.3–9 (i.e., a broad definition of schizophrenia without a duration criterion). All patients had experienced a recent "first-ever" onset of psychotic illness; fulfilled the age criteria (15–44 years); had no evidence of organic brain disease; had no severe mental retardation nor alcohol or drug dependency; and had at least one of the following symptoms: hallucinations, delusions of nonaffective type, bizarre or grossly inappropriate behavior, thought or speech disorder. All patients but one had been admitted to a psychiatric hospital immediately after onset or in due course. Patients were assessed three times over a period of 2 years, and the results were reported by Giel et al. (1980, 1984, 1987), Wiersma et al. (1983, 1988), de Jong et al. (1984, 1985, 1986), and Slooff (1984).

The present followup, 15 years later, occurred in the context of the WHO Coordinated International Study on Schizophrenia (ISoS; Sartorius et al. 1996) combining the efforts of 15 research centers participating in the International Pilot Study of Schizophrenia (IPSS; Sartorius et al. 1987), the Determinants of Outcome of Severe Mental Disorders (DOSMeD) (Jablensky et al. 1992), or the Disability Study (Jablensky et al. 1980) in order to pro-

vide a comprehensive picture of the long-term course of schizophrenia in various cultures based on standardized instruments. All patients were tested with instruments used in earlier research to assess psychopathology (e.g., the Present State Examination [PSE; Wing et al. 1974]) and social disability (e.g., the Disability Assessment Schedule [WHO/DAS 1988]). An interview with an informant took place in many cases. The Life Chart Schedule (LCS; Sartorius et al. 1996), which covers the followup period in addition to the previously used WHO Past and Followup History and Sociodemographic Schedule (Jablensky et al. 1980), allowed for retrospective recording of the course of the illness in terms of psychotic episodes; negative symptomatology, anxiety/depression symptoms; the treatment history in terms of admissions; outpatient treatment; medication; sheltered accommodation; living arrangements; daily activities; and dependency on welfare, disability pension, or other benefits. The LCS was extended using a tailor-made course schedule with a time-line format, in order to retrospectively record treatment and nonpsychotic/psychotic episodes in 1-month units. In addition to information from the respondent and informants, all medical records were consulted to complete the course schedule. In cases where the psychosis was mainly affective (manic or depressive) this fact was coded as well.

The illness course was divided into psychotic and nonpsychotic episodes. A psychotic episode was defined as a discrete period of symptomatology characterized by overt psychotic signs and symptoms of hallucinations, delusions, cognitive disorganization, marked psychomotor disturbance, or grossly inappropriate behavior. Such an episode must be preceded or followed by at least 30 days during which the patient had no psychotic symptoms. Nonpsychotic episodes refer to periods without psychotic signs and symptoms, classified either as predominantly neurotic (anxiety or depressive symptoms) states or as a residual state with negative symptoms, such as loss of interest and social withdrawal. Complete remission means that the subjects are symptom free and show their usual premorbid personality (i.e., no positive ratings in any schedule like PSE and DAS). A remission or partial remission cannot be rated as present if it has lasted for less than 30 days. The distinction between a psychotic episode and a remission must be based on symptoms only, regardless of treatment (including effects of medication). The type of episode and remission was judged by the interviewer, based on subject and informant information, and case notes. This judgment resulted in rating a period on the LCS as an episode with psychotic symptoms, symptoms of anxiety/depression, or negative symptoms, or as a complete remission.

Treatment history contains spells of (1) day, outpatient, or community treatment; (2) hospital admission; (3) sheltered living or supervised residence outside the mental hospital; and (4) contacts solely with a general practitioner or with social services. Length of stay in the hospital or sheltered accommodation is easily established, but length of outpatient episodes is less so. According to the definition used in case-register studies (Tricot 1986), an outpatient episode ends if there are no contacts during a 90-day period. We have recorded the beginning and end of treatment periods and dated them back to the month of supposed onset of psychosis. In many cases, treatment, including the prescription of antipsychotic medication, started in the same month as the onset of psychosis with admission to a psychiatric hospital or with outpatient treatment. We have no exact or reliable data on the adequacy of or compliance with the prescribed medication. However, we established that after the onset of psychosis, 40 percent of the patients had no contact at all with healthcare during an average of 3 months; 54 percent were immediately admitted to a hospital; and 6 percent started with a period of outpatient treatment. In almost all cases, antipsychotic medication was prescribed.

Dates of onset and end of illness and treatment episodes were checked as much as possible with staff members of the hospital (e.g., discharge letters) or community service. The starting point was the time of first onset of psychosis, and a timeline of the followup period was made for each patient, containing treatment and illness episodes in 1-month units up to 186 months (i.e., end of the 15-year followup).

Onset was recorded at first assessment in 1978–79 as acute (symptoms fully developed from a clearly non-symptomatic state within 7 days), subacute (between 1 and 4 weeks to develop), and insidious or slow (occurs when psychotic symptoms fully develop over more than 1 month or when the beginning of an episode is difficult to determine with any precision). The study design did not systematically record prodromal signs (although there were signs of premorbid social and occupational disabilities) or the precise duration of the insidiousness.

All information was used for a diagnostic classification of the present state and the main overall condition by the research team of two psychiatrists, two clinical psychologists, and a sociologist, according to ICD-10 (World Health Organization 1992) and *DSM-IV* (American Psychiatric Association 1994).

Cohort Characteristics at Onset. Table 1 presents the sociodemographic characteristics of 82 patients at the onset of psychosis. Males and females are equally represented and most patients fell ill before the age of 25.

Table 1. Sociodemographic variables at onset of first psychosis ($n = 82$)

Variable	Percentage
Male	52
Under 25 years of age	61
Higher education > 10 yr	41
Living alone	23
Living with parents	38
Own family/partner	39
Never married	63
Having children	21
Student	28
Housewife	16
Working	37
Unemployed	19
On social welfare	28
Premorbid disabilities	36
Insidious onset	26
In mental health treatment at onset	60

Nearly two-thirds were single. A relatively high percentage of the patients were students. The overall level of education was significantly higher than in the general population (Wiersma et al. 1983), but this did not affect occupational status. The educational level of the patients (and of their fathers) is higher than expected compared to the general population, probably because the main city of the catchment area has a university and offers many other higher educational and occupational training opportunities. Our patient population is relatively upwardly mobile in educational terms contrasting sharply with the downward occupational mobility in the cohort. About one-third of the patients already showed premorbid social and occupational disabilities: about 25 percent were dependent on social welfare, including disability pensions. Seventy-five percent had an acute or subacute onset of psychosis, while 60 percent had received some form of mental health treatment at the time of onset.

After tracing the 82 patients at the 15-year followup, it appeared that 9 had died (8 definite suicides, 1 uncertain), 6 were untraceable (2 had moved abroad), and 4 refused any contact. The last followup concerned 63 persons (response rate = 76.8%). There are no statistically significant differences between the responders and nonresponders according to sex, age, and diagnosis (ICD 295 schizophrenia vs. ICD 298 acute reactive psychosis). We have reports on the course of illness and treatment of those who died during followup. Four suicides had occurred during a psychotic episode and five during partial remission with symptoms of anxiety or depression. For those who were not traceable or refused contact, we used the available information (at least the first 3 years) in the survival analysis and Cox regression.

Epidemiology. Comparison with other properly defined (first lifetime onset or first-ever contact because of psychosis, including the broad inclusion criteria) incidence cohorts in other countries shows remarkable correspondence to our study with respect to gender, age, and marital status but much less so with respect to educational and occupational status, due to the socioeconomic situation in the country. Examples are Mannheim, Germany, $n = 70$ (Schwarz et al. 1980); Madras, India, $n = 90$ (Thara et al. 1994); or the centers participating in the WHO 10-country study (DOSMeD study), $n = 1,379$ (Jablensky et al. 1992). Susser and Wanderling (1994) calculated for six industrialized cities (Aarhus, Denmark; Dublin, Ireland; Honolulu, Hawaii; Moscow, Russia; Nagasaki, Japan; Nottingham, England) participating in that study a year incidence of 1.14 per 10,000 of the population, which is quite similar to what we found for the Netherlands population (1.12) (Giel et al. 1980). This suggests that our findings could be representative of patient populations in other countries as well, or at least those in the Western world.

Data Analysis. Linear regression and Cox regression were used to analyze the effects of (1) sociodemographic and premorbid characteristics, (2) mode of illness onset and the time lag between the outbreak of psychosis and the initiation of mental health treatment on length of time in psychosis or remission, and (3) length of stay in hospital treatment or in any kind of mental health care. Cox regression or the proportional hazards model identifies the relative risk of a variable affecting the duration of psychosis (e.g., remission or inpatient treatment) taking into account the effect of covariates (age, marital status). The hazard ratio is the relative risk at time t to experience an event (e.g., the end of an episode) of those who survived until time t . If the hazard ratio equals 1, there is no difference in risk between the two categories of the gender variable: men (first category) versus women (second category). If the hazard ratio is greater than 1, the duration of the episode tends to be longer for the first or reference category of the variable, and if it is smaller than 1, the duration of an episode tends to be shorter. For example, a hazard ratio of 2.5 for the gender variable (male vs. female) with respect to the duration of a hospital admission would imply 2.5 times greater risk of a long stay for men than for women at each time point during followup (Sytema et al. 1996).

Results

Pattern of Course. The courses of psychosis over the 15 years are presented in table 2. About one-quarter of the cohort (26.7%) has remitted completely, which is less

Table 2. Course of nonaffective functional psychosis over 15 years (n = 82)

Course	n (%)
One episode followed by complete remission	10 (12.2)
Two or more episodes followed by complete remission	12 (14.6)
One episode followed by partial remission (anxiety/depression)	5 (6.1)
Two or more episodes followed by partial remission (anxiety/depression)	9 (11.0)
One episode followed by negative syndrome	3 (3.7)
Two or more episodes followed by negative syndrome	24 (29.3)
Chronic psychotic all the time (one episode)	9 (11.0)
Course unknown (refused or untraceable)	10 (12.2)

than we found after the 3-year followup (35%). Partial remission is most common (50.1%), mainly with a negative syndrome after several episodes. At least 1 of 10 were psychotic all the time.

It turned out that 27 patients (32.9%) had only one psychotic episode: 10 remitted completely, 8 only partially, and 9 remained psychotic. Thus, chronicity developed from the first episode and afflicted 63 percent (17 of 27) of those who did not have a relapse. Two-thirds had one or more relapses. The probability of chronicity increased with each subsequent episode, not because of continuing psychotic symptoms but because of the appearance of negative symptoms.

Table 3 presents data on the course of each subsequent psychotic episode in terms of either persisting psychotic symptoms or negative symptoms. We considered a maximum of four episodes per patient because the numbers became too small to be significant (<10).

Two findings seem striking. First, on average 17 percent (range = 8–27%) of the patients, one of every six, does not remit from an episode of nonaffective functional psychosis, irrespective of whether it is the first episode or not. Second, about 21 percent (range = 15–25%), one out of every five, remit only partially with negative symptoms. Adding up both percentages for each episode reveals that chronicity in terms of continuing psychotic

Table 3. Chronicity of psychosis: No remission (chronic psychosis) or partial remission (negative symptoms)

Course of psychotic episodes	Persisting psychotic symptoms (%)	Negative symptoms (%)
First episode (n = 82)	12	15
Second episode (n = 49)	8	25
Third episode (n = 27)	19	22
Fourth episode (n = 15)	27	20

symptoms or the persistence of negative symptoms, gradually increase from 27 percent after the first episode to 47 percent after the fourth episode. Although the chronic psychotic cases from each earlier episode are discarded, their percentage in each subsequent episode still increases. With the exception of the first episode (mean duration = 20 months), there was also a gradual increase of mean duration of each subsequent psychotic episode: 9 months for the second, 15 months for the third, and 27 months for the fourth episode.

Suicide. Nine patients (of which one is uncertain) or 11 percent committed suicide: two within 2 years, three within 3 years, two within 5 years and two patients even 10 and 13 years after onset. Four patients killed themselves during their first or second psychotic episode, while the others did so during a period of partial remission with predominantly symptoms of depression and anxiety. The mean duration of their first psychotic episode was nearly 7 months, and of all episodes, 32 months.

Relapse. Relapse is a recurrent phenomenon in the course of this disorder. The recurrence of psychotic symptoms could include symptoms of affective as well as non-affective type. Thirteen patients suffered from relatively short affective psychotic episodes in the course of time. Eight of these had more than one episode of an affective type. In table 4, we calculated percentages of patients at risk for a relapse of nonaffective type only, excluding the data of those who did not remit or were lost to followup.

Table 4. Risk of subsequent relapses of psychotic episodes of nonaffective type in relation to time of previous remission

	Within 1 year (%)	Between 1–2 years (%)	Longer than 2 years (%)	Total (%)
First relapse (n = 72)	36	17	15	68
Second relapse (n = 49)	30	11	17	58
Third relapse (n = 31)	23	16	10	49
Fourth relapse (n = 17)	12	6	29	47

The probability of a first, second, third, and fourth relapse gradually decreased from 68 to 47 percent. Most relapses occurred within 1 to 2 years after remission from the previous episode, although the time span tends to expand between remissions and relapses. If we take episodes of an affective type into account as well, the probability of a second to a fourth psychotic relapse increases to 72, 77, 68, and 76 percent, respectively.

Time to Remission and Relapse. Over a period of 15 years, we counted 192 nonaffective and 33 affective psychotic episodes, an average of 2.7 episodes per patient. Forty percent had only one nonaffective episode, 60 percent had one or more relapses, 33 percent had two or more, and 18 percent had three or more relapses. Two patients had a maximum of nine nonaffective episodes. The average time (since first onset) after which these relapses started was more than 2 years for the first relapse, 4 years for the second, almost 6 years for the third, and more than 7 years for subsequent relapses. Affective episodes started on average of 6 years after the first onset and continued to occur during the rest of the followup.

Figures 1 and 2 show the survival curve of the first episode or time to remission, the first remission or time to first relapse, and the average of the next four relapses. Time to remission, that is, *length of time in psychosis*, appears to be the same for first and subsequent episodes: more than 80 percent of the patients remitted within 1 year (most within a few months), a small percentage remitted in the year after, and as noted previously, about one of six patients (17%) remained psychotic. The graph of time to relapse, that is, *length of time in remission*, demonstrates that 43 percent of the patients relapsed within 1 year, and another 12, 8, 7, and 2 percent in the subsequent 4 years, so that about 70 percent of the patients had suffered a

Figure 1. Survival curves for probability of remaining psychotic for first and subsequent episodes

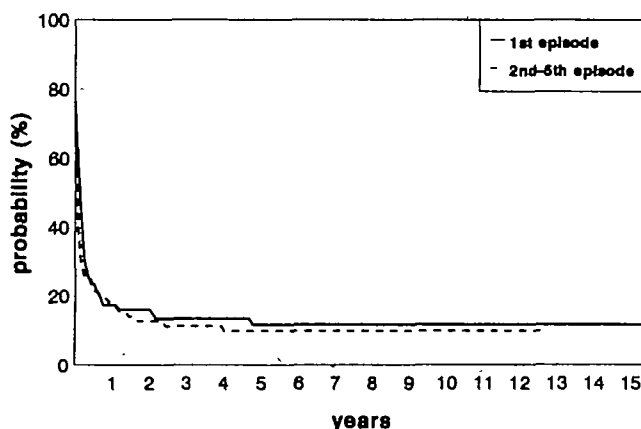
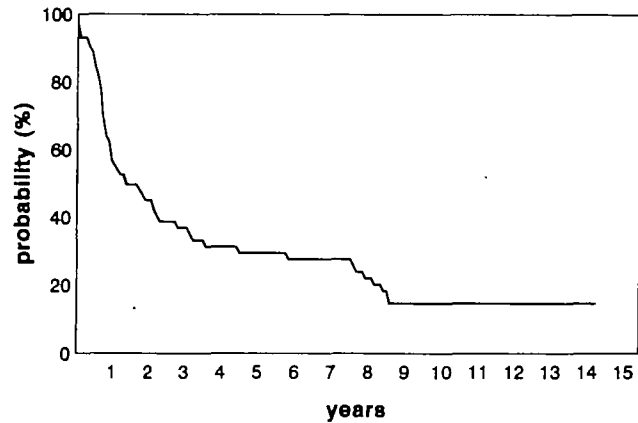


Figure 2. Survival curve for probability of remaining in remission after first episode



relapse within 5 years after first onset. After about 9 years, the risk of relapse seems to disappear; 15 percent are still in remission at the end of the final followup. No significant differences between graphs for gender, age at onset, education, or marital status were found.

Prediction of Time in Psychosis, Remission, and Treatment. We analyzed the influence of sociodemographic and illness variables on the duration of psychosis, remission, and treatment to find early predictors and risk factors of the course of the psychotic condition. All predictor variables are related to the time of first onset of psychosis and therefore are not biased by a delay of contact with the mental health system or a late assessment. Poor premorbid functioning and dependency on social assistance already indicate a level of social disability that could be due to personality traits, other mental health problems, or prodromal signs of psychosis. Cox regression (see table 5) for three types of episodes shows the value of the hazard ratios of the variables. The reference value of the variables is chosen for its "known negative" influence (Strauss and Carpenter 1977; Westermeyer and Harrow 1986), that is, a longer duration of psychosis expressed by a hazard ratio greater than 1.

Gender and age at onset did not have a significant influence. The finding that an early age at onset (<25 years) does not go with a longer duration of psychotic episodes (hazard ratios smaller than unity) is rather unexpected. The other variables have the expected direction of the relationship with duration: married, not dependent on social assistance, good premorbid functioning, acute onset, and immediate treatment predict shorter first and subsequent psychotic episodes. Acute onset and prompt treatment have a statistically significant hazard ratio. The duration of the first remission period could not be predicted by any of the selected variables.

Table 5. Cox regression of duration of first psychotic episode, first remission, and subsequent (2nd–5th) episodes

Variable	Reference		Hazard ratio, first episode (n = 81)	Hazard ratio, first remission (n = 71)	Hazard ratio, subsequent episodes (n = 99)
	Males	Females	Males and Females	Males and Females	Males and Females
Gender	–	–	0.88	0.97	1.15
Age	<25 yrs	>25 yrs	0.77	0.99	0.85
Never married	Yes	No	1.19	1.11	1.04
Social assistance	Yes	No	1.49	0.91	1.07
Premorbid functioning	Poor	Good	1.25	1.06	1.01
Onset of first psychosis	Insidious	<1 month	1.62	0.86	1.88 ¹
Mental health treatment	Delayed	Prompt	2.33 ²	1.26	1.24

¹p = 0.07.
²p < 0.01.

Multiple regression was used to examine the influence of the predictor variables on the *total proportion of time* in psychosis, full or partial remission, and time in a mental hospital, versus all kinds of mental health treatment during the 15-year followup (see table 6).

Gender did not play a significant role in any of the dependent time variables. Late and insidious onset and dependency on social assistance predicted a longer time with psychotic symptoms; older age, being unmarried, and delayed treatment strengthened this relationship. The overall effect of these seven predictor variables accounts for about 10 percent of the variance ($r^2 = 0.29$) of the dependent variable of time in psychosis ($p < 0.05$). Acute onset and prompt treatment predicted the time in remission; being married and early onset (<25 years) strengthened the prediction. Therefore, the total effect is a multiple regression coefficient of 0.24 ($p < 0.05$; about 6 percent explained variance). Neither the duration of negative symptoms or anxiety/depression nor the length of in-

or outpatient mental health treatment was significantly related to any of the variables, with the exception of an insidious onset and longer mental hospital care (0.18).

Discussion

The description of the 15-year course of schizophrenic disorders, broadly defined by the diagnostic categories of ICD-9 (ICD 295, 297, and 298.3–9) and included in the cohort at the onset of illness, yields a variety of course and outcome patterns. There was complete remission, that is, no symptoms, no care (Wiersma et al. 1996), in 27 percent of the patients; chronic psychosis in 11 percent; and a negative syndrome after one or more episodes in 43 percent. Suicide occurred in 11 percent of all cases. Our study demonstrated the high risk of relapse, suicide, and chronicity in this cohort. As far as we could ascertain through contact by telephone, medical files, or on the

Table 6. Regression analysis on proportion of time in psychosis, in remission, in mental hospital care, and in any kind of mental health care over 15 years after first onset

Variable	Reference	Psychosis	Negative symptoms	Anxiety/ depression	Full remission	Hospital care	Any mental health care
		β	β	β	β	β	β
Constant		0.72	0.25	0.11	-0.08	0.37	0.47
Gender	Males	-0.02	-0.01	-0.07	0.09	-0.00	-0.07
Age	<25 yrs	0.16 ¹	-0.00	-0.02	-0.11	-0.01	-0.07
Unmarried	Yes	-0.12	-0.06	0.05	0.14	-0.07	-0.03
Social assistance	Yes	-0.18 ²	-0.00	0.10	0.06	-0.03	-0.08
Premorbid functioning	Poor	-0.02	-0.05	0.09	-0.00	-0.01	-0.10
Onset	Insidious	-0.29 ³	-0.02	0.03	0.29 ³	-0.18 ⁴	-0.14
Treatment	Delayed	-0.12	-0.11	0.02	0.19 ⁵	-0.08	-0.09
R ²		0.29	0.06	0.05	0.24	0.13	0.07

Note.—Significance of beta (β) coefficients: ¹ = 0.09; ² = 0.05; ³ < 0.01; ⁴ = 0.02; ⁵ = 0.03. R² = explained variance.

basis of information at their 3-year assessment, the outcome of the 10 untraced patients would not have significantly changed this pattern. Four respondents refused any contact because they did not want to be reminded of their psychotic experience. We do not know how they fared, but we are satisfied that they have not been chronically psychotic, nor are they currently in a mental hospital. We did not locate the remaining six respondents, their status is completely unknown.

As for representativeness, one might speculate about the sampling procedure and the inclusion criteria. We screened all the relevant inpatient and outpatient psychiatric facilities in the catchment area during 21 months and registered all first and recent onset cases. We did not conduct a leakage study as in the DOSMeD study, and we could have missed new cases who came to the attention of only private practitioners, general practitioners, social workers, the police, etc. We learned afterward that one or two of the patients who fell ill during those 21 months of screening should have been included into the study but were not referred to a mental health facility in a timely manner. We think that the total number of missed cases is very small partly due to the organization of mental health care in the Netherlands, although we have no hard evidence for this.

One could argue that the inclusion criteria were too broad and that we have included disorders that may be too different from the narrow-band definition of schizophrenia in *DSM-III-R* (American Psychiatric Association 1987). Half the cohort received an initial diagnosis of reactive psychosis at first assessment. We examined the possible differences of symptomatology, onset, precipitating and predisposing factors in patients with a diagnosis of schizophrenia (295), and reactive psychosis (298) and found hardly any discrepancies. The descriptions in ICD-9 were broad and not mutually exclusive, which made the choice of a 295 or 298 classification somewhat arbitrary in some cases. There was also a certain reluctance to make the diagnosis of schizophrenia in the late 1970s. In a reclassification exercise (Nienhuis et al., submitted for publication), all subjects were reexamined at first onset using *DSM-III-R* and ICD-10 criteria. A much greater proportion of the patients were diagnosed with schizophrenia at first onset.

At the 15-year followup, we classified 31 patients (38%) as having schizophrenia according to *DSM-III-R* criteria and based on the information from standardized assessments, 18 patients as completely remitted (no *DSM-III-R* diagnosis), and 5 patients with bipolar disorder in remission. There was no unequivocal relationship between early diagnosis and predicting the remission type or course type. Bipolar disorder was not diagnosed during the first 3 years since onset, but was diagnosed later dur-

ing followup, which could be considered as part of the outcome of complete remission. As our analysis focused on episodes of nonaffective psychosis, it seems unlikely that these five patients constitute a bias.

We do not know to what extent mental health care has influenced the naturalness of the illness course. Compared with other countries, mental health care in the Netherlands is relatively well provided with respect to the number of psychiatrists, beds, and outpatient services (e.g., Breemer ter Stege and Gittelman 1987). But the delivery of care to psychotic patients was equivocal during the late 1970s and the 1980s: readily available psychotherapeutic community treatment for the better educated subjects with a diagnosis of psychogenic and reactive psychosis but poor aftercare with a lack of rehabilitation for the more difficult patients with a more conspicuous diagnosis of schizophrenia. We observed inconsistent and less adequate psychopharmacological treatment and lack of a coherent rehabilitative effort focusing on daily living, work, and independence (Wiersma et al. 1988).

Relapse and a chronic course do not happen only in the first stages of the disorder; deterioration also occurs later on. One-third of the cohort had three or more psychotic episodes occurring on average 6 years after first onset, each time with an increased probability of chronic psychosis or persisting negative symptoms. The level of remission (complete or partial) was not predictive of recurrence of a psychotic episode. The average risk of a relapse, whatever the state of remission, was about 70 percent. Therefore, we doubt that progressive amelioration, as suggested by Eaton et al. (1992), is a valid observation. Their conclusion is based primarily on case register data and is related to the decreasing risk of readmission to a mental hospital as a proxy for relapse. We observed at followup that 14 patients (17%) had been in a hospital or a supervised sheltered living facility for about 8 years; 3 (4%) had died in hospital after a stay of 3.5 years; 16 (20%) were still in outpatient treatment; and at least 6 patients (7%) had serious needs but were not in care (Wiersma et al. 1996). Jonsson and Nyman (1990) found a worse outcome at the 14- to 17-year followup than after 5–8 years, which may be an indication that schizophrenia does not tend to plateau at about 5 years as Carpenter and Strauss (1991) suggest. Our findings do not seem to support the notion of schizophrenia becoming less chronic than it used to be (Shepherd et al. 1989); they are probably more in line with the conclusion of Hegarty et al. (1994) that the percentage with a good outcome has been decreasing over the last few decades.

The risk of relapse and a chronic course is to some extent predictable at the very onset on the basis of characteristics of the disorder (insidious onset), the person (age more than 25 years), functioning (economically depend-

ent), and delays in the initiation of mental health care. Our results find support in the literature (Watt and Szulecka 1979; Soni et al. 1994). Schmid et al. (1991) concluded that chronicity at onset and premorbid status dominated all other variables accounting for the variance in outcome. Recent findings of Lieberman et al. (1993) from an inception cohort followed over 1 year show that baseline demographic measures do not generally predict either time to remission or time to relapse. There is some evidence (Wyatt 1991) that early intervention with neuroleptics in first-break schizophrenia patients increases the likelihood of an improved long-term course. Our finding of a relationship between delays in mental health treatment and a longer duration of the psychosis seems to support this.

The study of Thara et al. (1994) on the 10-year course of schizophrenia offers a good opportunity for a comparison with ours. Of the 90 first-onset cases from the Madras, India center (included according to the ICD-9 diagnosis), they observed 4 suicides, 10 patients lost to followup (5 because of death) other than suicide, 4 not traceable, and 1 refusal, and 76 (84%) patients willing to participate. Of the patients, 53 percent (48 of 90) had completely remitted (three-quarters after one or more relapses), 25 percent had a partial remission, 6 percent were continuously psychotic, and 4.4 percent had committed suicide. The average number of psychotic episodes did not differ much (Madras, India = 2; Groningen, The Netherlands = 2.3), but the duration of psychotic symptoms appeared to be shorter. The proportion of time in psychosis during followup in Madras ($n = 76$) was 0.21 and in Groningen 0.30. In Madras the resulting outcome is more favorable than ours: complete remission 53 percent versus 27 percent, suicide 4 percent versus 11 percent, and chronic psychosis 6 percent versus 10 percent. Female sex and in particular young age at onset (<20 years) predict less time with psychotic symptoms. This comparison again demonstrates the difference in the course of schizophrenia in a European versus an Asian country, in favor of the latter. This finding supports the short-term outcome seen in the WHO 10-country study (Jablensky et al. 1992).

Conclusion

The 15-year natural course of schizophrenia and other nonaffective functional psychoses in the Netherlands shows a pattern of chronicity and relapse with a high risk of suicide: two-thirds had at least one relapse; after each relapse one of six patients did not remit from the episode. One in 10 committed suicide, making this a fatal disorder for 10 percent of the patients. One of seven had also at

least one episode with affective psychotic symptoms that started on average 6 years after onset of the schizophrenic disorder. This resulted in five patients having a diagnostic reclassification according to *DSM-III-R* of bipolar disorder instead of schizophrenia. The predictive power of demographic, illness, and treatment variables (in terms of time in psychosis and partial or full remission) was very limited. Insidious onset and delays in mental health treatment are risk factors, predicting a longer duration of first or subsequent episodes. The importance of mental health treatment, in regard to outcome, is probably subject to change because an early warning and interventions strategy could prevent further damage and deterioration. Our data support the need for an adequate relapse prevention program as a priority for our mental health services (Wyatt 1991; Hogarty 1993).

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Acknowledgments

This article is based on the data and experience obtained during the participation of the authors in the World Health Organization (WHO) International Study on Schizophrenia funded by WHO, the Laureate Foundation, and the participating field centers. The research in the Dutch center is supported by grant 28-2143 from the Praeventiefonds. The authors thank Dr. A.J. Oldehinkel for her statistical support, Dr. H. Kluiters for his useful comments, and Mrs. E.G. Lindeboom for her substantial and continuous support throughout the project.

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