First-Episode Schizophrenia: I. Early Course Parameters

by Tor K. Larsen, Thomas H. McGlashan, and Lars Conrad Moe

Abstract

Concepts and definitions pertaining to the early course of schizophrenia are reviewed, along with recent illustrative studies of first-episode schizophrenia. Early course parameters of a Norwegian first-episode sample are presented. This sample (n = 43) demonstrated strong gender differences, with male patients having significantly higher frequency of single marital status, lower educational status, schizophrenia, early age at onset, and lower Global Assessment of Functioning scores the last year before hospitalization. The duration of untreated psychosis (DUP) was long (mean = 114 weeks), as in other studies. Longer DUP was associated with poorer work, social, and global functioning in the year before admission, with more insidious onset of psychosis, and with more negative symptoms at first clinical presentation. Longer DUP was not associated with the age at onset of psychosis. These findings were mostly gender independent. The data help to frame questions about why patients can be psychotic for so long before getting help. Finally, suggestions are offered for the definition and measurement of early course parameters for schizophrenia.

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Reasons for Focusing on the Early Course

Recent findings suggest that early treatment in schizophrenia may correlate with a more favorable short-term (Falloon 1992; Loebel et al. 1992; Lieberman et al. 1993) and long-term (Helgason 1990) outcome, and may also change the natural history of the disorder for the better (Wyatt 1991). As a result of this, greater attention is being focused on the early course of schizophrenia and the duration of untreated psychosis (DUP).

The first aim of this article is to present findings about DUP in a Norwegian sample of first-episode psychosis and compare these with other recent studies of DUP. In the course of this investigation, we encountered problematic variations in assessment definitions and variables pertaining to the early course of psychosis. Accordingly, the second aim of this article is to highlight these variations and recommend assessment standards for further investigation of early course and DUP.

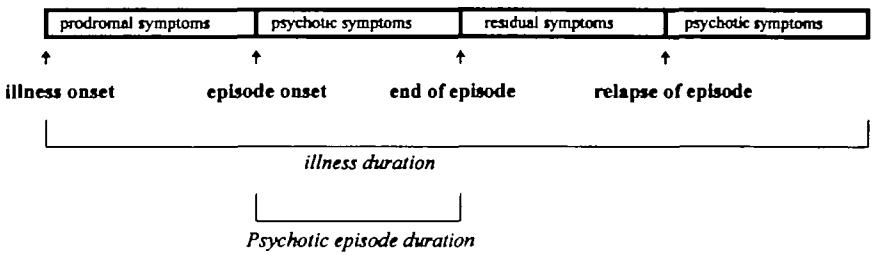
Early Course of Schizophrenia

According to most writers, the early course of schizophrenia has three phases: the premorbid period, the prodromal period, and the acute psychosis (Haas and Sweeney 1992; Keshavan and Schooler 1992; Loebel et al. 1992; Beiser et al. 1993). Keshavan and Schooler (1992) have proposed several key variables.

As we can see from figure 1, Keshavan and Schooler distinguish prodromal symptoms from psychotic symptoms, defining the illness onset as the time when the patient first experiences prodromal symptoms. The onset of psychotic

Reprint requests should be sent to Dr. T.K. Larsen, Psychiatric Hospital of Rogaland, Armauer Hansensv. 20 4011 Stavanger, Norway.

Figure 1. Definitions of course[1]



[1]Adapted from Keshavan and Schooler (1992).

symptoms is called episode onset. Since the prodromal symptoms are not specific for schizophrenia, the illness onset must be defined retrospectively or, when described prospectively, only set as a possibility (Cannon-Spoor et al. 1982; Malla and Norman 1994).

The premorbid period has been defined as "the individual's psychosocial functioning before the onset of the schizophrenic illness" (Cannon-Spoor et al. 1982, p. 470) or "not disease-related characteristics prior to first admission" (Häfner et al. 1992, pp. 209–210). The premorbid concept indicates the period before the illness onset and is therefore dependent on the definition of illness onset. When illness onset is defined as the first appearance of any psychiatric symptoms (Rabiner et al. 1986), the premorbid period will on average be shorter than if the illness onset is defined as the time when the patient first met diagnostic criteria for psychosis (Turner et al. 1986).

Insofar as the term "premorbid" implies a normal or nonpathological state, the term can be misleading and, at times, grossly inaccurate. A "deteriorating" premorbid subtype, for example, has been described that may be the earliest manifestation of the morbid psychotic process (Haas and Sweeney 1992). A more accurate term would be "preonset" or "preprodromal."

The prodromal period is the period when the manifest disease process begins, but without any prominent psychotic symptoms (Malla and Norman 1994). This period has been recognized for a long time and its symptoms are listed in *DSM–III–R* (American Psychiatric Association 1987) as follows: marked withdrawal, impairment in role functioning, peculiar behavior, impairment in personal hygiene, blunted or inappropriate affect, disturbances in speech, odd beliefs or magical thinking, unusual perceptual experiences, and marked lack of initiative, interest, or energy. There are many additional phenomena that can be prodromal to a psychosis. Keshavan and Schooler (1992) suggest that the following should be considered: decline in social functioning regardless of relationship to psychopathology, first onset of any psychiatric symptoms, first onset of early psychotic symptoms, and first onset of negative symptoms. The prodromal symptoms are nonspecific and can be the early phase of other psychiatric illnesses such as other psychoses, personality disorders, or stress reactions (Herz and Melville 1980; Keith and Matthews 1991; Falloon 1992).

Prodromal Symptoms and Symptoms of Relapse. All prospective studies of prodromal symptoms study their emergence just before relapse, not onset (Herz and Melville 1980; Subotnik and Nuechterlein 1988; Birchwood 1992; Malla and Norman 1994). In many studies, it is also presumed that the prodromal symptoms of relapse are the same as the prodromal symptoms retrospectively described prior to first psychotic episode (Kissling 1994). With the exception of Yung et al. (1996, this issue), we are not aware of any studies that compare symptoms prodromal to relapse with symptoms prodromal to onset.

The onset of an episode of psychosis is the period when the patient experiences prominent psychotic symptoms that can be identified by the patient or by people observing the patient. Keshavan and Schooler (1992) offer the following description: "a period with a specified minimum duration, during which the patient manifests a specified minimum of symptoms to fulfill syndromal criteria for a given category of psychotic disorder" (p. 503). They recommend that the onset of a psychotic episode should be quantified with scales that measure the severity of psychotic symptoms such as the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984), or Posi-

tive and Negative Syndrome Scale for schizophrenia (PANSS; Kay et al. 1987). Attempts at defining onset vary between whether the psychosis begins when the patient fulfills the criteria of a syndrome or when the weak psychotic symptoms are beginning to emerge, the latter "contaminating" the prodromal period with psychotic symptoms.

First-Episode Studies in Schizophrenia and DUP. Keshavan and Schooler reviewed the assessment methods used in first-episode studies in schizophrenia in 1992 and found that 53 studies met their criteria for inclusion in the review. They found marked inconsistencies in the definitions of key variables, such as time of onset and onset type, in the use of structured diagnostic interviews, and in the description of exclusion criteria and severity measures. They proposed that the descriptive heterogeneity of early schizophrenia can partly be attributed to these differences in definitions. They conclude that it is important for future researchers to apply criteria that can be meaningfully compared.

We extended Keshavan and Schooler's review to some key studies published after their article, listed in table 1.

Haas and Sweeney (1992) studied 71 first-episode patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder. They divided their sample into two groups: a long-term symptom group (LTS) with a DUP longer than 1 year (56.2%) and a short-term symptom group (STS) with duration less than 1 year. There was no difference in the age at onset of psychotic symptoms between the groups, but the LTS group was older at hospitalization and showed a trend for having received more neuroleptics before being hospitalized. There was also a trend for the LTS group to have better global functioning at hospitalization than the STS group. The mean duration of psychotic symptoms before hospitalization was 3 years; duration of prodromal symptoms is not given. First treatment and first hospitalization were considered to be equivalent.

Beiser et al. (1993) found that schizophrenia patients (n = 72) had a mean DUP (treatment lag time) of 56.1 weeks (median 8.2) and a mean duration of prodromal symptoms of 112.8 weeks (median 52.7). They made a checklist of symptoms described by the patients, relatives, or friends that consisted of first noticeable symptoms, prominent psychotic symptoms, and treatment seeking. They found that for schizophrenia, women were younger than men both at the onset of first noticeable symptoms and at the onset of prominent psychotic symptoms. This atypical finding could be explained by the fact that the study had an upper age limit of 54 years, which could exclude very-late-onset schizophrenia in women. Most studies report that schizophrenia develops later in women than in men (Loranger 1984). Beiser et al. (1993) found that clinicians can define the onset of psychotic symptoms with good reliability, but that dating first noticeable symptoms proved more difficult, probably because of the greater nonspecificity of the early symptoms. First treatment meant first treatment, whether or not that involved hospitalization.

Häfner et al. (1993) used a standardized Interview for Retrospective Assessment of the Onset of Schizophrenia (IRAOS; Häfner et al. 1992) and early course of schizophrenia in a study of 165 schizophrenia patients (a subgroup of the total sample of n = 267), where it was possible to compare the patient's own descriptions with the observations of a family member or with available objective data. They found that the descriptions of the earliest signs of mental disorder and first psychotic symptoms were not significantly different. The only marked difference was that psychotic symptoms were noticed by relatives or documented in case records 12 months later than perceived by the patients. They explain this difference as a consequence of the fact that psychotic symptoms, such as hallucinations, are subjectively experienced long before others can perceive them. Häfner et al. (1993) defined the onset of schizophrenia as follows: Illness onset is the first (nonspecific) sign of mental disturbance; episode onset is the first first-rank symptom (specific sign) or the first point in time when the operational criteria of a diagnostic system (like *DSM–III–R*) are fulfilled. They found that the patients described the DUP to be 2.1 years (mean) and the duration of the earliest sign of mental disorder until first admission for schizophrenia to be 4.6 years (mean). They also found that 70 percent of the cases began with negative symptoms. They, like Haas and Sweeney, equated first treatment with hospitalization.

Loebel et al. (1992) studied 70 first-episode schizophrenia and schizoaffective patients and found that the duration of psychotic symptoms before treatment was

Table 1. Duration of untreated psychosis: Definitions and data

	Untreated illness (onset of prodromal symptoms to hospitalization)			Untreated psychosis (onset of psychotic symptoms to hospitalization)		
Study	**Duration**	**Definition of illness onset**	**Measure of severity**	**Duration**	**Definition of episode onset**	**Measure of severity**
Haas and Sweeney (1992) *n* = 71 SCZ: 52 SCA: 11 SCF: 8	None	None	None	Weeks: 156 (mean), 43.8% < 1 year 56.2% > 1 year	Age at onset of first symptoms	None
Beiser et al. (1993) *n* = 72 SCZ	Weeks: 112.8 (mean) 142.9 (SD) 52.7 (median) (in addition to duration of psychosis)	First noticeable psychiatric symptoms	None	Weeks: 56.1 (mean), 148.2 (SD), 8.2 (median)	Checklist of symptoms considered to be possible first signs of psychosis	None
Häfner et al. (1993) *n* = 267 SCZ	Years: 4.6 (mean)	First (nonspecific) sign of mental disturbance	None	Years: 2.1 (mean)	(a) First first-rank symptoms, or (b) Fulfill the criteria for a syndrome	Definition (a) does not, and definition (b) does imply a measurement of severity
Loebel et al. (1992) *n* = 70 SCZ: 54 SCA: 16	Weeks: 150.8 (mean), 716.6 (SD), 8 (median)	Behavioral changes that, in retrospect, appear to have been related to the patient's illness	None	Weeks: 51.9 (mean), 82.3 (SD), 39 (median)	After psychosis was clearly explained, the patient (or the family member) was asked when symptoms were first experienced (or noticed)	None

Note.—SCZ = schizophrenia, SCA = schizoaffective disorder, SCF = schizophreniform disorder, SD = standard deviation

51.9 weeks (mean). This period was preceded by a period of 150.8 weeks (mean) with prodromal symptoms before treatment. The DUP was significantly associated with time to remission and level of remission; it was not correlated with age at onset, mode of onset, premorbid adjustment, or severity of illness. Men had a much longer DUP than women (mean = 69.7 weeks vs. 29.4 weeks, respectively). Poor premorbid functioning in early and late adolescence were also correlated with poorer outcome. When we compare these studies with Keshavan and Schooler's recommendations, we

find that they define onset of illness in different ways.

Illness Onset. Haas and Sweeney used the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al. 1982) to measure premorbid functioning; the PAS defines the period of 6 months before first positive symptoms as *premorbid*, and does not provide any description of the prodromal phase or definition of illness onset. Häfner et al. (1993) and Beiser et al. (1993) have developed a checklist of first noticeable symptoms and first signs of mental disorder; they also make retrospective descriptions of the time of first appearance of such symptoms. Loebel et al. (1992) simply asked open questions about the timing of behavioral changes that, in retrospect, appeared to have been related to the patient's becoming ill. No measures of severity or duration of prodromal symptoms are given in any of the studies.

Episode Onset. All studies describe the onset of psychosis. Haas and Sweeney (1992) define it as the age at onset of first psychotic symptoms, without giving any clear description of which symptoms are included or what duration and intensity these symptoms must have be to be considered as present. They also do not report any reliability on these ratings. Häfner et al. (1993) describe onset not only as the first first-rank symptoms without a severity and duration rating, but also as the first point in time when the operational criteria of a diagnostic system (like *DSM–III–R*) are fulfilled, including a severity rating as described in *DSM–III–R*. They report overall good interrater reliability on these measures. Loebel et al. (1992) do not report using any quantitative scales for rating the severity of psychotic symptoms at onset, but they do describe their procedure for defining the onset of psychotic symptoms as follows: "After explaining psychosis in clear language, we asked when the patient (or the family member) first experienced (or noticed) psychotic symptoms" (p. 1184). Reliability of these measures is not reported. Beiser and colleagues (1993) list some of the psychotic symptoms that are considered to be possible first signs of psychosis, but they describe no severity rating. Their criteria for duration of first psychotic symptoms are unclear, but they reported good interrater reliability.

Initiation of Treatment Versus First Hospitalization. All studies report age at first hospitalization. Haas and Sweeney (1992) also describe age at first neuroleptic medication and lifetime duration of neuroleptics, without indicating whether this use of neuroleptics was assumed to be adequate treatment. Beiser et al. (1993) report good interrater reliability on the description of initiation of treatment, but they do not discuss the definition of treatment. Häfner et al. (1993) carefully describe each episode of psychosis, including descriptions of all outpatient and inpatient contacts, including type of therapy and compliance. We cannot see that they have discussed the concept of adequate treatment; the age at first neuroleptic treatment is not reported in the publications cited. Loebel et al. (1992) report hospitalization, but not treatment seeking. Loebel et al. (1992) and Beiser et al. (1993) report median values of DUP to be significantly shorter than the mean value, indicating that some patients have a very long duration. They also report that the subjects included in the study had not received more than 12 weeks of neuroleptic treatment in their lifetime, but it is unclear whether this is considered adequate treatment.

In summary, these studies describe an average length of time with prominent psychotic symptoms before treatment or hospitalization of about 1 year, and there seems to be a period with prodromal symptoms of about the same length of time before the onset of the psychosis. The various definitions of illness onset, episode onset, and treatment onset overlap, but they are by no means identical. Nevertheless, these definitions appear to be more comparable than those used in the studies reviewed by Keshavan and Schooler (1992); even so, some definitions need further clarification. Is it possible to use a standardized description of prodromal symptoms or to describe the severity of psychotic symptoms retrospectively so that one can separate the onset of psychotic symptoms from the onset of a syndrome? At the end of this article we use our early course definitions to describe DUP and its demographic and clinical correlates in a Norwegian first-episode sample, compare this to other studies, and develop hypotheses about the origins of lengthy DUP.

Methods

Subjects. We studied 43 first-episode patients with nonaffective psychoses in a followup program at Rogaland Psychiatric Hospital,

Stavanger, Norway, as part of an early-identification-and-treatment program for first-episode schizophrenia. The project consists of a training program for general practitioners, with a strong emphasis on early identification and treatment of psychosis. All first-episode nonaffective psychotic patients of Rogaland County between the ages of 15 and 55 who were identified in 1993 and 1994 were hospitalized and evaluated with diagnostic, clinical, prognostic, and premorbid assessments. To our knowledge, no first-episode patient was treated before being hospitalized or without being hospitalized. The structured assessments were explained to all patients, but no written consent was deemed necessary, as long as the assessment methods were an integral part of the general assessment procedures at the hospital. Informed consent for a 1-year research followup assessment was later obtained from all subjects. A history of severe head trauma, previous hospitalization for psychosis or adequate treatment for psychosis, evidence of neurological or serious medical disorder, and intoxication with narcotics were criteria for exclusion.

Diagnosis. Patients admitted to the Rogaland psychiatric system with a possible first-episode psychosis were evaluated by one member of the research team (T.K.L.) and given a screening interview with the PANSS. Patients meeting inclusion criteria and giving consent underwent a diagnostic interview with the Structured Clinical Interview for *DSM–III–R*–Patient Edition (SCID–P; Spitzer et al. 1990), given by T.K.L. and the primary therapist. The diagnosis according to *DSM–III–R* was set after admission clinical assessment and the SCID–P interview. All diagnostic information, including the results of other interviews such as the PANSS and PAS, was reviewed in a consensus meeting with the treating therapists and the research team. A final *DSM–III–R* diagnosis was set at this meeting.

Prodrome and Mode of Onset. In this study, we developed a manual for the early identification of psychosis, which was used as a part of the training program for the general practitioners (GPs). It consisted of the prodromal symptoms in *DSM–III–R* (0 = absent, 1 = uncertain, 2 = present) and the positive subscale of PANSS. We did a preliminary screening of the patients with this manual. However, we did not estimate the duration of prodromal symptoms in each patient, because we felt the definition of prodromal symptoms was not very precise, and others have shown that it is difficult to achieve good reliability (Beiser et al. 1993). The mode of onset was described with the Reactivity of Psychosis Rating Form (Guldberg et al., in press), in which the development of psychosis is rated on a scale from 1 to 6, 1 meaning developed in less than 48 hours and 6 developed continuously or during more than 12 months. This variable gives us a picture of how long the patients were ill before the onset of psychosis.

Onset Measures and DUP. Psychosis onset in our study was defined as the first appearance of psychotic symptoms, which in Keshavan and Schooler's model (1992) is described as "episode onset." We defined the onset of psychotic symptoms as follows: a score 4 or higher on the PANSS positive subscale and manifestation of psychotic symptoms such as delusions, hallucinations, thought disorder, or inappropriate or bizarre behavior in which the symptoms are not apparently due to organic causes. These symptoms must have lasted throughout the day for several days or appeared several times a week, not for just a few brief moments. We did not rate syndrome onset or the time when the patient met duration and severity criteria for a specific *DSM–III–R* diagnostic category, that is, brief reactive psychosis.

DUP was defined as the interval between the onset of psychotic symptoms and hospitalization for psychosis or initiation of adequate treatment. Symptom onset was estimated by T.K.L. either during the PANSS or during the SCID interviews. When patients acknowledged a targeted psychotic symptom, they were asked to trace back to when the symptom began. Similar questions were asked of the family by the treating clinician. We defined adequate treatment biologically as an antipsychotic drug given in sufficient time and amount that it would lead to clinical response in the average nonchronic schizophrenia patient (e.g., haloperidol 5 mg/day for 3 weeks). A patient who had received treatment according to this definition was not considered to be in an untreated first episode and was excluded from the study.

DUP was rated for every patient in the project on the basis of all available information from structured interviews, from other interviews with the patients and relatives, and from the subject's

hospital records. A final score was achieved by consensus between the research team and the primary therapist (psychiatrist or psychologist).

A test-retest study of DUP was carried out with the first 20 patients included in the study. A trained psychiatrist, blind to previous ratings, reinterviewed patients and in some cases also the relatives. The interviews were carried out at least 6 months after the first evaluation. The test-retest showed a good reliability (intraclass correlation: $r = 0.96$, $p < 0.001$).

We also measured the severity of psychosocial stressors at onset (adult Axis IV *DSM–III–R*) and the mode or rapidity of onset (acute vs. insidious).

Manifest Illness Measures. When patients were initially screened as having a first episode of psychosis and were hospitalized, a PANSS interview was conducted within the first week. The scale included 30 items, each scored from 1 to 7 (1 = absent, 7 = extreme). The PANSS has three subscales: 7 items for positive symptoms, 7 for negative symptoms, and 16 for general psychopathology. The items are rated after a semistructured interview with the patient, and all available information from relatives, staff, and others is taken into consideration. Interrater reliability was determined in a study where two raters familiar with and experienced in the use of the PANSS rated 20 patients. Both raters were present during patient interviews and independently completed the PANSS. The intraclass correlation for the two raters was as follows: positive subscale $r = 0.90$ ($p < 0.001$); negative subscale $r = 0.83$ ($p < 0.001$); general subscale $r = 0.65$ ($p < 0.001$); and total score $r = 0.82$ ($p < 0.001$).

Functional Measures. The Global Assessment of Functioning (GAF; American Psychiatric Association 1987) scale was used to describe general functioning during the previous week and the best score during a 1-month period the last year before hospitalization; the scale ranges from 0 to 90. The Strauss-Carpenter (1994) scale describes functioning the last year before hospitalization in four areas: work, social activity, symptoms (last month before hospitalization), and global functioning. All items are rated on a scale from 0 to 4, 4 being the best and 0 the worst score (Strauss and Carpenter 1974).

Results

All statistical analyses were carried out using the *Statistical Package for the Social Sciences for Windows* (1993).

Sample. Characteristics of the sample are listed by gender in table 2. Eighty-one patients were referred to the project and assessed with the PANSS; 43 cases met the criteria for inclusion and were also assessed with the other measures. Only one patient refused to be interviewed with the assessment protocol and was excluded from the project. In the group of excluded cases ($n = 37$), 57 percent were male; 35 percent had a personality disorder, 35 percent an affective disorder, 11 percent depression, 11 percent earlier hospitalization or treatment, 6 percent a drug-induced psychosis, and 2 percent a panic disorder.

Sixty-five percent of the study sample were men; all were Caucasian. The majority of the cases were single, the males were single to a significantly greater frequency than females. The subjects' educational level varied widely as shown, with females achieving higher levels overall. By the time of admission, the majority of the males but not of the females were on social security or were unable to work; they received social security payments from the county and were registered with some form of nonpsychotic disability in the social security system. Most of the patients, both male and female, had not received any medication before hospitalization. Those who did receive medication did not receive it in sufficient time and in an amount that would be considered an adequate trial.

Diagnosis, Onset, Hospitalization, and DUP. Table 3 presents the diagnostic distribution, characteristics of onset, functioning around onset, and DUP, with gender and prior treatment breakdowns. The vast majority of the patients met full *DSM–III–R* criteria for schizophrenia, but males received a *DSM–III–R* diagnosis of schizophrenia with significantly greater frequency. The mean age at onset was 26.3 years with a typical gender split; that is, the age at onset for males (24.5 years) was significantly less than that for females (29.7 years). The mode of onset typically ranged widely from acute to insidious, and there were no significant gender differences. Functioning at admission was poor (mean GAF = 32) for both sexes. Women had the best functioning for at least a 1-month period dur-

Table 2. Sample characteristics by gender

	Female, *n* = 15	Male, *n* = 28	*p*
Marital status, %			
Single	67	96	
Married or living with someone	33	—	
Divorced or separated	—	4	
Not married, *n*	10	27	
Married, *n*	5	1	0.03
Educational status, %			
Completed study at university or graduate school (> 15 years)	21	4	
Gymnasium and some additional education (> 12 years)	36	18	
Only completed gymnasium (12 years)	—	7	
Completed public school and some additional education (9–11 years)	14	43	
Completed public school (9 years)	22	21	
Less than public school (< 9 years)	7	7	
University, *n*	8	*n* 6	
Gymnasium, *n*	2	*n* 14	
Public school, *n* (1 missing)	4	*n* 8	0.03
Employment status year before hospitalization, %			
Social security	14	46	
Unemployed but able to work	7	11	
Part-time employment	50	18	
Full-time employment	29	25	
Not working, *n*	4	*n* 16	
Working, *n* (1 missing)	10	*n* 12	0.20
Treatment before hospitalization, %			
None	57	23	
Treatment without neuroleptics	29	54	
Treatment with neuroleptics (inadequate dose or duration)	14	23	
Not treated, *n*	8	*n* 6	
Treated, *n* (1 missing)	6	*n* 20 (2 missing)	0.07

Note.—Eighty-one cases were referred, 43 of which were included in the study. *p* Values are based on chi-square test of significance. Gymnasium is a European secondary school that prepares students for university study.

ing the year before admission (mean GAF = 64).

DUP was 114.2 weeks (mean), with a large variation. Almost half the sample (46.5%) had a mean DUP of 1 year or longer. The median of 26 weeks strongly suggests some lengthy outliers on this variable. The gender split in DUP is

Table 3. Diagnosis, onset, hospitalization, and duration of untreated psychosis (DUP), (n = 43)

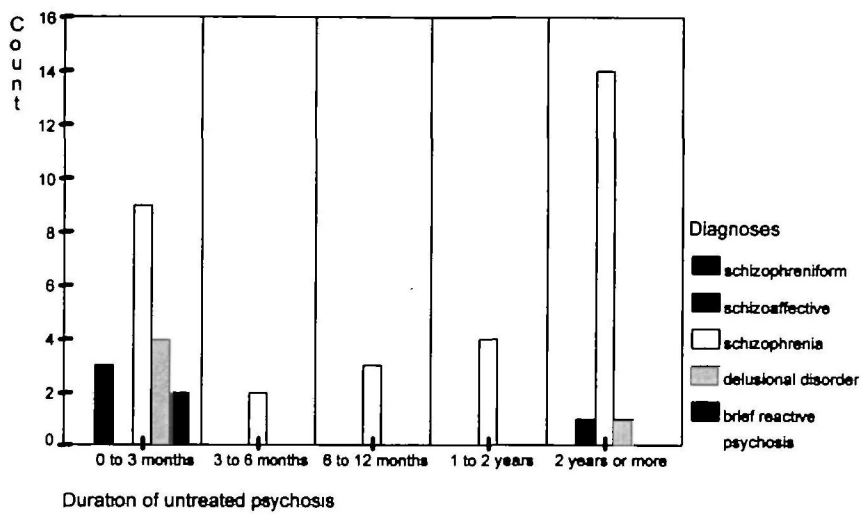
Criteria	Female	Male	p
DSM–III–R diagnosis			
Schizophrenia	8	24	
Schizophreniform disorder	3	—	
Schizoaffective disorder	—	1	
Delusional disorder	2	3	
Brief reactive psychosis	2	—	
Schizophrenia	8	24	
Nonschizophrenia	7	4	0.05
Age at onset of psychosis, mean years (SD)			
Total sample	26.3 (8.3)		
Female	29.7 (10.0)		
Male	24.5 (6.9)		0.055
Age at hospitalization, mean years (SD)			
Total sample	28.4 (8.3)		
Female	30.2 (9.8)		
Male	27.5 (7.4)		0.4
Mode of onset, %			
Continuous or more than 12 months	7	18	
4–12 months	13	11	
1–3 months	13	28	
1–4 weeks	33	32	
2 days to 1 week	27	11	
Less than 48 hours	7	—	
Continuous or more than 12 months, n	1	5	
1–12 months, n	4	11	
Less than 48 hours to 4 weeks, n	10	12	0.3
GAF, mean (SD)			
Last week before hospitalization	32 (8)		
Female	30 (7)		
Male	34 (8)		0.14
Last year before hospitalization	56 (14)		
Female	64 (15)		
Male	52 (11)		0.02
DUP, mean (SD)			
Total sample, 26 weeks median	114.2 (173.6)		
Female, 4 weeks median	39.0 (64.7)		
Male, 78 weeks median	154.4 (199.7)		0.04
Short vs. long DUP, %			
1 year or longer (n = 20)	20	61	
Shorter than 1 year (n = 23)	80	39	0.02
DUP and prior treatment with neuroleptics			
Female			
No prior treatment, 85% mean weeks (SD)	34.3 (62.3)		
Prior treatment, 15% mean weeks (SD)	86.5 (98.3)		0.3
Male			
No prior treatment 77%, mean weeks (SD)	101.8 (120.5)		
Prior treatment 23%, mean weeks (SD)	316.3 (324.9)		0.02

Note.—p Values are based on t-tests of significance (continuous variables) and chi-square (categorical variables). GAF = Global Assessment of Functioning (American Psychiatric Association 1987); SD = standard deviation; *DSM–III–R* = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed., revised (American Psychiatric Association 1987).

striking, with the mean DUP for men (154.4 weeks) almost four times the mean DUP for women (39 weeks). There was also a wide split in DUP depending on whether or not the treatment system had been contacted before first hospitalization or first definitive treatment. Among the males, but not the females, those who had made contact had a significantly longer DUP.

A frequency distribution of the DUP is shown in figure 2. Twenty of the schizophrenia patients had a DUP of 1 year or longer. A relatively large proportion of the short DUP patients had schizophreniform, delusional, or brief reactive disorder.

Figure 2. Frequency distribution of duration of untreated psychosis according to diagnosis



Clinical Correlates of DUP. Table 4 presents clinical characteristics of this sample and how they vary with DUP. DUP and characteristics of premorbid functioning as measured by the PAS are presented in Larsen et al. (1996, Part II, this issue).

DUP and level of education achieved are not significantly correlated. However, long DUP is associated with a significant loss in functioning in the year before hospitalization as measured by the Strauss-Carpenter functioning scale and the GAF. According to the Strauss-Carpenter scale, this loss is particularly striking in social functioning. These losses may have started more than 1 year before admission, but our measures were not able to capture this. There is no association between DUP and the age at onset of first psychotic symptoms, the age at first hospitalization, or stressors at onset. However, long DUP is associated with a more insidious mode of onset. At hospitalization, DUP was not associated with the total PANSS scores for positive symptoms or for general symptoms. Among the latter, however, longer DUP was associated with more motor retardation and unnatural movements (awkward, stilted, disorganized, or bizarre appearance). Longer DUP was also associated with more negative symptoms at hospitalization, especially with stereotyped thinking.

Because of the extensive gender differences in this sample (see tables 2 and 3), the correlations in table 4 were repeated for each gender. The number of significant results diminished because of loss of statistical power, but the patterns of results remained more or less the same. For example, among both men and women longer DUP was associated significantly with loss of functioning in the year before admission by the Strauss-Carpenter scale (female: $r = -0.57$, $p < 0.05$; male: $r = -0.57$, $p < 0.001$) and by the GAF (female: $r = -0.61$, $p < 0.05$; male: $r = -0.54$, $p < 0.01$), as well as with a less acute mode of onset (female: $r = -0.76$, $p < 0.001$; male: $r = -0.51$, $p < 0.01$). Long DUP was associated with an older age at first hospitalization among men ($r = 0.38$, $p < 0.05$), but not among women. The association of longer DUP with the negative symptom of emotional withdrawal was significant for women ($r = 0.53$, $p < 0.05$), and the association with stereotyped thinking was significant for men ($r = 0.37$, $p < 0.05$).

Discussion

DUP. The mean DUP for our sample is very long indeed, but it is comparable to the findings of others. This means that new patients can emerge and function for a remarkably long period of time in the community with severe psy-

Table 4. Pearson correlations of duration of untreated psychosis (DUP) with other clinical features

	n	DUP	*p*
Preonset features			
Education level (0–6: 0 is highest, 6 lowest)	42	0.23	0.15
Strauss-Carpenter (0–4: 0 is lowest, 4 highest)			
Employment status last year before hospitalization	42	–0.34	0.03
Social activity last year	43	–0.43	0.004
Symptoms last month before hospitalization	43	–0.17	0.28
Global functioning last year	43	–0.53	0.000
Global Assessment of Functioning (0–90: 0 is lowest, 90 highest)			
Last week before hospitalization	43	–0.007	0.967
Last year before hospitalization	43	–0.53	0.000
Onset and reactivity			
Age at onset of first psychotic symptoms	43	–0.20	0.19
Age at first hospitalization	43	0.20	0.21
Axis 4 *DSM–III–R* (1–6: 1 is no stressor, 6 is severe)	43	–0.27	0.08
Mode of onset (1–6: 1 is insidious, 6 is rapid)	43	–0.54	0.000
Manifest illness			
PANSS at hospitalization (1–7: 1 is lowest, 7 is highest)			
Positive symptoms	43	0.006	0.97
Negative symptoms	43	0.31	0.04
Stereotyped thinking	43	0.36	0.02
General symptoms	43	0.12	0.43
Unnatural movements	43	0.32	0.04
Motor retardation	43	0.31	0.05

Note.—*p* Values are based on *t*-tests of significance. PANSS = Positive and Negative Syndrome Scale (Kay et al. 1987); Strauss-Carpenter scale (Strauss and Carpenter 1974), *DSM–III–R* = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed., revised (American Psychiatric Association 1987).

chopathology. Given how difficult and potentially dangerous it must be to live and try to cope in our society with an active psychosis, reducing the DUP becomes a major public health directive for psychiatric services.

We found that the DUP was significantly longer for men than for women (mean = 154 weeks vs. 39 weeks). Our findings replicate those of Loebel et al. (1992), who reported that men had a significantly longer duration of psychotic symptoms before hospitalization than women (mean = 70 weeks vs. 29 weeks). They found no significant gender differences on the duration of prodromal symptoms. In contrast, Beiser et al. (1993) did not find this gender difference in DUP, but women in their sample tended to experience longer prodromes than men ($p = 0.11$). Häfner et al. (1993) did not report such gender differences, but they found that male schizophrenia patients between ages 12 and 24 had negative symptoms for a much longer period before hospitalization than women (8 years vs. 3 years).

Despite the strong gender differences in DUP, most of the clinical correlates of DUP tested here were not gender specific. Therefore, it is difficult to explain why men are generally identified with psychosis and given adequate treatment later than women. This is an important area for future studies on early identification strategies: What personal characteristics or sociocultural behaviors influence patterns of help-seeking?

Clinical Correlates of DUP. Haas and Sweeney (1992) found that 93.3 percent of their short-term symptom first-episode group (DUP < 1 year) had never been exposed to neuroleptic medication,

but only 19 percent of the long-term symptom group (DUP > 1 year) were neuroleptic naive. We divided our sample into short and long DUP, using the same criteria as Haas and Sweeney, and found that 36.8 percent of the long-DUP group had received some neuroleptics, compared with only 4.8 percent of the short-DUP group ($p < 0.01$). When we used this dichotomy and looked at the relationship between long and short DUP and neuroleptics for each gender, we found a significant correlation only for the males. When we used DUP as a continuous variable, long DUP was clearly associated with receiving neuroleptics more frequently before hospitalization for both males and females (table 3). Since we excluded patients who had received adequate treatment for their psychosis, it seems that one-third of the long-DUP patients were at times identified as having a psychosis without being offered proper treatment.

It appears that there is a limited tradition within the primary health services for treating psychosis with neuroleptics. There may also be a tendency not to refer treatment-resistant cases to the specialist services. In the Northwick Park Study of first episodes of schizophrenia, Johnstone et al. (1986) found that 41 percent of the patients had made two or more contacts with GPs without getting proper help, and 13 percent of the sample had made nine or more contacts with GPs. From this point of view, it seems important to include GPs in developing early identification strategies. There may also be a tendency, even within the psychiatric services, not to regard the risk of developing a psychosis seriously enough.

It is also important to remember that the patient must accept that treatment is needed and therefore motivation may be an essential goal in early treatment. Helgason (1990) studied patient compliance and found that only 54 percent of the schizophrenia patients who were considered to need inpatient care accepted this fact. This study included all first-episode schizophrenia patients, hospitalized or not, in Iceland between 1966 and 1967 ($n = 107$).

Our sample shows a typical age at onset of psychosis (26.3 years), with women being older than men (29.7 years vs. 24.5 years, $p = 0.055$). There is also an expected wide range of onset modes from insidious to acute (Ciompi 1980; Huber et al. 1980; McGlashan 1984).

We found no association between DUP and the age at onset of psychosis or the age at hospitalization, thus confirming previous research. Haas and Sweeney (1992) reported that the age at first hospitalization was higher in their long-term symptom group ($p < 0.01$), but there was no difference in the age at onset of psychotic symptoms. Loebel et al. (1992) correlated DUP with age at onset, age at onset of psychotic symptoms, and age at study entry, finding no significant differences. Beiser et al. (1993) found that women with schizophrenia had a lower age at onset of first noticeable symptoms ($p = 0.02$), but the age at onset of psychosis was not different. The mean age at initiation of treatment-seeking was also not different in their study. Häfner et al. (1993) reported no relationship between the duration of psychosis and age at onset, but they found that women fell ill with schizophrenia later (3–4 years) than men, whether onset was defined as first hospitalization, first appearance of psychotic symptoms, or first sign of mental disorder.

We found a plunge in GAF scores from the last year before hospitalization to the last week before hospitalization, showing the emergence of active, disabling psychosis (table 3). There is also a significant difference between men and women in their GAF scores 1 year before hospitalization, women having the higher level of functioning (table 3). Worse GAF scores and Strauss-Carpenter scale scores on employment, social activities, and global functioning are also significantly associated with long DUP (table 4). Overall, general functioning capacity proves to be a sensitive and powerful indicator of trouble for both men and women. Unfortunately, its nonspecificity is such that its significance is usually grasped only retrospectively.

We found a correlation between longer DUP and negative symptoms at the time of hospitalization, especially emotional withdrawal in women and stereotyped thinking in men. Haas and Sweeney (1992) did not report any symptom associations, while Bean et al. (1995) found treatment delay associated with disorganized symptoms. In these studies, gender differences are not reported. Overall, symptomatic differences were not frequent or strong in our sample. The differences noted were more functional than symptomatic, especially a deficiency in social relations.

It appears that in the early course of these patients, changes are hidden, ignored, or explained away retrospectively. The patients

may be experiencing obvious psychotic symptoms, but they are able to hide them in society and at home. Very few people are able to observe or understand what is happening. For example, one of our patients did visit the psychiatric services 5 years before her psychosis was properly treated. A psychologist noted that she had no insight despite the occurrence of withdrawal and strange ideas. She also did not want treatment. No suggestion was made about the possibility of her being in a prodromal stage of illness, and no further examination of her thought disturbance was conducted. The psychiatric service decided to wait and see if she would be more willing to receive treatment, but no followup plan was made even though it now seems obvious that she was at the onset of a psychosis. Her parents were concerned, but, when things got even worse they did not want to bother the specialists with more "stupid" questions. Nobody had told them that their daughter was at high risk for developing a major mental illness that could be treated. As "good parents," they accepted her accelerating disability and literally enlarged their house so that she could have her own space for being psychotic. As Loebel et al. (1992) found, long DUP predicted a long time to remission; in this case, when the patient finally received proper treatment, her psychosis did not resolve completely within the first year, and a severe negative profile was found at a 2-year followup assessment.

Measuring Early Course for Future Studies. Figure 3 attempts to integrate the definitions of early course suggested by Keshavan and Schooler (1992; figure 1) with subsequent first-episode studies summarized in table 1, as well as our own experience with the first-episode sample reported here.

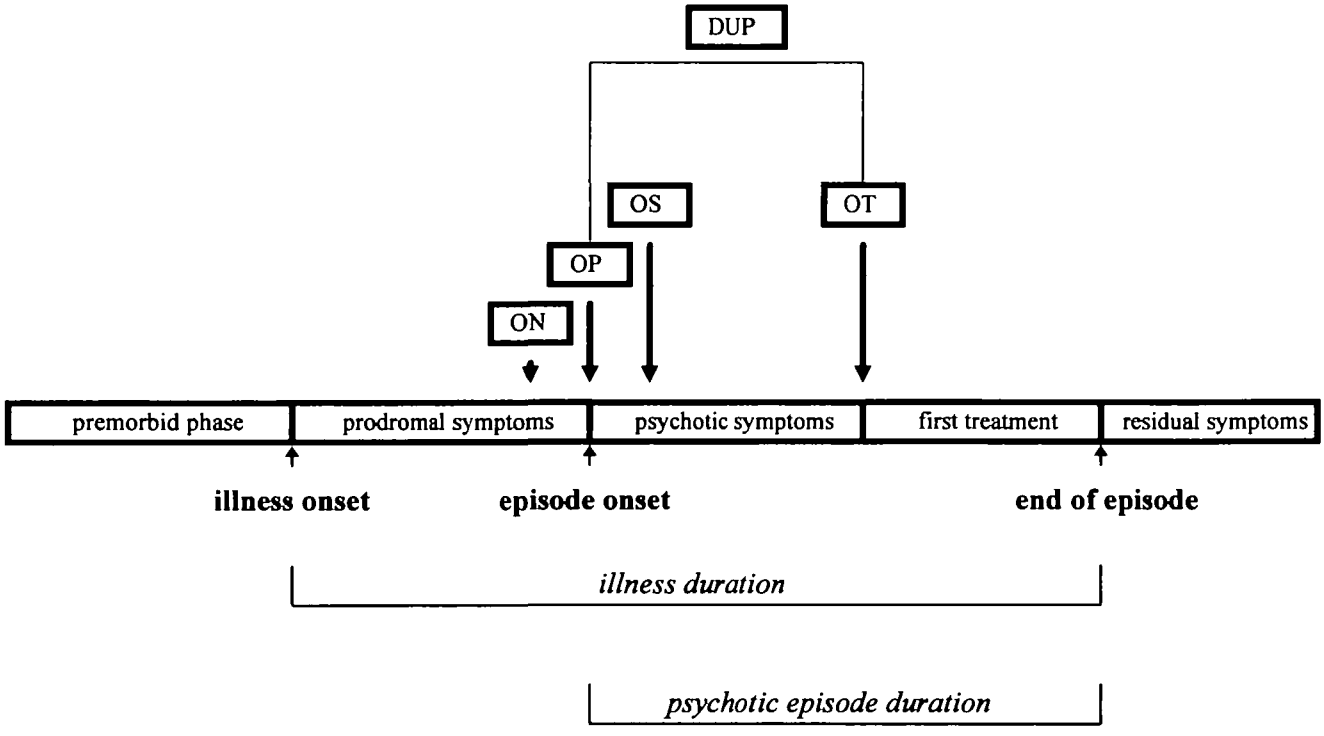
Premorbid phase and illness onset. First of all, it is important to use a scale that describes the premorbid phase over several time periods and levels of functioning in the individual's life. The premorbid scale should describe functioning from early age on, taking the onset of illness or psychosis into consideration. The PAS is largely sufficient. As described in Larsen et al. (1996, Part II, this issue), our only problem was that the PAS arbitrarily defines the prodrome as 6 months prior to psychosis onset, and therefore the scale does not consider *illness onset* as defined by Keshavan and Schooler (onset of prodromal symptoms). It is therefore important to combine the PAS with a rating of illness onset, a description of the prodromal symptoms, and a scale to quantify them retrospectively. Current scales or lists of prodromal symptoms include that of Häfner et al. (1992), the prodromal symptoms of *DSM–III–R* schizophrenia, and a new scale from the Personal Assistance and Crisis Evaluation clinic in Melbourne, Australia (see Yung et al. 1996, this issue).

Episode onset. The next step is to rate episode onset. In principle, this can be done at three levels: (1) onset of psychosis, positive symptoms; (2) onset of negative symptoms; and (3) onset of psychotic syndrome. Onset of first positive psychotic symptoms is identical with episode onset, and we recommend using defined scales on strength and duration of symptoms. In our study, we defined onset as a score of 4 or higher on the PANSS positive subscale and manifestation of psychotic symptoms such as delusions, hallucinations, thought disorder, or inappropriate or bizarre behavior in which the symptoms are not apparently due to organic causes. These symptoms must have lasted throughout the day for several days or several times a week, not limited to a few brief moments. We determined that this definition could be rated reliably and that it gave a good clinical description of the disease process.

If it seems important to rate the onset of negative symptoms, we suggest a definition equivalent to the onset of positive symptoms, such as the use of the SANS or PANSS.

The onset of a psychotic syndrome must be related to the criteria that are described in a diagnostic system such as *DSM–IV* (American Psychiatric Association 1994) or the International Classification of Diseases, 10th revision (ICD–10; World Health Organization 1993), for example, brief reactive psychosis. A structured interview should be used to maximize reliability. The strategy for eliciting this information varies across studies. Loebel et al. (1992), for example, gathered the patient and family together, explained what was meant by psychosis, and asked them when the patient first experienced psychotic symptoms. Others, like us, gathered onset information in the context of a structured symptom or diagnostic interview. A patient who acknowledged one of the target symptoms was asked when that symptom first began. This information was then shared with the family or

Figure 3. Early course of schizophrenia: Future studies



ON = onset of negative symptoms
OP = onset of psychosis, positive symptoms
OS = onset of psychotic syndrome
OT = onset of treatment
DUP = duration of untreated psychosis

compared with their impressions for a consensus rating. Such a procedure achieved good test-retest reliability in our hands. We recommend it but also recommend any procedure that focuses on the timing of symptom development in a systematic fashion, such as that of Loebel et al. (1992) or Häfner et al. (1993).

The final step will be to decide when the treatment started. This issue has not been considered frequently in the studies of first-episode patients. We feel it is important not to equate first treatment with hospitalization, because it is typical for first-episode patients with a long DUP to have received treatment with neuroleptics before hospitalization. We suggest the following definition for "adequate" treatment: antipsychotic medication in sufficient amount (e.g., haloperidol 5 mg/day) given for a sufficient period of time (e.g., 3 weeks) that would generally lead to a clinically significant response in nonchronic, non-treatment-resistant patients. The definition of DUP will then be the time from the onset of positive psychotic symptoms to the time when the patient receives adequate treatment. Using these definitions will also make it possible to figure out a value for the duration of untreated illness, the duration of untreated negative symptoms, and eventually the duration of untreated syndrome, in addition to the DUP (see figure 3). Future studies may be able to determine which of these durations have the strongest prognostic influence.

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The Authors

Tor K. Larsen, M.D., is Research Fellow, Psychiatric Hospital of Rogaland, Stavanger, Norway. Thomas H. McGlashan, M.D., is Executive Director, Yale Psychiatric Institute and Professor of Psychiatry, Yale University School of Medicine, New Haven, CT. Lars Conrad Moe is a certified Psychologist, Department of Child Psychiatry, Psychiatric Hospital of Rogaland, Stavanger, Norway.